

Single Technology Appraisal

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

**Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia
[ID765]**

Contents:

- 1. Pre-Meeting Briefing**
- 2. Final Scope and Final Matrix of Consultees and Commentators**
- 3. Company submission from Amgen UK**
 - **Appendix 5**
- 4. Clarification letters**
 - NICE request to the company for clarification on their submission
 - Company response to NICE's request for clarification
- 5. Addendum 1 to Company submission prepared by Amgen**
- 6. Patient group, professional group and NHS organisation submission from:**
 - HEART UK
 - Royal College of Pathologists
- 7. Expert statements from:**
 - Professor A Wierzbicki – clinical expert, nominated by HEART UK
 - Mr S Foster – patient expert, nominated by HEART UK
- 8. Evidence Review Group report prepared by School of Health and Related Research (SchARR)**
- 9. Addendum 2 to Company submission prepared by Amgen**
- 10. Company PAS Submission prepared by Amgen**
- 11. Evidence Review Group report – factual accuracy check**
- 12. Evidence Review Group critique of Addendum and PAS submission**
- 13. Evidence Review Group – Erratum**
- 14. Addendum 3 to Company submission prepared by Amgen**

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

Premeeting briefing

Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information on the clinical-effectiveness evidence from the company's original submission. The cost-effectiveness results are based on the company's PAS submission to reflect the latest set of amendments made by the company and the PAS discount. For further details, see section 5 on page 28.

Key issues for consideration

Clinical effectiveness

- The company stated that the priority for using evolocumab would be in patients with primary (familial and non-familial) hyperlipidaemia and mixed dyslipidaemia who are at high risk of cardiovascular disease. Is this the population in which evolocumab would principally be used?
- None of the trials provided evidence for evolocumab compared with ezetimibe in patients with heterozygous familial hypercholesterolaemia (HeFH), or evolocumab in combination with ezetimibe in any population. Is the RCT evidence sufficient to

give an indication on the clinical effectiveness of evolocumab compared with ezetimibe in the HeFH population, or that of evolocumab plus ezetimibe in any population?

- Is it plausible to assume that the reduction in LDL-C concentration with evolocumab would have the same benefit on cardiovascular (CV) outcomes as the reduction with by statins?
- The clinical experts advised that patients treated with evolocumab are likely to need more follow-up appointments than those treated with statins or ezetimibe because with evolocumab, neutralising antibodies can develop and treatment may lose its effectiveness. Would the effect of evolocumab be maintained over time?
- The clinical trials for evolocumab measured primarily the effect of treatment on hypercholesterolemia (LDL-C concentration). Could this effect be extrapolated to mixed dyslipidaemia, in which both LDL-C and triglyceride concentrations are elevated?
- What proportion of patients receiving evolocumab, if any, will transition from secondary to primary care?

Cost effectiveness

- Population, intervention and comparators
 - The ERG suggested that the company – having modelled only patients with an LDL-C concentration over 2.5 mmol/L – was likely to have excluded most UK patients with primary non-familial hypercholesterolaemia who can have an LDL-C concentration of 2.0 mmol/L on statins. Does the modelled population represent patients in clinical practice in England?
 - The company assumed patients who can tolerate statins have the same characteristics as those who cannot. The ERG noted that the risk of cardiovascular disease (CVD) was likely to be related to whether or not LDL-C concentration can be controlled on statins. Is the company's assumption appropriate?
 - HeFH population only. The modelled HeFH population included patients with, and those without, existing CVD, whereas the clinical and cost effectiveness of evolocumab may differ in these groups. Does the modelled population reflect patients with HeFH who are likely to present in clinical practice?

- The intervention modelled in the base-case analysis was evolocumab 140 mg every 2 weeks, with the monthly dose of evolocumab explored in scenario analyses. Which dose is more appropriate for the consideration of the cost effectiveness of evolocumab?
- The ERG noted the lack of data to inform clinical effectiveness in some states of the model, particularly the composite states which it considered to be largely populated using assumptions. Are the states used in the model appropriate given the existing data?
- Estimation of CVD risks
 - The ERG considered that, whereas the company predicted risks using published equations then adjusted them to reflect real-world data, it could have estimated the risks directly from the real-world data (CPRD and HES analysis) without using risk equations. Which approach is more appropriate?
 - The ERG stated that the company added arbitrary constraints to prevent the model from generating negative transition probabilities. Is the company's method for estimating transition probabilities appropriate?
 - HeFH population only. The company applied the relative risk from the study by Benn et al. to the clinical trial population that was already at high risk of CVD, whereas this study compared the risk of CV events between the general population and patients with HeFH. The ERG stated that this was likely to underestimate the ICERs for evolocumab. How should the risk of CVD be adjusted for the HeFH population?
- Treatment effect
 - Is it appropriate for the company to have used changes in LDL-C concentration, as opposed to changes in other lipid markers, as a surrogate for changes in CV events?
 - Are the following assumptions in the model about treatment effects appropriate:
 - ◇ For patients with non-familial hypercholesterolaemia who can tolerate statins, the treatment effect from LAPLACE-2 could be generalised to the subset of patients with an LDL-C concentration over 2.5 mmol/L.
 - ◇ The same treatment effect would apply to patients whether or not they have risk factors for CVD (for example, diabetes).

- ◇ When evolocumab is combined with ezetimibe, the effect of evolocumab alone could be added to the effect of ezetimibe alone.
- ◇ The treatment effect would be maintained indefinitely.
- The company made the following assumptions about the relationships between changes in LDL-C concentration and changes in CV events observed in the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis. Would these be considered appropriate?
 - ◇ The relationship was the same in patients with, and those without, a history of CVD.
 - ◇ The relationship was the same for the first recurrent, and subsequent CV events.
 - ◇ The effect of reducing LDL-C concentration on non-fatal myocardial infarction was the same as that on heart failure.
 - ◇ The relationship observed for non-fatal myocardial infarction (secondary prevention) would apply to patients moving from the 'no CVD' state to the 'established CVD' state.
 - ◇ Reducing LDL-C concentration had no effect on death from stroke.
 - ◇ The reduction in fatal CV events per mmol/L reduction in LDL-C concentration would apply whether or not the patient had had previous events.
- The ERG noted that some of the utility values used in the model did not correspond to the states for which they were used. Are the utility values used in the model appropriate?

1 Remit and decision problems

- 1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of evolocumab within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG

Population	People with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies, in line with current NICE guidance, would be considered.	Same as final scope.	The priority for using evolocumab would be in patients who are at the highest residual risk of, and who are most vulnerable to, having cardiovascular events. These include: - patients without existing cardiovascular disease but who are at high residual risk because of additional risk factors (based on the QRESEARCH Cardiovascular Risk Algorithm [QRISK2] score) - patients with existing cardiovascular disease who are at high residual risk because of additional risk factors (e.g. diabetes mellitus or chronic kidney disease) - patients with heterozygous familial hypercholesterolaemia. For the place of evolocumab in the treatment pathway proposed by the company, see figure 3-3 on page 55 of the company's submission.	The population was consistent with the scope. Whether patients in the trials who could tolerate statins were on the maximum tolerated dose of statins, as required by the marketing authorisation, was uncertain.

Intervention	Evolocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe.	For all patients: • Evolocumab in combination with a statin • Evolocumab in combination with a statin and ezetimibe • Evolocumab alone or in combination with ezetimibe For patients in whom statins are contraindicated or not tolerated only: • Evolocumab alone or in combination with ezetimibe	None. The decision problem addressed in the submission was in line with the final scope.	The clinical trials provided evidence for most of the evolocumab treatments included in the scope, although data on evolocumab plus ezetimibe plus statins were available only from trial subgroups. No evidence existed for evolocumab plus ezetimibe in patients with non-familial hypercholesterolemia or HeFH who cannot tolerate statins.
Comparators	• When optimised statin therapy does not appropriately control LDL-C: – Ezetimibe in combination with a statin • When statins are contraindicated or not tolerated: – Ezetimibe	Same as final scope.	None.	The comparators used were in line with the scope.

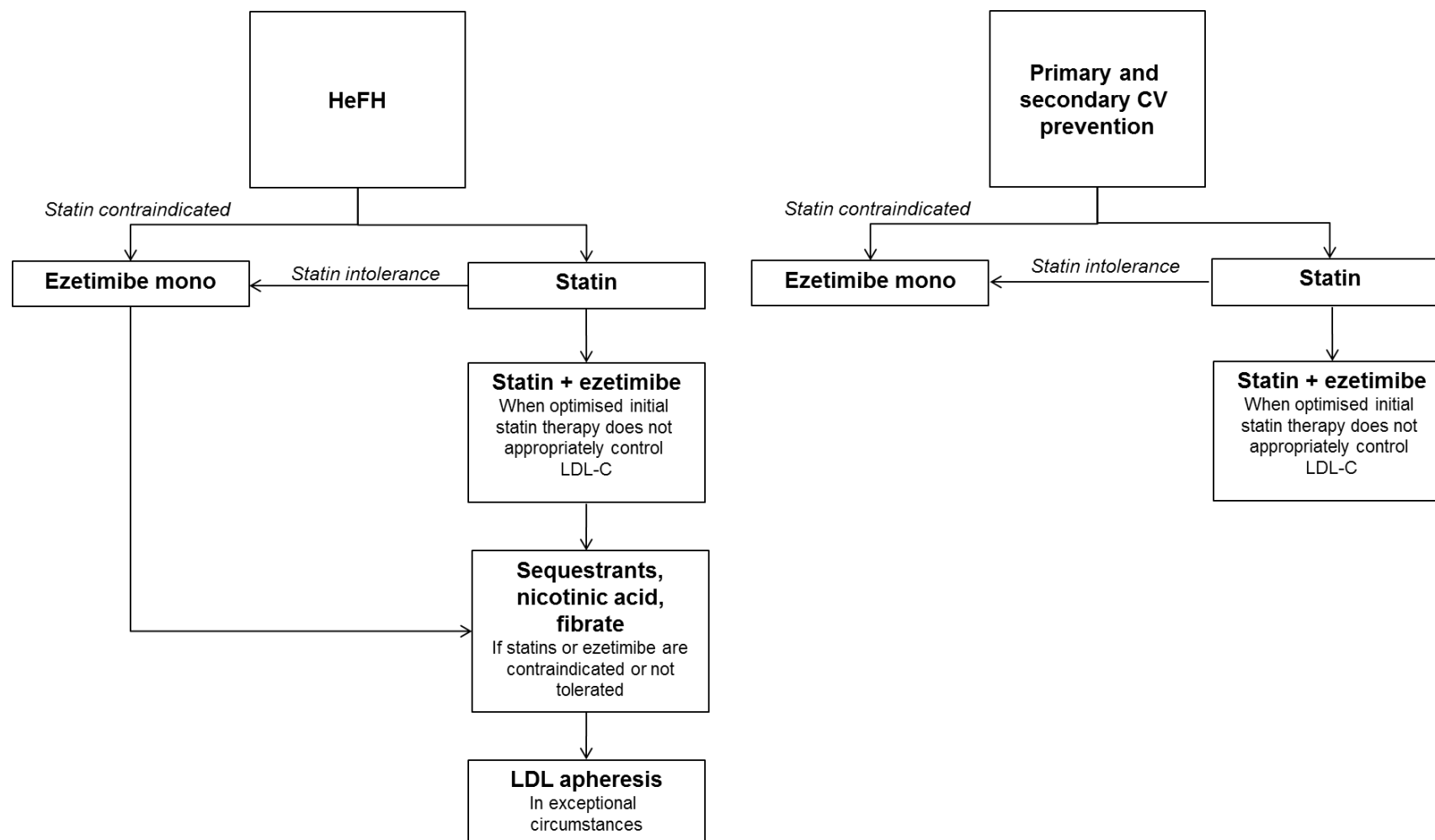
Outcomes	• Plasma lipid and lipoprotein levels, including LDL cholesterol, non-HDL-cholesterol, apolipoprotein B and lipoprotein a • Requirement of procedures including LDL apheresis and revascularisation • Fatal and non-fatal cardiovascular events • Mortality • Adverse effects of treatment • Health-related quality of life	Same as final scope except that health-related quality of life was excluded.	The clinical trial programme for evolocumab did not collect data on health-related quality of life. However, the economic evaluation included utility estimates associated with CV events.	All the outcomes were reported in the RCTs for evolocumab. Using LDL-C concentration as a surrogate for CVD is generally accepted for statin therapy. However, the effect of evolocumab on CV outcomes was yet to be established from long-term data. The principal safety outcomes were all considered in the company's submission.

Subgroups	If the evidence allows, consideration will be given to the following subgroups: • Presence or risk of cardiovascular disease • People with heterozygous familial hypercholesterolaemia • People with statin intolerance • Severity of hypercholesterolaemia	Same as final scope plus additional subgroups of patients with existing cardiovascular disease who are at high residual risk because of additional risk factors.	The additional subgroup analyses were to identify patient groups in whom evolocumab may be particularly cost effective because of the increased baseline risk of having CVD.	Clinical evidence was presented for each of the subgroups included in the scope.

2 The technology and the treatment pathway

- 2.1 Hypercholesterolaemia is the presence of high concentrations of cholesterol in the blood, typically including elevated low-density lipoprotein cholesterol (LDL-C). Primary hypercholesterolaemia is associated with an underlying genetic cause, which may be caused by a single genetic defect (familial), or more commonly, by the interaction of several genes with dietary and other factors such as smoking or physical inactivity (non-familial). In heterozygous-familial hypercholesterolaemia, one of the pair of LDL-C receptor genes is defective or mutated and impairs the LDL-C receptor activity. Mixed dyslipidaemia is defined as elevations in LDL-C and triglyceride concentrations that are often accompanied by low concentrations of high-density lipoprotein cholesterol.
- 2.2 People with hypercholesterolaemia are at increased risk of cardiovascular disease (CVD) because long-term elevations of cholesterol accelerate the build-up of fatty deposits in the arteries (atherosclerosis). Primary non-familial hypercholesterolaemia affects about 4% of the adult population, totalling approximately 1.5 million people in England, of whom an estimated 600,000 are diagnosed and 460,000 are receiving treatment. Primary heterozygous-familial hypercholesterolaemia affects an estimated 1 in 500 people, totalling 106,000 in England (although only 15–17% are diagnosed).
- 2.3 Managing primary hypercholesterolaemia involves dietary and lifestyle changes (such as smoking cessation, weight loss and increased physical activity) and treatment with a lipid-regulating drug, if appropriate (see Figure 1). Starting drug treatment is generally based on an assessment of the person's cardiovascular risk.

Figure 1 Treatment pathway



Source: company's submission; figure 3-2 (page 49)

- 2.4 Statins are usually the first-choice drugs. The NICE guideline on [lipid modification](#) (CG181) recommends that when a decision is made to prescribe a statin, a statin of high intensity and low acquisition cost should be used. It recommends atorvastatin 20 mg for the primary prevention of CVD in people who have a 10% or greater 10-year risk of developing CVD, as estimated using the QRESEARCH Cardiovascular Risk Algorithm (QRISK2) assessment tool.
- 2.5 [NICE technology appraisal 132](#) recommends ezetimibe as an option for treating primary (heterozygous familial or non-familial) hypercholesterolaemia, as a monotherapy when statins are contraindicated or not tolerated and in combination with statins when initial statin therapy does not provide appropriate control of LDL-cholesterol. A technology appraisal review of this guidance is underway to allow new data to be taken into account.

Table 2 Technologies

	Evolocumab	Ezetimibe	Statins (atorvastatin)
Marketing authorisation	Evolocumab 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.	Ezetimibe co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone. Ezetimibe monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.	<u>Hypercholesterolaemia</u> Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate. Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable. <u>Prevention of cardiovascular disease</u> Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event (see section 5.1), as an adjunct to correction of other risk factors.

			Details of the marketing authorisations for other statins can be found here .
Administration method	Subcutaneous	Oral	Oral
Cost information	Without the PAS, a 140-mg prefilled pen or syringe costs £170.10. With the PAS, a 140-mg prefilled pen or syringe costs [REDACTED]. <u>Dosing frequency</u>: 1 injection (140 mg) every 2 weeks, or 3 injections (420 mg) monthly. <u>Cost per patient per year (without PAS)</u>: £4,448.60 for 140 mg every 2 weeks, and £6,123.60 for 420 mg (3 injections) monthly.	A 28-tab pack of ezetimibe 10 mg costs £26.31 (BNF, 2015). <u>Dosing frequency</u>: 1 tablet (10 mg) daily. <u>Cost per patient per year</u>: £343.20.	A 28-tab pack of atorvastatin costs £1.18 for 10-mg tablets, £1.59 for 40 mg tablets, and £2.71 for 80-mg tablets (BNF, 2015). See the BNF for prices of the other statins. <u>Dosing frequency</u>: 1 tablet (10 mg, 40 mg, or 80 mg) daily. <u>Cost per patient per year</u>: £15.40 for 10 mg daily, £20.70 for 40 mg daily, and £35.40 for 80 mg daily.

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

- 3.1 Patient experts stated that patients want to reduce their cholesterol concentrations to avoid early heart problems and premature death. They noted that evolocumab was a non-statin belonging to a new class of drugs, which can reduce cholesterol concentrations by 60% on top of current standard of care. This is vital for patients who cannot tolerate statins and risk developing cardiac problems if they do not have LDL apheresis. The patient experts stated that for some patients, statins plus other lipid-lowering medications do not reduce cholesterol concentrations sufficiently, and add-on therapy such as evolocumab becomes necessary.
- 3.2 The clinical experts stated that, in line with NICE guidance, the mainstay of treatment for primary hypercholesterolemia and mixed dyslipidaemia is with statins if tolerated. They pointed out that recent national and international guidelines recommend treatment based on the risk of CVD rather than LDL-C concentration targets. The clinical experts considered that evolocumab would be predominantly used in patients who cannot tolerate, or whose disease did not adequately respond to, high-intensity statin therapy, for whom ezetimibe is presently the standard of care.
- 3.3 The clinical experts considered that patients included in the clinical trials for evolocumab represented UK patients with primary hypercholesterolaemia, and that how the condition was managed in the trials and UK clinical practice was likely to be coincident. The clinical experts noted that large studies measuring 'real-world' outcomes were unlikely to be conducted, and that long-term studies in patients who cannot tolerate statins were not available. The clinical experts advised that with evolocumab, neutralising antibodies can develop and treatment may lose its effectiveness. Because of this, patients are likely to need more follow-up appointments than those treated with statins and ezetimibe (every 3–6 months rather than annually).

- 3.4 The clinical experts highlighted subgroups which may need special consideration because of the high LDL-C concentration. These include patients with HeFH, particularly those with severe HeFH (such as patients with an LDL-C concentration higher than 8.0 mmol/L, or those who have HeFH caused by mutations in the PCSK9 gene), and patients who cannot tolerate statins. The experts stated that patients are normally considered to be statin-intolerant when they cannot tolerate 3 statins after varying the dosage of the drug, although this definition was not clear-cut. The clinical experts also advised that patients who have established CVD are at the highest risk of further CVD, and need to be considered separately.

4 Clinical-effectiveness evidence

Overview of the clinical trials

- 4.1 The company carried out a systematic literature review, and identified 4 randomised controlled trials (RCTs) of evolocumab for primary hypercholesterolemia and mixed dyslipidaemia; LAPLACE-2, RUTHERFORD-2, GAUSS-2, and DESCARTES. Of these, LAPLACE-2 and GAUSS-2 provided head-to-head evidence for evolocumab compared with ezetimibe, whereas RUTHERFORD-2 and DESCARTES compared evolocumab with placebo only. GAUSS-2 and RUTHERFORD-2 studied evolocumab exclusively in subgroups specified in the scope; patients who cannot tolerate statins, and those with HeFH respectively. DESCARTES was a long-term study (52 weeks) of evolocumab.
- 4.2 All the trials were phase III, double-blind RCTs, including a total of 3500 patients. They all used a 2:1 randomisation to the evolocumab or control treatment arm. The methodology of the RCTs is summarised below and in Table 3:
- **LAPLACE-2:** evaluated evolocumab, compared with placebo or ezetimibe, in combination with moderate- to high-intensity statin therapy for primary hypercholesterolaemia and mixed dyslipidaemia. The minimum LDL-C concentration required at baseline differed

depending on whether the patient was taking an intensive statin, a non-intensive statin, or no statin. In general, patients had to have an LDL-C concentration of 2.1 mmol/L or more. Eligible patients were randomised to one of 5 open-label statin cohorts; atorvastatin 10 mg or 80 mg, rosuvastatin 5 mg or 40 mg, or simvastatin 40 mg. Patients in the atorvastatin cohorts were then randomised to one of 6 treatment arms, and those in the rosuvastatin or simvastatin cohort were randomised to one of 4 treatment arms (see Table 3 for further details). All patients continued background statin therapy during the trial.

- **RUTHERFORD-2:** compared evolocumab with placebo for HeFH (as per the Simon Broome criteria) in patients whose LDL-C concentrations remained higher than 2.6 mmol/L despite receiving a statin with or without other lipid-regulating drugs. Patients were randomised to one of 4 treatment arms (see Table 3 for further details), and continued background lipid-lowering therapy.
- **GAUSS-2:** compared evolocumab with ezetimibe in patients with primary hypercholesterolaemia and mixed dyslipidaemia who could not tolerate an effective dose of statin. These were defined as patients who had tried at least 2 statins, but could not tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects. The trial included patients who had an LDL-C concentration above their National Cholesterol Education Program (NCEP) Adult Treatment Panel III goal (minimum 2.6 mmol/L). Patients were randomised to one of 4 treatment arms (see Table 3 for further details).
- **DESCARTES:** compared the long-term effect evolocumab with that of placebo, when added to background lipid-lowering therapy, for primary hypercholesterolaemia and mixed dyslipidaemia. Patients with LDL-C concentrations of 1.9 mmol/L or more were stratified according to the risk categories outlined by the Adult Treatment Panel III of the NCEP. Based on this classification, patients received background lipid-lowering therapy with diet alone or in combination with atorvastatin, ezetimibe, or both, for 4–12 weeks. Patients whose LDL-C

concentration was 2.0 mmol/L or more were then randomised to evolocumab 420 mg or placebo monthly.

Table 3 Trial methodologies

	LAPLACE-2	RUTHERFORD-2	GAUSS-2	DESCARTES
n	1896	329	307	901
Location	Multicentre (international; includes UK sites)	Multicentre (international; includes UK sites)	Multicentre (international; includes UK sites)	Multicentre (international; no UK sites)
Duration	12 weeks	12 weeks	12 weeks	52 weeks
Therapeutic setting	Statin combination (familial and non-familial)	HeFH (familial)	Statin-intolerant (familial and non-familial)	Range of CV risk (familial and non-familial)
Fasting LDL-C	≥2.1 mmol/L	≥2.6 mmol/L	≥2.6 mmol/L	≥1.9 mmol/L
Intervention arms	Within the atorvastatin cohort: • Evolocumab 140 mg Q2W + placebo od • Evolocumab 420 mg QM + placebo od Within the rosuvastatin or simvastatin cohort: • Evolocumab 140 mg Q2W • Evolocumab 420 mg QM	• Evolocumab 140 mg Q2W • Evolocumab 420 mg QM	• Evolocumab 140 mg Q2W + placebo od • Evolocumab 420 mg QM + placebo od	• Evolocumab 420 mg QM
Control arms (respective to the intervention arm)	Within the atorvastatin cohort: • Placebo Q2W + ezetimibe od • Placebo Q2W + placebo od • Placebo QM + ezetimibe od • Placebo QM + placebo od Within the rosuvastatin or simvastatin cohort: • Placebo Q2W	• Placebo Q2W • Placebo QM	• Placebo Q2W + ezetimibe • Placebo QM + ezetimibe	• Placebo QM

	• Placebo QM			
Background therapy	Moderate- to high-intensity statin therapy	Statin ($\pm$ other lipid-lowering therapy)	Non-ezetimibe lipid lowering therapy	Diet $\pm$ atorvastatin $\pm$ ezetimibe
od, once daily; Q2W, every 2 weeks; QM, every month				

Source: company's submission, table 4-3 (page 72) and 4-4 (page 75)

- 4.3 The co-primary end points in LAPLACE-2, RUTHERFORD-2 and GAUSS-2 were the percent change from baseline in LDL-C level at week 12, and the mean percent change from baseline in LDL-C level at weeks 10 and 12 (the latter end point was used because the averaging of weeks 10 and 12 better reflects average LDL-C reduction with monthly dosing). In DESCARTES, the primary end point was the percent change from baseline in LDL-C level at week 52. Other plasma lipid and lipoprotein levels, including non-HDL-C, apolipoprotein B and lipoprotein, were measured as secondary end points. None of the trials collected data on health-related quality of life.

ERG comments

- 4.4 The ERG stated that the systematic review of RCT evidence was generally robust. It considered the trials identified for evolocumab to be relevant, good-quality RCTs, which the company described in detail in its submission. The ERG generally considered the RCTs for evolocumab to be consistent with the scope. However, it did not consider that DESCARTES was totally consistent with the decision problem partly because evolocumab was not compared with ezetimibe, but also because patients were neither statin-intolerant nor on a maximum tolerated dose of a statin (evolocumab is indicated in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or in those who are statin-intolerant or for whom a statin is contraindicated).
- 4.5 The ERG indicated that patient characteristics were generally well-balanced across treatment arms in all trials. However, all 4 trials excluded patients with type 1 diabetes, or newly diagnosed or poorly controlled type 2 diabetes, a group which the ERG considered highly likely to have

co-morbid hypercholesterolaemia and mixed dyslipidaemia. In addition, the ERG noted that the HeFH population in RUTHERFORD-2 with a confirmed genetic mutation was higher than in UK clinical practice. It also noted that more patients who received evolocumab in RUTHERFORD-2 had chronic heart disease (30–36%) than those who would present with HeFH in clinical practice, or those who were included in the other trials.

- 4.6 The ERG noted that none of the trials provided evidence for evolocumab compared with ezetimibe in patients with HeFH, or evolocumab in combination with ezetimibe in any population. It also noted that only 12-week evidence was available for the dose received every 2 weeks, whereas the monthly dose had some data for 52 weeks.
- 4.7 The ERG pointed out that the reduction in LDL-C concentration is not in itself clinically important, but its importance stems from it being a surrogate for CVD. Although the relationship between LDL-C reduction from statins and reduced CV events is established, the effect of evolocumab on CVD has not been demonstrated. The ERG noted that the ongoing FOURIER RCT was important because it will test the assumption that LDL-C is a viable surrogate for CV outcomes for evolocumab (albeit only in patients who already had a CV event), which the ERG considered to be a key area of uncertainty in the current evidence base.

Clinical trial results

- 4.8 All efficacy and safety analyses were based on the modified intention-to-treat populations; that is, all patients who received at least 1 dose of study treatment. Table 4 and Table 5 present the difference in efficacy between evolocumab, and placebo or ezetimibe for the primary end points. For the efficacy in each treatment arm, see table 4-11 and tables 4-13 to 4-17 from page 107 onward in the company's submission.

Table 4 Results for primary or co-primary end points in LAPLACE-2

Study	Baseline LDL-C (mmol/L)	Evolocumab dose	Background therapy	Difference in percent change from baseline in LDL-C level at week 12 (%; 95% CI)		Difference in mean percent change from baseline in LDL-C level at weeks 10 and 12 (%; 95% CI)	
				Versus placebo	Versus ezetimibe	Versus placebo	Versus ezetimibe
LAPLACE-2 (n=1899) Statin combination (familial and non-familial)	2.8	140 mg Q2W	Atorvastatin 10 mg	-74* (-81 to -68)	-44* (-50 to -37)	-73* (-78 to -67)	-41* (-47 to -35)
			Atorvastatin 80 mg	-80* (-91 to -68)	-50* (-61 to -39)	-78* (-88 to -68)	-48* (-58 to -38)
			Any atorvastatin ¹	–	-47* (-53 to -41)	–	-45* (-50 to -39)
			Rosuvastatin 5 mg	-71* (-78 to -64)	–	-70* (-76 to -63)	–
			Rosuvastatin 40 mg	-71* (-80 to -63)	–	-69* (-77 to -62)	–
			Simvastatin 40 mg	-74* (-80 to -67)	–	-73* (-78 to -67)	–
			Any statin ¹	-74* (-77 to -70)	–	-72* (-75 to -69)	–

Study	Baseline LDL-C (mmol/L)	Evolocumab dose	Background therapy	Difference in percent change from baseline in LDL-C level at week 12 (%; 95% CI)		Difference in mean percent change from baseline in LDL-C level at weeks 10 and 12 (%; 95% CI)	
				Versus placebo	Versus ezetimibe	Versus placebo	Versus ezetimibe
LAPLACE-2 (cont.)	2.8	420 mg QM	Atorvastatin 10 mg	−61* (−68 to −54)	−43* (−50 to −36)	−65* (−71 to −58)	−45* (−52 to −39)
			Atorvastatin 80 mg	−74* (−84 to −65)	−41* (−51 to −32)	−78* (−86 to −70)	−46* (−54 to −38)
			Any atorvastatin ¹	—	−43* (−48 to −37)	—	−46* (−51 to −41)
			Rosuvastatin 5 mg	−66* (−73 to −59)	—	−69* (−75 to −62)	—
			Rosuvastatin 40 mg	−59* (−70 to −48)	—	−67* (−76 to −58)	—
			Simvastatin 40 mg	−62* (−71 to −52)	—	−70* (−79 to −61)	—
			Any statin ¹	−65* (−69 to −61)	—	−70* (−73 to −66)	—
*p<0.001							
¹ Using a fixed-effects model (that is, assuming that the trial estimates exactly the same treatment effect and that the variability between individual study arms occurs by chance)							
CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly							

Table 5 Results for primary or co-primary end points in GAUSS-2, RUTHERFORD-2, and DESCARTES

Study	Baseline LDL-C (mmol/L)	Evolocumab dose	Background therapy	Difference in percent change from baseline in LDL-C level at week 12 ¹ (% , 95% CI)		Difference in mean percent change from baseline in LDL-C level at weeks 10 and 12 (% , 95% CI)	
				Versus placebo	Versus ezetimibe	Versus placebo	Versus ezetimibe
GAUSS-2 (n=307)	5.0	140 mg Q2W	Non-ezetimibe lipid lowering therapy	–	–39* (–45 to –34)	–	–38* (–44 to –33)
Statin-intolerant (familial and non-familial)		420 mg QM		–	–38* (–43 to –33)	–	–39* (–44 to –35)
RUTHERFORD-2 (n=331)	4.0	140 mg Q2W	Statin (± other lipid-lowering therapy)	–61* (–67 to –55)	–	–61* (–67 to –55)	–
HeFH (familial)		420 mg QM		–60* (–68 to –53)	–	–66* (–72 to –61)	–
DESCARTES (n=901)	2.7	420 mg QM	Diet ± atorvastatin ± ezetimibe	–59* (–64 to –55)	–	–	–
Range of CV risk (familial and non-familial)							
*p<0.001							
¹ week 52 in DESCARTES							
CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly							

Subgroups

- 4.9 The company presented subgroup analyses that were pre-specified in the study protocols for the relevant trials for evolocumab. These were based on the factors on which patients were stratified when they were randomised, and other variables at baseline. For an overview of the pre-specified subgroup analyses presented, see table 4-18 on page 122 of the company's submission.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The company also performed post hoc subgroup analyses (that is, after the trial results had been compiled). Specifically, it explored whether the effect of evolocumab depended on the presence of CVD when a broad definition of CVD was used, or the severity of hypercholesterolaemia.

- 4.10 The company presented results from the subgroup analyses only for the primary or co-primary end points in the relevant RCTs (see section 4.3). It stated that in all subgroup analyses, evolocumab was consistently effective, compared with placebo or ezetimibe, in lowering LDL-C, including in subgroups by the presence or risk of CVD and the severity of hypercholesterolaemia, with no notable differences between subgroups. For detailed results of each subgroup analysis, including forest plots, see Appendix VI to the company's submission.

ERG comments

- 4.11 The ERG noted that evolocumab effectively reduced LDL-C concentration from baseline compared with ezetimibe or placebo ($p < 0.001$), with consistent results observed for the other lipid parameters. The ERG noted that evolocumab, at both licensed doses, and in patients who can or

cannot tolerate statins, was consistently effective compared with placebo and ezetimibe across all subgroup analyses.

4.12 The ERG noted that, although none of the RCTs explicitly studied evolocumab in combination with ezetimibe, RUTHERFORD-2 and DESCARTES included a subgroup that received ezetimibe as background therapy (with [DESCARTES] or without [RUTHERFORD-2] high-dose atorvastatin). The ERG reported the following results in these subgroups:

- **DESCARTES.** The difference in percent change from baseline in LDL-C level at week 52 between evolocumab (monthly) plus ezetimibe plus statins and placebo plus ezetimibe plus statins was -49.3% (95% confidence interval [CI] -59.5% to -39.1% , $p < 0.001$) in favour of evolocumab.
- **RUTHERFORD-2.** At week 12, the percent change from baseline in LDL-C level favoured evolocumab every 2 weeks plus ezetimibe compared with placebo plus ezetimibe, with a difference of -58.4% (95% CI -67.1% to -49.7% , $p < 0.001$). Evolocumab monthly plus ezetimibe was also more efficacious than placebo plus ezetimibe, with a difference of -60.9% (95% CI -71.0% to -50.8% , $p < 0.001$).

Long-term and non-RCT evidence

4.13 The company reported interim results from 2 ongoing, long-term, extension studies, OSLER (n=1324) and OSLER-2 (n=2928), which compared evolocumab plus standard of care (defined as per local guidelines) with standard of care alone. Eligible patients were those who completed treatment in a 'parent' study, including the relevant RCTs identified for evolocumab. Because of this, the company considered the populations in OSLER and OSLER-2 to be mixed, and did not include the studies in its review of clinical evidence. Evolocumab led to a statistically significant reduction in LDL-C from baseline at weeks 12 and 52 in OSLER and at week 12 in OSLER-2 compared with standard of care ($p < 0.001$ in both studies). The company stated that the effect of evolocumab was shown to be maintained for over 2 years.

- 4.14 TAUSSIG was an ongoing non-randomised, non-controlled, 5-year extension study of evolocumab for severe familial hypercholesterolaemia, including homozygous familial hypercholesterolaemia (which is not included in the scope). The company presented interim results including 142 patients with severe HeFH. At week 36, the percent reduction from baseline in LDL-C level was 50.5%, with reductions ranging from 42.0% to 54.3% at earlier time points.

ERG comments

- 4.15 The ERG stated that the evidence from OSLER and OSLER-2 was arguably not relevant to this appraisal. This was because the studies included populations from trials that were themselves excluded from the systematic review of clinical evidence.

Meta-analyses/indirect comparison/MTC

- 4.16 The company considered whether a network meta-analysis was feasible for patients with HeFH because no head-to-head evidence comparing evolocumab with ezetimibe existed for this population (the only RCT for HeFH, RUTHERFORD-2, compared evolocumab with placebo). It identified 2 potentially useful RCTs that it could use in this analysis; RUTHERFORD-2 and another RCT which compared ezetimibe with simvastatin for HeFH (ENHANCE). However, the company stated that the concentrations of LDL-C at baseline differed between the 2 RCTs, and so changes in this concentration were not comparable. Because of this, the company considered that a network meta-analysis for HeFH was neither appropriate nor feasible.

ERG comments

- 4.17 The ERG agreed that a network meta-analysis for patients with HeFH would not be appropriate. However, it considered that it would have been useful to have a network meta-analysis combining evidence for patients with primary non-familial hypercholesterolaemia (LAPLACE-2 and DESCARTES) with that for patients with HeFH (RUTHERFORD-2) to

strengthen the estimate of treatment effect with the evidence from the HeFH population.

Adverse effects of treatment

4.18 The company provided data on adverse effects from all the studies presented in its submission, including the long-term and non-RCT studies (see table 4-23 on page 136 of the company's submission for further details). In addition, it presented integrated analyses of safety data from 6026 patients with primary hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidaemia who received any dose of evolocumab. The key results of these analyses are summarised below:

- Overall, evolocumab had a safety profile similar to that observed in the control treatment (placebo or ezetimibe) arms (51.1% compared with 49.6%), with most adverse events being mildly to moderately severe.
- Serious adverse events occurred in 2.8% and 2.1% of patients who received evolocumab or any control treatment (placebo or ezetimibe) respectively.
- Of patients who received evolocumab, 1.9% stopped treatment because of an adverse event compared with 2.3% of those who received placebo or ezetimibe.
- The most common adverse events for evolocumab compared with placebo or ezetimibe were: nasopharyngitis (5.9% compared with 4.8%), upper respiratory tract infection (3.2% compared with 2.7%), headache (3.0% compared with 3.2%) and back pain (3.0% compared with 2.7%).
- The safety profile of evolocumab did not vary with the different recommended dosages (140 mg every 2 weeks, or 420 mg monthly).
- The overall frequency of adverse events associated with evolocumab was 51.1% across the parent studies, 65.4% across year 1 of the extension studies (controlled period), and [REDACTED] from year 2 onward across the extension studies (open-label extension period).

ERG comments

- 4.19 The ERG stated that evolocumab appeared to have an acceptable safety profile.

5 Cost-effectiveness evidence**Please note the following:**

- At clarification stage, the ERG identified an issue whereby it was possible for some transition probabilities to be negative in the model.
- NICE provided the company with the opportunity to consider this issue given its potential implications on the validity of the model as a whole.
- The company acknowledged that negative transition probabilities could occur in the model. In an attempt to resolve this issue, it submitted an addendum and a revised model – this is ‘addendum 1’ within the Committee papers.
- The ERG did not feel that this issue had been fully resolved by the company, and also noted in its report other issues relating to model implementation and misspecification of evidence inputs.
- The company requested to submit ‘addendum 2’ to resolve the key issues raised by the ERG and re-run all the analyses. By that point, the PAS had been approved, so the company also made a PAS submission which reflected ‘addendum 2’ and the PAS discount.
- The ERG provided a review of addendum 2 and the PAS submission.

All results presented here are based on the PAS submission to reflect the latest set of amendments made by the company (that is, addendum 2) and the PAS discount. The ERG critique of addendum 2 has been taken into account; however, the ERG’s exploratory analyses are not presented here.

- 5.1 The company submitted a de novo Markov economic model to assess the cost effectiveness of evolocumab in reducing CVD for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. The perspective of the analysis was that of the NHS and personal social services. Costs and health effects were modelled over a

lifetime time horizon, and discounted at an annual rate of 3.5%. The cycle length in the model was 1 year.

Population, intervention and comparators

5.2 The company modelled 3 separate subpopulations:

- patients with primary non-familial hypercholesterolaemia **without** existing CVD
- patients with primary non-familial hypercholesterolaemia **with** existing CVD
- patients with HeFH (with or without existing CVD).

The company modelled the 2 populations with non-familial hypercholesterolaemia based on the characteristics of the respective population in LAPLACE-2 with or without a history of CVD. However, it used data only from the subset of patients who had an LDL-C concentration over 2.5 mmol/L to represent a population at high risk of CVD. For patients with HeFH, the company used the modified intention-to-treat population in RUTHERFORD-2. For the characteristics at baseline of the modelled populations, see table 5-5 on page 183 of the company's submission.

5.3 The intervention modelled in the base case was evolocumab 140 mg every 2 weeks; the company explored using the monthly dose of evolocumab in scenario analyses (see sections 5.36 and 5.37). For each population modelled, the company presented separate results for 4 treatment comparisons; 2 relevant to patients who can tolerate statins, and 2 relevant to those who cannot:

- For patients who can tolerate statins:
 - evolocumab plus atorvastatin compared with ezetimibe plus atorvastatin
 - evolocumab plus ezetimibe plus atorvastatin compared with ezetimibe plus atorvastatin.

- For who cannot tolerate statins:
 - evolocumab compared with ezetimibe
 - evolocumab plus ezetimibe compared with ezetimibe.

Patients who could tolerate statins received atorvastatin as background therapy; those who could not did not receive any background lipid-lowering therapy. The company represented statins with atorvastatin because this is the statin recommended in NICE clinical guideline 181 for patients with or without existing CVD.

ERG comments

- 5.4 The ERG's clinical advisers suggested that the company's model was likely to have excluded most patients with primary non-familial hypercholesterolaemia. This was because the company modelled only patients with an LDL-C concentration over 2.5 mmol/L, whereas most UK patients can have an LDL-C concentration of 2.0 mmol/L on statins. Furthermore, the ERG stated that it was unclear whether this population fully reflected the marketing authorisation for evolocumab (that is, patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or those who are statin-intolerant or for whom a statin is contraindicated).
- 5.5 The ERG noted that the company assumed that patients who can tolerate statins have the same characteristics as those who cannot. However, the risk of CVD was likely to be related to whether or not LDL-C concentration can be controlled on statins. The ERG advised that GAUSS-2 would have better represented patients with primary non-familial hypercholesterolaemia who cannot tolerate statins than LAPLACE-2. The ERG considered that the company's analyses reflected the overall populations in LAPLACE-2 and RUTHERFORD-2, which included both patients who can and cannot tolerate statins, rather than either of these individual groups.
- 5.6 HeFH population only. The modelled HeFH population included patients with, and those without, existing CVD. The ERG advised that it may be

appropriate to model these groups separately because the clinical and cost effectiveness of treatment may differ in them.

Model structure

5.7 The company's model consisted of 24 mutually exclusive states:

- 3 'acute' states (in which the patient could stay for a maximum of 1 year unless the same event occurred in the next cycle)
 - acute coronary syndrome (including myocardial infarction and unstable angina)
 - ischemic stroke
 - heart failure
- 5 'chronic' states
 - no CVD
 - established CVD (including patients who had a history of any of the following: stable angina, transient ischaemic attack, carotid stenosis, revascularisation without history of myocardial infarction, abdominal aortic aneurism, or peripheral vascular disease)
 - 3 'post-event' states
 - ◇ post acute coronary syndrome
 - ◇ post ischaemic stroke
 - ◇ post heart failure
- 13 composite CVD states (formed of a combination of 2 or 3 'acute' and 'post-event' states; these were used to remember the history of CV events and model the corresponding outcomes of recurring CV events)
- 3 death states: death from CHD, death from stroke and death from other causes.

Therefore, patients who had CVD could have either one of the events modelled separately (acute coronary syndrome, ischemic stroke, or heart failure), or one of the events in the 'established CVD' state. This was because the events in the 'established CVD' state were less severe than those modelled separately, and so would be associated with lower costs

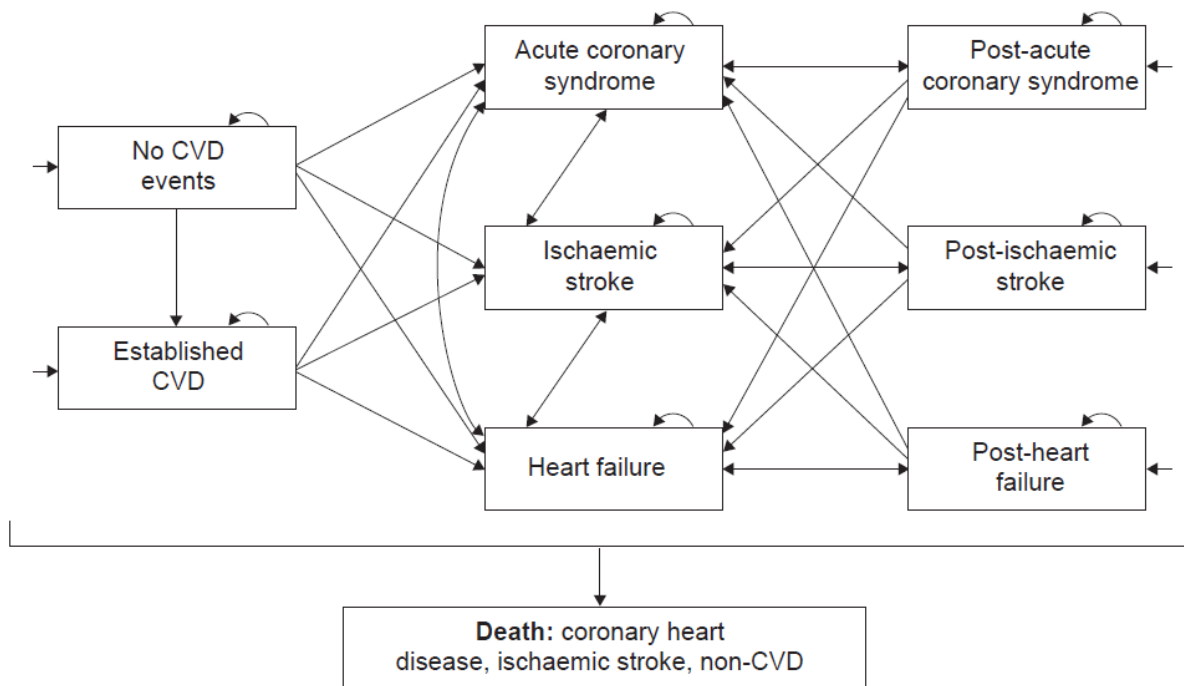
and better health outcomes. The company assumed that patients who started treatment in the model received it continuously over their lifetime.

5.8 Patients entered the model in different states depending on which population they belonged to:

- All patients without existing CVD entered the model in the 'no CVD' state.
- Patients with existing CVD entered the model in one of the 3 post-event states, or the 'established CVD' state.
- Patients with HeFH (with or without existing CVD) entered the model in one of the 3 post-CVD event states, the 'established CVD' state, or the 'no CVD' state.

Patients who entered the model in the 'no CVD' state remained in this state until they had CVD (that is, acute coronary syndrome, ischemic stroke, heart failure, or one of the events in the 'established CVD' state), or died. After the first CV event, patients could have no further CV events and move to the corresponding post-event state, have the same event again and remain in the same acute event state, have a different acute event and move to a composite state representing the post-event state for previous events and the new event, or die. Patients in a post-event state could have the same acute event and move to the corresponding acute state or composite state (if the patient had had other CV events), a different acute event (and move to the relevant composite state), or die. Patients who had a CV event could not return to a less severe state (so patients who had acute coronary syndrome, ischemic stroke, or heart failure could not move to the 'established CVD' state). A simplified diagrammatic representation of the model is provided in the company's submission, and reproduced in Figure 2.

Figure 2 Model structure



Source: Figure 5-2 (page 175) of the company's original submission

ERG comments

5.9 The ERG noted that the states in the model differed from those used in NICE clinical guideline 181 or other published models for primary hypercholesterolaemia and mixed dyslipidaemia. It considered that the company did not describe how it selected the states in the model, nor did it explain why they were more relevant than those used in previous models. The ERG was particularly concerned about the following states in the model:

- **Heart failure:** the ERG noted that limited data existed on the effect of lipid-lowering therapies on the risk of having heart failure, or on death from coronary heart disease once patients had heart failure.
- **Ischemic stroke:** the ERG stated that the company did not justify why it included ischemic stroke only, noting that existing data suggested that reducing LDL-C concentration reduced the risk of ischemic stroke

more than it reduced the risk of any stroke (relative risks of 0.69 and 0.74 respectively).

- **Composite states:** the ERG stated that no data existed to inform the various composite states in the model. Because of this, the company had to make a number of arbitrary assumptions about the risk CV events in these states, which increased the uncertainty in the model.

Estimation of CVD risks

5.10 To estimate the risk of CVD in the model, the company used a 3-step approach. Firstly, it predicted the risk of CVD before treatment in patients in LAPLACE-2 with an LDL-C concentration at baseline over 2.5 mmol/L (non-familial hypercholesterolaemia), and the modified intention-to-treat population in RUTHERFORD-2 (HeFH). To do so, the company used published risk equations from the Framingham Heart Study for patients without existing CVD, and the REduction of Atherothrombosis for Continued Health (REACH) registry for patients with existing CVD. Secondly, the company estimated calibration (adjustment) factors from an analysis of data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES). Thirdly, it adjusted the risks of CVD predicted using the Framingham Heart Study and REACH registry equations using these calibration factors to reflect real-world data (CPRD and HES data). Because no CV risk equation existed specifically for HeFH, the company adjusted the predicted risks of CVD using a relative risk of 7.1 for the HeFH population (relative to patients without HeFH) obtained from a study by Benn et al. This relative risk was not event-specific, so it increased the baseline risk of all CV events in the HeFH population by a factor of 7.1.

ERG comments

5.11 The ERG considered how the company estimated the risk of CVD in the model to be circular, unnecessarily complicated and counter-intuitive. This was because the company had to make a number of assumptions and adjustments to estimate and apply the calibration factors. The ERG

considered that, whereas the company used published equations to predict risks then adjusted these to reflect real-world data, it could have estimated the risks directly from the real-world data (CPRD and HES analysis) without using risk equations, which in the ERG's opinion did not provide additional information compared with the CPRD and HES data.

- 5.12 The ERG stated that the company did not sufficiently justify why it selected the US-based Framingham Heart Study risk equation, and not alternative equations such as the QRISK2, which was used in the model for NICE clinical guideline 181.
- 5.13 The ERG noted that the company added a number of constraints to prevent the model from generating negative transition probabilities. It considered that some of these constraints appeared arbitrary and the logic underpinning them was difficult to follow from the information provided by the company.
- 5.14 HeFH population only. The ERG noted that the company predicted the risks of CVD in the HeFH population using the Framingham Heart Study equations based on the entire RUTHERFORD-2 population (which included patients with or without existing CVD). It did not consider this to be appropriate because these equations were formulated only for patients without a history of CVD. Furthermore, the company used the study by Benn et al. to adjust the risk of CVD at baseline in patients with HeFH. The ERG noted that this study compared the risk of CV events between the general population and patients with HeFH. However, in the model, the relative risk was not applied to the general population, but to the trial population which was already at high risk of CVD. This was likely to overestimate the risk of CVD, and underestimate the ICERs for evolocumab. The ERG pointed out that a UK study by Neil et al. may be more appropriate to adjust the risk of CVD at baseline in patients with HeFH.

Treatment effect

- 5.15 The objective of the model was to capture the lifetime progression of CVD among adults with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. Because none of the clinical trials for evolocumab provided data on the direct effect of evolocumab on CVD, the company used estimates from the CTTC meta-analysis to translate the surrogate outcomes measured in the trials (LDL-C concentration) to 'real-world' outcomes (CV events).
- 5.16 The company obtained the estimates of treatment effect directly from the head-to-head RCTs comparing evolocumab with ezetimibe. For patients with non-familial hypercholesterolaemia, it used LAPLACE-2 for the treatment comparisons relevant to patients who can tolerate statins, and GAUSS-2 for the comparisons relevant to those who cannot (see section 5.3). To source the clinical effectiveness in patients with HeFH who can tolerate statins, the company used RUTHERFORD-2 for evolocumab and LAPLACE-2 for ezetimibe because RUTHERFORD-2 compared evolocumab with placebo only. For patients with HeFH who cannot tolerate statins, the company used GAUSS-2. For the comparisons in which evolocumab was combined with ezetimibe, the company added the effect of evolocumab alone to the effect of ezetimibe alone because none of the clinical trials provided data for this combination. The company assumed that the treatment effect in the model was maintained throughout the time horizon.

ERG comments

- 5.17 The ERG stated that the company did not justify why it used LDL-C concentration, as opposed to other lipid markers, as a surrogate for CVD. In response to a request for clarification, the company indicated that existing evidence support using LDL-C concentration as a surrogate for CV outcomes, whereas the relationship between other lipid markers and CVD was less well established. The ERG took the view that, without

robust data on the effect of evolocumab on CV outcomes, relying on a surrogate end point could be uncertain.

5.18 The company made the following assumptions about the treatment effects assumed in the model, which the ERG considered uncertain:

- For patients with primary non-familial hypercholesterolaemia who can tolerate statins, the treatment effect from LAPLACE-2 could be generalised to the subset of patients with an LDL-C concentration over 2.5 mmol/L.
- The treatment effects from LAPLACE-2 and GAUSS-2 would be the same in all patients whether or not they have diabetes or other risk factors for CVD.
- For the comparisons in which evolocumab was combined with ezetimibe, the effect of evolocumab alone could be added to the effect of ezetimibe alone.
- The treatment effect would be maintained indefinitely in the model.

5.19 To estimate the relationship between changes in LDL-C concentration and CV events, the company made the following assumptions about the relationships observed in the CTTC meta-analysis, which the ERG considered arbitrary, implausible or uncertain:

- The relationship between LDL-C concentration and CVD was the same for patients with, and those without, a history of CVD.
- The effect of reducing LDL-C concentration on non-fatal myocardial infarction was the same as that on heart failure (first event).
Furthermore, the ERG noted that the company assumed that reducing LDL-C concentration in patients with heart failure (either acute, post-event state or combined state) would reduce death from coronary heart disease despite acknowledging the lack of benefit for lipid-lowering therapies once patients had heart failure.

- The relationship between LDL-C concentration and non-fatal myocardial infarction (secondary prevention) would apply to patients moving from the 'no CVD' state to the 'established CVD' state.
- Reducing LDL-C concentration had no effect on death from stroke.
- The reduction in fatal CV events per mmol/L reduction in LDL-C concentration would apply whether or not the patient had had previous events.

Health-related quality of life and costs

5.20 The company identified 171 studies on health-related quality from a systematic literature review. It also provided details of a company-sponsored study that used the time trade-off method to estimate utility values for patients with CVD. However, neither of these sources was used to populate the base-case model with utility data. Instead, the company used the utility values informing the model developed for NICE clinical guideline 181. It stated that these data were derived from various published sources in which the estimates were mainly patient-reported using the EQ-5D questionnaire, and collected in the UK. However, the company adjusted the utility values from NICE clinical guideline 181 to match the states in the model as follows:

- **Acute coronary syndrome:** in the model, the acute coronary syndrome state included myocardial infarction and unstable angina. The original utility values for the acute events of these 2 diseases were 0.760 and 0.770 respectively. The company chose the higher utility value (0.770) for the acute coronary syndrome state. It did not need to adjust the post acute coronary syndrome state because the original utility values for post myocardial infarction and post unstable angina were both 0.880.
- **Established CVD:** this state in the model comprised of various CV events, including stable angina. The original utility value for stable angina was 0.808 (for both acute and post event), which was lower than the value for post myocardial infarction (0.880) and post unstable

angina (0.880). The company stated that this would not be expected because these events are more severe than stable angina. Because of this, it considered the utility value for the post-acute coronary syndrome state (0.880) to be a more valid estimate for the 'established CVD' state.

Table 6 shows the utility values applied in the base-case analysis.

Table 6 Base-case utility values

State	Mean utility value (SE)	95% CI (lower bound)	95% CI (upper bound)
No CVD	1.0000	–	–
Established CVD	0.8800 (0.018)	0.8447	0.9153
First year			
Acute coronary syndrome ¹	0.7700 (0.018)	0.7347	0.8053
Ischaemic stroke	0.6280 (0.040)	0.5496	0.7064
Heart failure	0.6830 (0.020)	0.6438	0.7222
Subsequent years			
Acute coronary syndrome ¹	0.8800 (0.018)	0.8447	0.9153
Ischaemic stroke	0.6280 (0.040)	0.5496	0.7064
Heart failure	0.6830 (0.020)	0.6438	0.7222
Death	0.0000	–	–
¹ Includes myocardial infarction and unstable angina			
CI, confidence interval; CVD, cardiovascular disease; SE, standard error			

The company used its time trade-off study in a scenario analyses (see sections 5.30 and 5.31).

- 5.21 The company's model included treatment and monitoring costs, and those associated with the model health states. The costs of atorvastatin and ezetimibe were based on the NHS Drug Tariff. Including the patient access scheme, the cost of evolocumab in the model was [REDACTED] for a 140-mg prefilled pen or syringe. The company assumed that patients who started treatment with evolocumab received 1-hour training by a nurse to self-administer at a cost of £84.00. Monitoring costs were based on assumptions in NICE clinical guideline 181; no additional monitoring was assumed for patients receiving evolocumab. To estimate the acute and long-term costs of CV events, the company used a retrospective,

longitudinal, observational, cohort study. For further details on these costs, see table 5-23 on page 232 of the company's original submission. Costs for revascularisation procedures, and death from ischaemic stroke or coronary heart disease, were also included in the model.

- 5.22 For a summary of the model inputs, see table 5-24 on page 234 of the company's original submission.

ERG comments

- 5.23 The ERG stated that, of the 7 acute and post-event states in the model, only 3 (acute coronary syndrome, heart failure and post heart failure) were based on the EQ-5D questionnaire. The other utility values were obtained from studies that used the time trade-off method, which does not meet the NICE reference case (the methods considered by NICE to be the most appropriate for technology appraisals). In addition, the ERG noted that some of the utility values used were derived from patients whose characteristics differed from those of patients in the model for whom the values were used.
- 5.24 Overall, the ERG did not have major concerns about the costs used in the company's model.

Company's base-case results and sensitivity analysis

- 5.25 In its PAS submission, the company presented the base-case analyses for all 3 populations as incremental cost-effectiveness analyses. In addition, it presented the following analyses:
- For the existing CVD and HeFH populations
 - deterministic sensitivity analysis
 - ◊ evolocumab plus statin compared with ezetimibe plus statin.
 - probabilistic sensitivity analysis
 - ◊ evolocumab plus statin compared with ezetimibe plus statin
 - ◊ evolocumab compared with ezetimibe.
 - scenario analyses

- ◇ evolocumab plus statin compared with ezetimibe plus statin.
- For the existing CVD population only
 - subgroup analysis
 - ◇ evolocumab plus statin compared with ezetimibe plus statin.

Base-case analysis

5.26 All populations: all treatment comparisons. Base-case results are presented in Table 7 (patients without existing CVD), Table 8 (patients with existing CVD), and Table 9 (patients with HeFH).

Table 7 Base-case results with the PAS: population without existing CVD

Treatment comparison	Total cost (£)	Total QALY	Inc. cost (£)	Inc. QALY	ICER (£/QALY)
Ezetimibe + statin	9,979	11.83	–	–	–
Evolocumab + statin	■	12.14	■	0.52	74,331
Ezetimibe	9,767	11.80	–	–	–
Evolocumab	■	12.10	■	0.48	78,879
Ezetimibe	Not presented.				
Evolocumab + ezetimibe					
Ezetimibe + statin	Not presented.				
Evolocumab + ezetimibe + statin					
ICER, incremental cost-effectiveness ratio; Inc., incremental; QALY, quality-adjusted life year					

Source: Tables 23 and 25 (p. 17 and 18) of the company's PAS submission

Table 8 Base-case results with the PAS: population with existing CVD

Treatment comparison	Total cost (£)	Total QALY	Inc. cost (£)	Inc. QALY	ICER (£/QALY)
Ezetimibe + statin	21,408	7.84	–	–	–
Evolocumab + statin	■	8.23	■	0.63	46,005
Ezetimibe	21,143	7.81	–	–	–
Evolocumab	■	8.18	■	0.57	49,278
Ezetimibe	21,143	7.81	–	–	–
Evolocumab + ezetimibe	■	8.24	■	0.42	52,811
Ezetimibe + statin	21,408	7.84	–	–	–
Evolocumab + ezetimibe + statin	■	8.28	■	0.44	50,880
ICER, incremental cost-effectiveness ratio; Inc., incremental; QALY, quality-adjusted life year					

Source: Tables 27, 29, 31 and 33 (p. 18–20) of the company's PAS submission

Table 9 Base-case results with the PAS: population with HeFH (with or without existing CVD)

Treatment comparison	Total cost (£)	Total QALY	Inc. cost (£)	Inc. QALY	ICER (£/QALY)
Ezetimibe + statin	20,672	10.03	–	–	–
Evolocumab + statin	■	10.89	■	1.33	22,902
Ezetimibe	20,472	9.97	–	–	–
Evolocumab	■	10.79	■	1.23	23,927
Ezetimibe	20,472	9.97	–	–	–
Evolocumab + ezetimibe	■	10.93	■	0.96	25,609
Ezetimibe + statin	20,672	10.03	–	–	–
Evolocumab + ezetimibe + statin	■	11.03	■	1.00	24,826
HeFH, heterozygous familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; Inc., incremental; QALY, quality-adjusted life year					

Source: Tables 35, 37, 39 and 41 (p. 21 and 22) of the company's PAS submission

Deterministic sensitivity analyses

5.27 Existing CVD and HeFH populations: evolocumab plus statin versus ezetimibe plus statin only. The company presented deterministic sensitivity analyses in which it varied input values in the model for 1 parameter at a time. The company presented results only for the comparison of evolocumab plus statin with ezetimibe plus statin in all 3 populations because the results for the other comparisons were not sensitive to changes in parameter values. Among the most influential parameters were the effect of reducing LDL-C concentration on death from coronary heart disease or ischemic stroke, the effect of ezetimibe on LDL-C in patients at high risk of CVD, and the CPRD and HeFH calibration rate ratios. For the tornado diagrams, see figures 1 and 2 (pages 34 and 35) of the company's PAS submission.

Probabilistic sensitivity analyses

5.28 Existing CVD and HeFH populations: (a) evolocumab plus statin versus ezetimibe plus statin, and (b) evolocumab versus ezetimibe. The company carried out probabilistic sensitivity analyses varying parameters simultaneously with values from a probability distribution. It reported results as probabilistic ICERs (Table 10), cost-effectiveness planes, and

cost-effectiveness acceptability curves (for further details, see pages 38–41 of the company's PAS submission).

Table 10 Probabilistic and deterministic ICERs with the PAS

Population	Intervention	Comparator	ICER (£/QALY)	
			Deterministic	Probabilistic
Secondary prevention	Evolocumab + statin	Ezetimibe + statin	46,005	47,079
	Evolocumab	Ezetimibe	49,278	50,321
HeFH	Evolocumab + statin	Ezetimibe + statin	22,902	23,504
	Evolocumab	Ezetimibe	23,927	24,604
HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year				

Source: Table 50 (p. 44) of the company's PAS submission

Table 11 shows the probability of evolocumab being cost effective at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained.

Table 11 Probability of evolocumab being cost effective at £20,000 and £30,000 per QALY gained

Population	Intervention	Comparator	Probability of evolocumab being cost effective	
			At £20,000/QALY	At £30,000/QALY
Existing CVD	Evolocumab + statin	Ezetimibe + statin	0.0%	0.0%
	Evolocumab	Ezetimibe	0.0%	0.0%
HeFH	Evolocumab + statin	Ezetimibe + statin	7.8%	95.9%
	Evolocumab	Ezetimibe	4.7%	91.0%
HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year				

Source: Table 51 (p. 44) of the company's PAS submission

Scenario analyses

Severity of hypercholesterolaemia

5.29 Existing CVD and HeFH populations: evolocumab plus statins versus ezetimibe plus statins only. The company explored how the severity of hypercholesterolaemia, as reflected in the LDL-C concentration at baseline, affected the cost effectiveness of evolocumab plus statins compared with ezetimibe plus statins. Results suggested that the higher

the concentration of LDL-C at baseline, the more cost effective evolocumab is. The company stated that the same trend would be expected for the other evolocumab treatments. The company reported the following results:

- Existing CVD population. When the company assumed an LDL-C concentration at baseline of 3.0 mmol/L, the ICER with the PAS for evolocumab plus statins compared with ezetimibe plus statins was £52,222 per QALY gained. This decreased to £34,685 per QALY gained at an LDL-C concentration of 6.0 mmol/L.
- HeFH population. At LDL-C concentrations at baseline of 3.0 mmol/L and 6 mmol/L, the ICERs with the PAS for evolocumab plus statins compared with ezetimibe plus statins were £29,250 and £17,328 per QALY gained respectively.

Other scenario analyses

5.30 Existing CVD and HeFH populations: evolocumab plus statins versus ezetimibe plus statins only. The company carried out further scenario analyses to assess the impact of dosing evolocumab monthly, administering treatment for 5, 10 and 20 years, applying alternative discount rates, capping the risk at age 75, applying costs derived from NICE clinical guideline 181, using utility values from the company-sponsored time trade-off study, and making alternative assumptions about nurse training.

5.31 Existing CVD and HeFH populations: evolocumab plus statins versus ezetimibe plus statins only. The company reported the following results, which included the PAS:

- Existing CVD population. Compared with the base-case ICER of £46,005 per QALY, the lowest ICER was £34,450 per QALY gained from using the utility values from the company's time trade-off study, and the highest was £104,346 per QALY gained from applying an annual discount rate of 0% and 6% for costs and health effects

respectively. Evolocumab monthly increased the base-case ICER to £69,229 per QALY gained.

- HeFH population. Compared with the base-case ICER of £22,902 per QALY gained, the company obtained the lowest and highest ICER (£17,555 and £112,741 per QALY gained) when it varied the annual discount rate for costs and health effects. Evolocumab monthly increased the base-case ICER to £34,037 per QALY gained. Using the utility values from company's time trade-off study had little impact on the ICER in this population.

Subgroup analyses

5.32 Population with existing CVD: evolocumab plus statin compared with ezetimibe plus statin only. The company presented 3 sets of subgroup analyses based on the following variables in LAPLACE-2:

- patients with individual risk factors for CVD, including LDL-C concentration of 3.0–6.0 mmol/L (in increments of 0.5 mmol/L), sex, diabetes, vascular beds (2 or 3), atrial fibrillation, and CV events that occurred in the previous year
- patients with individual risk factors for CVD (diabetes, atrial fibrillation, number of vascular beds, or history of CVD events) combined with LDL-C concentration at baseline (3.5–4.5 mmol/L), age and sex
- patients with 2 individual risk factors (including diabetes, atrial fibrillation, number of vascular beds, and history of acute coronary syndrome) combined with baseline LDL-C (3.0–4.0 mmol/L), age and sex.

5.33 Population with existing CVD: evolocumab plus statin compared with ezetimibe plus statin only. The company reported the following results:

- **Patients with individual risk factors for CVD:** the ICERs for evolocumab plus statins compared with ezetimibe plus statins ranged from £28,550 per QALY gained (patients with 3 vascular beds) to £98,139 per QALY gained (when all patients were assumed to have

ischemic stroke when they started treatment). For further details, see table 45 (page 28) of the company's PAS submission.

- **Patients with individual risk factors for CVD combined with LDL-C concentration at baseline, age and sex:** the ICERs ranged from £22,138 per QALY gained (men with LDL-C concentration of 4.5 mmol/L and 3 vascular beds who are 10 years older than the average cohort age) to £100,609 per QALY gained (women of the average age of the cohort with LDL-C concentration of 3.5 mmol/L and a history of ischemic stroke). For further details, see table 46 (page 29) of the company's PAS submission.
- **Patients with 2 individual risk factors combined with baseline LDL-C concentration at baseline, age and sex:** the ICERs ranged from £18,784 per QALY gained (men with LDL-C concentration of 4.0 mmol/L, diabetes and 3 vascular beds who are 10 years older than the average cohort age) to £42,418 per QALY gained (women of the average age of the cohort with LDL-C concentration of 3.0 mmol/L, heart failure and 2 vascular beds). For further details, see table 47 (page 31) of the company's PAS submission.

ERG comments

5.34 In summary, the ERG advised some caution in the interpretation of the company's results because of:

- the circular approach used by the company to predict risks of CVD (see section 5.11)
- the selected populations used in the model (see section 5.4)
- the likely overestimation of the risk of CVD in the HeFH population (see 5.14)
- the uncertainty about the relationship between LDL-C reduction and reductions in CV events (see section 5.17)
- the use of multiple composite states which were populated using many assumptions and little evidence (see section 5.9).

Innovation

5.35 Justifications for considering evolocumab to be innovative:

- First-in-class therapy with a novel, targeted mechanism of action, and convenient fortnightly or monthly subcutaneous self-administration, without needing to adjust the dose.
- Consistent and sustained reductions in LDL-C concentrations of approximately 70% compared with placebo and 45% compared with ezetimibe.
- Reduction in the risk of major CV events in high-risk patients who would otherwise remain vulnerable to CV events.
- Favourable safety and tolerability profile.

6 Equality issues

6.1 At the scoping stage, the following potential equality issues were raised by consultees:

- Inequality of access to LDL-apheresis is a major issue owing to the high set up costs for treatment and the existence of few established centres with appropriate expertise.
- Administration of evolocumab by subcutaneous injection may not be acceptable to certain ethnic minority groups who do not accept injection based therapies.

The first issue was considered an equity, rather than equality, issue. The second issue will be highlighted to the Committee for consideration during the course of the appraisal.

6.2 The clinical experts noted that there is a need for community nursing support to administer treatment to patients who cannot self-inject whether because of disability or personal preference. They also noted that patients in geographically remote areas may have difficulty accessing specialist care to start therapy.

7 Authors

Ahmed Elsada

Technical Lead

Nicola Hay

Technical Adviser

with input from the Lead Team (Anna O'Neill, Rachel Elliott, and Judith Wardle).

Appendix A: Clinical efficacy section of the draft European public assessment report

The European public assessment report for evolocumab can be found [here](#).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**Single Technology Appraisal****Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia****Final scope****Remit/appraisal objective**

To appraise the clinical and cost effectiveness of evolocumab within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia.

Background

Dyslipidaemia is a broad term describing a number of conditions, including hypercholesterolaemia, hyperlipidaemia and mixed dyslipidaemia, in which disturbances in fat metabolism lead to changes in the concentrations of lipids in the blood.

Hypercholesterolaemia is the presence of high concentrations of cholesterol in the blood, typically including elevated low-density lipoprotein (LDL) cholesterol. Primary hypercholesterolaemia is associated with an underlying genetic cause, which may be caused by a single genetic defect (familial), or more commonly, by the interaction of several genes with dietary and other factors such as smoking or physical inactivity (non-familial). In heterozygous-familial hypercholesterolaemia, 1 of the pair of LDL cholesterol receptor genes is defective or mutated and impairs the LDL cholesterol receptor activity.

Most people with hypercholesterolaemia have cholesterol concentrations that are only mildly or moderately elevated, and show no clinical symptoms. Severe hypercholesterolaemia, however, can cause xanthomas (lesions on the skin containing cholesterol and fats) and arcus corneae (cholesterol deposits in the eyes).

Mixed dyslipidaemia is defined as elevations in LDL cholesterol and triglyceride levels that are often accompanied by low levels of high-density lipoprotein (HDL) cholesterol.

It is estimated that 6 in 10 adults in England have cholesterol levels above 5 mmol/litre. Primary non-familial hypercholesterolaemia affects about 4% of the adult population, totalling approximately 1.5 million people in England, of whom an estimated 600,000 are diagnosed and 460,000 are receiving treatment. Primary heterozygous familial hypercholesterolaemia affects an estimated 1 in 500 people, totalling 106,000 in England (although only 15–17% are diagnosed).

People with hypercholesterolaemia are at increased risk of cardiovascular disease (CVD) because long-term elevations of cholesterol accelerate the build-up of fatty deposits in the arteries (atherosclerosis). The narrowed arteries can cause diseases such as angina, myocardial infarction and stroke, particularly in familial hypercholesterolaemia. CVD is a common cause of death in England, accounting for approximately 148,000 deaths in 2012, and it is a major cause of disability and reduced quality of life.

The current management of primary hypercholesterolaemia and mixed dyslipidaemia involves dietary and lifestyle changes such as smoking cessation, weight loss and increased physical activity. NICE clinical guideline 181 for lipid modification to prevent cardiovascular disease and NICE clinical guideline 71 for familial hypercholesterolaemia recommend initial treatment with statins. NICE technology appraisal 132 (currently being reviewed) recommends ezetimibe as an option for treating primary hypercholesterolaemia, as a monotherapy when statins are contraindicated or not tolerated and in combination with statins when initial statin therapy does not provide appropriate control of LDL-cholesterol. LDL apheresis (a process similar to dialysis which removes low density lipoprotein from the blood stream) may be considered in exceptional instances for people with heterozygous familial hypercholesterolaemia.

The technology

Evolocumab (Repatha, Amgen) is a monoclonal antibody which inhibits an enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9) involved in down-regulation of low-density lipoprotein receptors. Evolocumab therefore increases receptor density and lowers LDL- cholesterol. It is administered by subcutaneous injection.

Evolocumab does not currently have a marketing authorisation in the UK for primary hypercholesterolaemia and mixed dyslipidaemia. It has been studied in clinical trials for treating primary hypercholesterolemia and mixed dyslipidaemia, both alone (as a monotherapy) and in combination with other lipid-modifying therapies, compared with placebo, ezetimibe, statins and other lipid-modifying therapies.

Intervention(s)	Evolocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe.
Population(s)	People with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies, in line with current NICE guidance, would be considered.

Comparators	• When optimised statin therapy does not appropriately control LDL-C: ○ Ezetimibe in combination with a statin • When statins are contraindicated or not tolerated: ○ Ezetimibe
Outcomes	The outcome measures to be considered include: • plasma lipid and lipoprotein levels, including LDL-cholesterol, non-HDL-cholesterol, 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.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows, consideration will be given to the following subgroups: • Presence or risk of cardiovascular disease • People with heterozygous familial hypercholesterolaemia • People with statin intolerance • Severity of hypercholesterolaemia 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.

Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 132, November 2007, 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia'. Currently being reviewed, earliest anticipated date of publication May 2016. Proposed Technology Appraisal, 'Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia'. Earliest anticipated date of publication TBC. Related Guidelines: Clinical Guideline No. 181, July 2014, 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease' Review Proposal Date September 2016. Clinical Guideline No. 71, August 2008, 'Identification and management of familial hypercholesterolaemia'. Review Proposal Date September 2016. Related Quality Standards: Quality Standard No. 41, August 2013, 'Familial hypercholesterolaemia'. Review Proposal Date August 2018. http://www.nice.org.uk/guidance/QS41 Related NICE Pathways: NICE Pathway: Familial hypercholesterolaemia. Pathway created August 2013. http://pathways.nice.org.uk/pathways/familial-hypercholesterolaemia NICE Pathway: Cardiovascular disease prevention, Pathway created: July 2014. http://pathways.nice.org.uk/pathways/cardiovascular-disease-prevention
Related National Policy	National Service Frameworks: Coronary Heart Disease Department of Health (2013): NHS Outcomes Framework 2014–2015 NHS England (November 2012) Inherited Heart Disease Services - Familial hypercholesterolaemia: services for these patients are commissioned by Clinical Commissioning Groups. Source: Manual for prescribed

	specialised services Page 32

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia
[ID765]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
<u>Company</u> - Amgen <u>Patient/carer groups</u> - Afiya Trust - Black Health Agency - British Cardiac Patients Association - Cardiovascular Care Partnership - Coronary Prevention Group - Equalities National Council - Genetic Alliance UK - HEART UK - Muslim Council of Britain - Network of Sikh Organisations - South Asian Health Foundation - Specialised Healthcare Alliance <u>Professional groups</u> - British Association for Nursing in Cardiac Care - British Cardiovascular Intervention Society - British Cardiovascular Society - British Dietetic Association - British Geriatrics Society - British Heart Foundation - British Inherited Metabolic Disease Group - British Society for Genetic Medicine - National Metabolic Biochemistry Network - Primary Care Cardiovascular Society - Royal College of General Practitioners - Royal College of Nursing - Royal College of Pathologists	<u>General</u> - Allied Health Professionals Federation - Board of Community Health Councils in Wales - British National Formulary - Care Quality Commission - Department of Health, Social Services and Public Safety for Northern Ireland - Healthcare Improvement Scotland - Medicines and Healthcare products Regulatory Agency - National Association of Primary Care - National Pharmacy Association - NHS Alliance - NHS Commercial Medicines Unit - NHS Confederation - Scottish Medicines Consortium <u>Comparator companies</u> - Abbott Healthcare (fenofibrate) - Accord Healthcare (fluvastatin, pravastatin, simvastatin) - Actavis (atorvastatin, bezafibrate, fenofibrate, fluvastatin, pravastatin, simvastatin) - Arrow Generics (atorvastatin, pravastatin, simvastatin) - Aspire Pharma (atorvastatin, fluvastatin) - AstraZeneca (rosuvastatin) - Aurobindo Pharma (simvastatin) - Bristol Laboratories (simvastatin) - Bristol-Myers Squibb (colestyramine, pravastatin) - Chanelle Medical UK (simvastatin) - Dexcel Pharma (atorvastatin,

Appendix C

Consultees	Commentators (no right to submit or appeal)
- Royal College of Physicians - Royal Pharmaceutical Society - Royal Society of Medicine - Society for Cardiological Science & Technology - Society for Endocrinology - Society for Vascular Technology - Society of Vascular Nurses - UK Clinical Pharmacy Association - UK Genetic Testing Network - UK Health Forum - Vascular Society of Great Britain and Ireland <u>Others</u> - Department of Health - NHS Barking & Dagenham CCG - NHS England - NHS Walsall CCG - Welsh Government	simvastatin) - Discovery Pharmaceuticals (simvastatin) - Dr Reddy's Laboratories (atorvastatin) - Genus (fenofibrate) - Medreich (pravastatin, simvastatin) - Merck Sharp & Dohme (ezetimibe, simvastatin, simvastatin with ezetimibe) - Mylan (benzafibrate, fluvastatin, pravastatin, simvastatin) - Novartis Pharmaceuticals (fluvastatin) - Pfizer (acipimox, atorvastatin, colestipol, gemfibrozil) - Ranbaxy UK (atorvastatin, pravastatin, simvastatin) - Sandoz (bezafibrate, fenofibrate, fluvastatin, pravastatin, simvastatin) - Sanofi (colesevelam) - Teva UK (atorvastatin, bezafibrate, colestyramine, fenofibrate, fluvastatin, gemfibrozil, pravastatin, simvastatin) - Wockhardt UK (atorvastatin, simvastatin) - Zentiva (atorvastatin, ciprofibrate, fenofibrate, fluvastatin, pravastatin, simvastatin) <u>Relevant research groups</u> - British Society for Cardiovascular Research - Central Cardiac Audit Database - Cochrane Cystic Fibrosis and Genetic Disorders Group - Cochrane Heart Group - Health Research Authority - MRC Clinical Trials Unit - National Centre for Cardiovascular Preventions and Outcomes - National Institute for Health Research - Society for the Study of Inborn Errors of Metabolism - Wellcome Trust - Cardiovascular Research Initiative <u>Evidence Review Group</u>

Appendix C

Consultees	Commentators (no right to submit or appeal)
	• School of Health and Related Research (ScHARR) • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Clinical Guidelines Centre <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement¹, respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*).

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

¹Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia

Company evidence submission

July 2015

File name	Version	Contains confidential information	Date
		Yes CIC: Redacted AIC: Redacted	November 2015

Contents

1	Executive summary.....	13
1.1	Statement of decision problem	15
1.2	Description of the technology being appraised	18
1.3	Summary of the clinical effectiveness and safety/tolerability analysis	19
1.4	Summary of the cost-effectiveness analysis	23
1.5	Conclusion	30
2	The technology.....	32
2.1	Description of the technology	32
2.2	Marketing authorisation/CE marking and health technology assessment	33
2.3	Administration and costs of the technology.....	34
2.4	Changes in service provision and management	35
2.5	Innovation.....	36
3	Health condition and position of the technology in the treatment pathway	38
4	Clinical effectiveness	60
4.1	Identification and selection of relevant studies.....	61
4.2	List of relevant randomised controlled trials.....	67
4.3	Summary of methodology of the relevant randomised controlled trials	69
4.4	Statistical analysis and definition of study groups in the relevant randomised controlled trials	80
4.5	Participant flow in the relevant randomised controlled trials.....	87
4.6	Quality assessment of the relevant randomised controlled trials.....	100
4.7	Clinical effectiveness results of the relevant randomised controlled trials	103
4.8	Subgroup analysis.....	121
4.9	Meta-analysis	128
4.10	Indirect and mixed treatment comparisons	128
4.11	Non-randomised and non-controlled evidence	130
4.12	Adverse reactions.....	135
4.13	Interpretation of clinical effectiveness and safety evidence.....	150
4.14	Ongoing studies	156
5	Cost effectiveness.....	160
5.1	Published cost-effectiveness studies	161
5.2	De novo analysis	173
5.3	Clinical parameters and variables.....	181
5.4	Measurement and valuation of health effects	201
5.5	Cost and healthcare resource use identification, measurement, and valuation	221
5.6	Summary of base case de novo analysis inputs and assumptions	233
5.7	Base case results.....	240

5.8	Without existing CVD	241
5.9	Existing CVD	246
5.10	Heterozygous familial hypercholesterolaemia.....	250
5.11	Sensitivity analyses	255
5.12	Scenario analysis	267
5.13	Subgroup analysis.....	275
5.14	Validation	283
5.15	Interpretation and conclusions of economic evidence.....	284
6	Assessment of factors relevant to the NHS and other parties	286
7	References.....	292

List of tables

Table 1-1	Description of the decision problem	15
Table 1-2	Summary of the technology being appraised ^a	18
Table 1-3	Treatment differences in mean percent change from baseline in LDL-C in the relevant RCTs 20	
Table 1-4	Threshold analyses of baseline LDL-C and 10 year CVD risk according to willingness-to-pay thresholds for evolocumab and statin versus ezetimibe and statin	24
Table 1-5	Incremental cost-effectiveness results: existing CVD	26
Table 1-6	Cost-effectiveness analysis (incremental cost (£) per QALY gained) of evolocumab and statin versus ezetimibe and statin with one additional CV risk factor (Scenario 1) 27	
Table 1-7	Cost-effectiveness analysis (incremental cost (£) per QALY gained) of evolocumab and statin versus ezetimibe and statin with two additional CV risk factors (Scenario 1) 28	
Table 1-8	Incremental cost-effectiveness results: HeFH	29
Table 2-1	Administration and costs of evolocumab ^a	35
Table 3-1	Grouping of statins by intensity of LDL-C reduction based on NICE clinical guideline 181 (Lipid modification: cardiovascular risk assessment and modification of blood lipids for the primary and secondary prevention of cardiovascular disease)	43
Table 3-2	Details of additional lipid-lowering therapies	44
Table 3-3	Summary of the most relevant NICE clinical guidelines and technology appraisal guidance on lipid modification therapy for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia	50
Table 3-4	ESC/EAS risk categories	53
Table 3-5	Patient characteristics relevant for identifying patients with existing CVD at high residual risk due to additional risk factors	57
Table 4-1	Inclusion and exclusion criteria for the broad clinical efficacy/safety systematic literature review	63
Table 4-2	List of relevant RCTs	68
Table 4-3	Summary of locations, design and trial drugs in the relevant RCTs	72
Table 4-4	Summary of eligibility criteria in the relevant RCTs	75
Table 4-5	Summary of outcome measures and pre-planned subgroups in the relevant RCTs 78	
Table 4-6	Statistical analyses in the relevant RCTs	81
Table 4-7	Baseline characteristics and lipid-lowering medication use in LAPLACE-2 (FAS) 93	
Table 4-8	Baseline characteristics and lipid-lowering medication use in RUTHERFORD-2, GAUSS-2, and DESCARTES (FAS)	96
Table 4-9	Quality assessment of the relevant RCTs	101
Table 4-10	Details of efficacy results presented from the relevant RCTs and LTE studies in the main submission	104
Table 4-11	Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS)	107
Table 4-12	Treatment difference in mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and week 12 in LAPLACE-2 (FAS)	109

Table 4-13	Combined statin analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS)	111
Table 4-14	Combined atorvastatin analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS)	112
Table 4-15	Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in RUTHERFORD-2 (FAS)	114
Table 4-16	Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in GAUSS-2 (FAS)	116
Table 4-17	Mean percent change in calculated LDL-C from baseline at week 12 and week 52 in DESCARTES (FAS)	117
Table 4-18	Summary of pre-specified subgroup analyses by stratification factor and other baseline covariates in LAPLACE-2, RUTHERFORD-2, GAUSS-2, and DESCARTES	122
Table 4-19		126
Table 4-20	Overview of study 20110271 (TAUSSIG)	130
Table 4-21	Key TAUSSIG eligibility criteria	131
Table 4-22	Mean percent change from baseline in calculated LDL-C by scheduled visit to week 36 in TAUSSIG (severe FH interim analysis set) ^{a,b}	134
Table 4-23	Summary of subject incidence of adverse events in the relevant RCTs, supplementary long-term, randomised, controlled, open-label extension studies, and non-randomised, non-controlled studies	136
Table 4-24	Safety analysis sets in the integrated primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia studies	140
Table 4-25	Overview of adverse events in the integrated primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia studies	142
Table 4-26	Overview of common adverse events (≥ 2% in the EvoMab 140 mg Q2W/420 mg QM group) in the integrated primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia parent studies (IPAS)	143
Table 4-27	Overview of positively adjudicated cardiovascular events and non-coronary revascularisations in the integrated primary hypercholesterolaemia and mixed dyslipidaemia studies	145
Table 4-28	Ongoing studies of evolocumab (as of 01 July 2015)	157
Table 5-1	Eligibility criteria used in the economic evaluations SLR	163
Table 5-2	Economic evaluation summary data extraction table of UK studies presenting a Markov model with a lifetime time horizon	167
Table 5-3	Features of the <i>de novo</i> analysis	179
Table 5-4	Marketing authorisation of ezetimibe and atorvastatin	180
Table 5-5	Baseline population characteristics	183
Table 5-6	Risk predictions – primary and recurrent CV events, included risk factors, and CV events	185
Table 5-7	Risk predictions – overview of risk prediction parameters	186
Table 5-8	Calibration estimates applied to Framingham and REACH registry predictions, based on CPRD analysis	190
Table 5-9	Baseline CV risk for population	192
Table 5-10	Mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe when used in combination with statins or as monotherapy	193
Table 5-11	Treatment effects applied in different modelled scenarios	196

Table 5-12	Proportion of change in CVD event risk per mmol/L LDL-C change	197
Table 5-13	Transition probabilities from 'ACS' to other health states	199
Table 5-14	Time trade-off study results.....	202
Table 5-15	Eligibility criteria used in the HRQoL SLR	205
Table 5-16	HRQoL summary data extraction table of UK studies using EQ-5D as utility methods of elicitation	209
Table 5-17	Utility multipliers of health states	220
Table 5-18	Eligibility criteria used in the cost and resource use SLR	223
Table 5-19	Summary of represented countries in cardiovascular event studies	226
Table 5-20	Cost summary data extraction of UK studies, presenting a Markov model with a lifetime time horizon	227
Table 5-21	Unit costs associated with the technology in the economic model.....	229
Table 5-22	Monitoring resource use and costs	230
Table 5-23	CV event costs for acute and long-term period from the CPRD study	232
Table 5-24	Summary of deterministic variables applied in the economic model.....	234
Table 5-25	Summary of the variables applied in the probabilistic sensitivity analysis of the economic model.....	236
Table 5-26	Model assumptions used in defining the cost-effectiveness of evolocumab for LDL-C reduction.....	238
Table 5-27	Modelled intervention and comparator for patients with and without existing CVD, and patients with HeFH	240
Table 5-28	Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin)	242
Table 5-29	Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin)	242
Table 5-30	Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone)	243
Table 5-31	Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone)	244
Table 5-32	Analysis C: Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab and statin versus ezetimibe and statin)	246
Table 5-33	Analysis C: Base case undiscounted CV event rates	246
Table 5-34	Analysis C: Base case summary of QALYs by health state	247
Table 5-35	Analysis C: Base case summary of costs by health state	247
Table 5-36	Analysis C: Base case summary of resource use by health state.....	248
Table 5-37	Analysis D: Base case incremental cost, incremental QALYs and ICER for patients with existing CVD	248
Table 5-38	Analysis D: Base case undiscounted CV event rates	249
Table 5-39	Analysis D: Base case summary of QALYs by health state	249
Table 5-40	Analysis D: Base case summary of costs by health state	250
Table 5-41	Analysis D: Base case summary of resource use by health state.....	250
Table 5-42	Analysis G: Base case incremental cost, incremental QALYs and ICER for the HeFH population (evolocumab and statin vs. ezetimibe and statin).....	251
Table 5-43	Analysis G: Base case undiscounted CV event rates	251

Table 5-44	Analysis G: Base case summary of QALYs by health state.....	252
Table 5-45	Analysis G: Base case summary of costs by health state.....	252
Table 5-46	Analysis G: Base case summary of resource use by health state	253
Table 5-47	Analysis H: Base case incremental cost, incremental QALYs, and ICER for the HeFH population	253
Table 5-48	Analysis H: Base case undiscounted CV event rates	254
Table 5-49	Analysis H: Base case summary of QALYs by health state	254
Table 5-50	Analysis H: Base case summary of costs by health state	255
Table 5-51	Analysis H: Base case summary of resource use by health state.....	255
Table 5-52	Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1]	257
Table 5-53	Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1]	258
Table 5-54	Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone) [scenario 2]	259
Table 5-55	Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone) [scenario 2]	260
Table 5-56	Probability of cost-effectiveness for evolocumab in different populations and maximum acceptable incremental cost-effectiveness ratios [scenarios 1 and 2]	264
Table 5-57	Deterministic and probabilistic incremental cost-effectiveness ratios.....	265
Table 5-58	Scenario analyses: Existing CVD and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1]	269
Table 5-59	Scenario analyses: HeFH and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1]	270
Table 5-60	Analysis E: Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab and ezetimibe versus ezetimibe alone)	271
Table 5-61	Analysis F: Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab, statin and ezetimibe versus statin and ezetimibe)	272
Table 5-62	Analysis I: Base case incremental cost, incremental QALYs and ICER for patients with HeFH (evolocumab and ezetimibe versus ezetimibe alone)	272
Table 5-63	Analysis J: Base case incremental cost, incremental QALYs, and ICER for patients with HeFH (evolocumab, statin and ezetimibe vs. statin and ezetimibe)	273
Table 5-64	Scenario analyses – without existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1].....	274
Table 5-65	Scenario analyses – existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1].....	274
Table 5-66	Scenario analyses – HeFH population (evolocumab and statin versus ezetimibe and statin) [scenario 1].....	275
Table 5-67	Patient characteristics relevant for identifying patients with existing CVD at enhanced risk	276
Table 5-68	Cost-effectiveness analysis of evolocumab and statin versus ezetimibe and statin in patients with existing CVD and additional risk factors	278

Table 5-69	Cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin with specific CV risk factors.....	279
Table 5-70	Cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin with two specific CV risk factors	281
Table 5-71	Model validation: Predicted rate ratio by CVD event for evolocumab versus high-intensity statin	283
Table 6-1	Without existing CVD eligible patient population – assumptions	286
Table 6-2	Estimated eligible adult population without existing CVD in England and Wales	286
Table 6-3	With existing CVD eligible patient population – assumptions	287
Table 6-4	Estimated eligible adult population with existing CVD in England and Wales.	287
Table 6-5	HeFH eligible patient population – assumptions.....	288
Table 6-6	Estimated eligible adult population with HeFH in England and Wales	288
Table 6-7	Absolute market share of ezetimibe and evolocumab (current and proposed) in eligible patient populations	289
Table 6-8	England and Wales budget impact – without existing CVD	290
Table 6-9	England and Wales budget impact – existing CVD	290
Table 6-10	England and Wales budget impact – HeFH.....	291

List of figures

Figure 1-1	Threshold analysis of baseline LDL-C and 10-year CVD risk for evolocumab and statin versus ezetimibe and statin	24
Figure 2-1	Mechanism of action of evolocumab	33
Figure 3-1	LDL-C distribution patterns in the UK	46
Figure 3-2	Summary of current UK clinical pathway of care for lipid-lowering therapy for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia based on NICE clinical guidelines and technology appraisal guidance	49
Figure 3-3	Proposed place of evolocumab in the treatment pathway	55
Figure 4-1	PRISMA flow diagram for the clinical efficacy/safety SLR	66
Figure 4-2	CONSORT participant flow diagram for LAPLACE-2 (atorvastatin cohorts) ..	88
Figure 4-3	CONSORT participant flow diagram for LAPLACE-2 (rosuvastatin and simvastatin cohorts)	89
Figure 4-4	CONSORT participant flow diagram for RUTHERFORD-2.....	90
Figure 4-5	CONSORT participant flow diagram for GAUSS-2	91
Figure 4-6	CONSORT participant flow diagram for DESCARTES.....	92
Figure 4-7	Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS)	106
Figure 4-8	Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in RUTHERFORD-2 (FAS)	113
Figure 4-9	Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and week 12 in GAUSS-2 (FAS)	115
Figure 4-10	Plot of mean percent change from baseline in calculated LDL-C by scheduled visit and IP in DESCARTES (FAS).....	118
Figure 4-11	Treatment differences (%; 95% CI) in percent change from baseline at the mean of weeks 10/12 (LAPLACE-2, RUTHERFORD-2, and GAUSS-2) and at week 52 (DESCARTES) in calculated LDL-C.....	119
Figure 4-12	PRISMA flow diagram for the clinical efficacy/safety SLR – identification of studies relevant for data synthesis in HeFH (evolocumab plus statin versus ezetimibe plus statin)	129
Figure 5-1	PRISMA flow diagram for the economic evaluations SLR	165
Figure 5-2	Economic model structure.....	175
Figure 5-3	Treatment pathway and modelled treatment scenarios	181
Figure 5-4	Step-wise sequence of estimating event-specific transition probabilities from patient-level characteristics	182
Figure 5-5	ACS – crude composite event rate over time	188
Figure 5-6	ACS long-term period – multinomial model event distribution results by age	189
Figure 5-7	Modelled LDL-C reductions based on evolocumab used in addition to background statin, monotherapy or addition to ezetimibe with or without background statin	195
Figure 5-8	Health state transitions.....	200
Figure 5-9	PRISMA flow diagram for HRQoL SLR from the database search	207
Figure 5-10	PRISMA flow diagram for costs and resources SLR from the database search	225
Figure 5-11	Threshold analysis for different baseline LDL-C for scenarios 1 and 2	245

Figure 5-12	Scatterplot for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1].....	261
Figure 5-13	Scatterplot for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2]	261
Figure 5-14	Scatterplot for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1].....	262
Figure 5-15	Scatterplot for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2]	262
Figure 5-16	Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1] ...	263
Figure 5-17	Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2]	263
Figure 5-18	Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]	264
Figure 5-19	Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2]	264
Figure 5-20	Tornado plot: evolocumab and statin versus ezetimibe and statin in patients without existing CVD (based on LAPLACE-2) [scenario 1].....	266
Figure 5-21	Tornado plot: evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1].....	266
Figure 5-22	Tornado plot: evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1].....	267
Figure 5-23	Existing CVD: Incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin according to severity of hypercholesterolaemia	268
Figure 5-24	HeFH: Incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin (scenario 1) according to severity of hypercholesterolaemia.....	270

Abbreviations

ACS	acute coronary syndrome
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ATP	adult treatment panel
BMI	body mass index
CABG	coronary arteries bypass graft
CG	clinical guideline
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CK	creatine kinase
CKD	chronic kidney disease
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CTTC	Cholesterol Treatment Trialists' Collaboration
CV	cardiovascular
CVD	cardiovascular disease
EAS	European Atherosclerosis Society
ECVD	established cardiovascular disease
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ENHANCE	Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression
EQ-5D	5-dimension European Quality of Life questionnaire
ESC	European Society of Cardiology
FAS	full analysis set
FH	familial hypercholesterolaemia
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolaemia
HES	Hospital Episode Statistics
HF	heart failure
HoFH	homozygous familial hypercholesterolaemia
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IMPROVE-IT	IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
IS	ischaemic stroke
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
Lp(a)	lipoprotein (a)
MA	marketing authorisation
MI	myocardial infarction
NHS	National Health Service
NHS EED	National Health Service Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
Non-HDL-C	non-high-density lipoprotein cholesterol

OR	odds ratio
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSSRU	Personal Social Services Research Unit
Q2W	every 2 weeks
QALY	quality-adjusted life year
QM	monthly
QRISK2	QRESEARCH Cardiovascular Risk Algorithm
RCT	randomised controlled trial
REACH	REduction of Atherothrombosis for Continued Health
SLR	systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMQ	standard MedRA query
SoC	standard of care
TA	technology appraisal
TIA	transient ischaemic attack
TTO	time trade-off
ULN	upper limit of normal

1 Executive summary

CVD is the largest cause of death and remains a national priority

Cardiovascular disease (CVD) is the largest cause of death in the UK; in 2013, a third of all deaths (approximately 192,000 annually or 500 per day) were estimated to be attributable to CVD, with approximately 99,000 due to coronary heart disease (CHD) and 34,000 due to ischaemic stroke (IS). The Department of Health CVD Outcomes Strategy has recognised that England underperforms when compared with similar countries in terms of cardiovascular (CV) mortality. Preventing premature mortality due to CVD therefore remains a national priority and is a key indicator in the Department of Health National Health Service (NHS) Outcomes and Public Health Outcomes Frameworks. Non-fatal major CV events can also lead to serious long-term consequences such as functional disability, impaired health-related quality of life (HRQoL), and an increased risk of subsequent CV events. CVD also represents a significant economic burden; in 2009, CVD was responsible for 6% (approximately £7 billion of total healthcare expenditure in the UK). Between 2014 and 2020, the estimated direct cost of CVD is expected to rise from approximately £10 billion per year to approximately £12 billion per year, underlying the importance of making available new therapeutic options to reduce the incidence and long-term costs of CVD.

LDL-C is the principal modifiable risk factor for CVD

The risk of a CV event is a composite of modifiable and non-modifiable risk factors. Elevated low-density lipoprotein cholesterol (LDL-C) plays a critical role in atherosclerotic plaque formation, and is the principal modifiable risk factor for CVD. Familial hypercholesterolaemia (FH), a hereditary condition, leads to life-long markedly elevated LDL-C levels. Additional risk factors for CV events include increased age, male gender, smoking, existing CVD, diabetes mellitus and chronic kidney disease (CKD). The evidence supporting LDL-C as a therapeutic target and surrogate for CV outcomes is robust and multi-faceted, and comes from epidemiological studies, studies of genetic variants, and interventional studies with LDL-C-lowering therapies. A meta-analysis of 26 interventional trials (169,138 individuals with a median follow-up of 4.9 years) conducted by the Cholesterol Treatment Trialists' Collaboration (CTTC) showed that for every 1 mmol/L reduction in LDL-C, the annual risk of major CV events was reduced by 22%, with a continued benefit observed even with low LDL-C levels (< 2.0 mmol/L).

Statins and other lipid-lowering therapies do not provide adequate LDL-C reduction for some patients who remain at high risk of CV events

Interventions to achieve LDL-C control in patients with elevated LDL-C and in those at high CV risk are prescribed to reduce the risk of CV events. Lowering LDL-C has been shown to significantly reduce the risk of CV events irrespective of the type of intervention. Following lifestyle changes, statins are considered the cornerstone of therapy to reduce LDL-C levels; however, the maximum dose of high-intensity statin licensed in the UK achieves a maximal LDL-C reduction of up to 55%. Further, some patients are statin intolerant and develop symptoms (e.g. myalgia) which can lead to treatment discontinuation or dose reduction, thereby limiting the ability of statins to lower LDL-C and prevent major CV events. For patients with elevated LDL-C levels despite treatment with statins, ezetimibe and other lipid-lowering therapies may be additionally prescribed, but their potency is limited, with LDL-C

reductions in the order of 10% to 20%. Existing treatment options adequately reduce LDL-C levels in most patients; however, there remains a cohort of high-risk patients (e.g. patients with non-familial hypercholesterolaemia at high residual risk due to presence of additional risk factors, and patients with HeFH) for whom existing treatment options are inadequate and who remain particularly vulnerable to CV events. These patients have a substantial unmet medical need.

Evolocumab delivers consistent and intensive LDL-C reductions in addition to background lipid-lowering therapy such as statins

Evolocumab (Repatha) is an innovative, first-in-class, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. It has a novel, targeted mechanism of action and convenient two-weekly or monthly subcutaneous self-administration, with no requirement for dose adjustment. Four robust phase 3, randomised controlled trials (RCTs) (LAPLACE-2, RUTHERFORD-2, GAUSS-2, and DESCARTES) demonstrated that evolocumab provided consistent and intensive reductions in LDL-C; up to approximately 72% compared with placebo and up to approximately 46% compared with ezetimibe, in addition to any background lipid-lowering therapies patients were receiving (e.g. statins). These reductions were consistent regardless of patient population and patient characteristics (including risk or presence of CVD and severity of hypercholesterolaemia); evolocumab dosing regimen; and presence and type of background lipid-lowering therapy. Supplementary evidence from ongoing, long-term extension studies (OSLER and OSLER-2) show that this reduction was maintained for more than 2 years. Analyses of the safety and tolerability data from individual studies and an integrated data set of over 6,000 patients (representing 7,235 patient-years of exposure) show that evolocumab has a favourable safety and tolerability profile. Further, exploratory safety data from the long-term extension studies suggest that evolocumab is associated with a reduction in CV events of approximately 50%, which is consistent with that predicted (per CTTC) given the magnitude of its LDL-C lowering. The robust and long-term effects of evolocumab on LDL-C and other lipids, combined with its favourable safety and tolerability profile, demonstrate that evolocumab represents a major clinical advancement and revolutionary step-change in the management of primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. Evolocumab will, for the first time, enable clinicians to provide high-risk patients who would otherwise remain vulnerable to CV events (because of inadequate LDL-C reduction with existing therapies) with consistent and intensive LDL-C reductions to reduce their future risk of major CV events.

Although evolocumab would be beneficial for many patients whose LDL-C remains inadequately controlled by maximally-tolerated doses of statins or who are statin intolerant/contraindicated (per its marketing authorisation [MA]), the priority for use of evolocumab is in those patients who are at the highest residual risk and are most vulnerable to CV events, where evolocumab represents both a clinically- and cost-effective treatment option for the NHS. These include:

- Patients without existing CVD but at high residual risk due to additional risk factors (based on QRISK2 score)
- Patients with existing CVD at high residual risk due to additional risk factors (e.g. diabetes mellitus or CKD)
- Patients with HeFH

1.1 Statement of decision problem

An overview of the decision problem is provided in Table 1.1.

Table 1-1 Description of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies, in line with current NICE guidance, would be considered	People with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies, in line with current NICE guidance, would be considered	N/A
Intervention	Evolocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe	• Evolocumab in combination with a statin (all) • Evolocumab in combination with a statin and ezetimibe (all) • Evolocumab alone or in combination with ezetimibe (all, when statins are contraindicated or not tolerated)	N/A
Comparators	• When optimised statin therapy does not appropriately control LDL-C: ▪ Ezetimibe in combination with a statin • When statins are contraindicated or not tolerated: ▪ Ezetimibe	• When optimised statin therapy does not appropriately control LDL-C: ▪ Ezetimibe in combination with a statin • When statins are contraindicated or not tolerated: ▪ Ezetimibe	N/A
Outcomes	The outcome measures to be considered include: • Plasma lipid and lipoprotein levels,	The outcome measures to be considered include: • Plasma lipid and lipoprotein levels,	• Detailed results for plasma lipid and lipoprotein levels other than LDL-C, including non-HDL-C, apolipoprotein B,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	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 • HRQoL	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	and lipoprotein (a), have been provided within the submission appendices instead of the main submission for brevity, as the association between LDL-C and CV events/mortality is substantially more established than other lipid parameters • HRQoL outcomes were not captured during evolocumab trial programme, however HRQoL (utilities) associated with CV events is included in the economic evaluation
Economic analysis	• The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year • 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 • Costs will be considered from an NHS and Personal Social Services perspective	• Cost-effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life-year • The lifetime time horizon reflecting any differences in costs or CV outcomes between the technologies being compared • Costs are considered from an NHS and Personal Social Services perspective	N/A
Subgroups to be considered	If evidence allows, consideration will be given to following subgroups: • According to presence or risk of CVD • Patients with HeFH • Patients with statin intolerance • According to severity of	Consideration has been given to following subgroups: • According to presence or risk of CVD • Patients with HeFH • Patients with statin intolerance • According to severity of	• Additional subgroups of patients with existing CVD at high residual risk due to additional risk factors were assessed in the cost-effectiveness section to identify patient groups where the technology is more cost effective due to increased baseline CVD risk

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	hypercholesterolaemia 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	hypercholesterolaemia • Additional subgroups of patients with existing CVD at high residual risk due to additional risk factors have also been assessed	
CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; HRQoL, health-related quality of life; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; non-HDL-C, non-high-density lipoprotein cholesterol.			

1.2 Description of the technology being appraised

A brief description of evolocumab is provided in Table 1-2.

Table 1-2 Summary of the technology being appraised^a

UK approved name and brand name	Evolocumab (brand name: Repatha)
Marketing authorisation/CE mark status	•An application for marketing authorisation (centralised process) was made by Amgen to the EMA on 29 August 2014 •CHMP positive opinion was received on 22 May 2015 •EU approval was received on 21 July 2015
Indications and any restriction(s) as described in the summary of product characteristics	Primary hypercholesterolaemia (familial and non-familial) and mixed dyslipidaemia Evolocumab 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 •Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated Restrictions •The use of evolocumab is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients •Evolocumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab •In addition, the safety and efficacy of evolocumab in children aged younger than 18 years has not been established in the indication for primary hypercholesterolaemia and mixed dyslipidaemia. No data are available Additional information The effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined
Method of administration and dosage	Posology Primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia: The recommended dose of evolocumab is either 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent Method of administration •Evolocumab is administered as a subcutaneous injection into the abdomen, thigh, or upper arm region. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard •Evolocumab is intended for patient self-administration after proper training. Administration of evolocumab can also be performed by an

	individual who has been trained to administer the product
^a Information on evolocumab for the treatment of HoFH has not been included in this table as it is outside of the scope of this appraisal. CHMP, Committee for Medicinal Products for Human Use; HoFH, homozygous familial hypercholesterolaemia; EMA, European Medicines Agency; EU, European Union; LDL-C, low-density lipoprotein cholesterol	

1.3 *Summary of the clinical effectiveness and safety/tolerability analysis*

Summary of key clinical evidence

A broad systematic literature review (SLR) was used to identify RCTs in patients with primary hypercholesterolaemia (including familial and non-familial) who are candidates for treatment of elevated lipid levels. Additional exclusion criteria were applied to the review to further align it with the decision problem outlined in the final scope, and to identify studies most relevant for inclusion in this submission (i.e. including evolocumab). A total of four relevant phase 3 RCTs that evaluated evolocumab were identified:

- **LAPLACE-2:** Evolocumab versus placebo and versus ezetimibe over 12 weeks in patients with primary hypercholesterolaemia and mixed dyslipidaemia receiving background moderate- to high-intensity statins.
- **RUTHERFORD-2:** Evolocumab versus placebo over 12 weeks in patients with HeFH receiving stable background lipid-lowering therapy (statins $\pm$ other lipid-lowering therapies).
- **GAUSS-2:** Evolocumab versus ezetimibe over 12 weeks in patients with primary hypercholesterolaemia and mixed dyslipidaemia and statin intolerance.
- **DESCARTES:** Evolocumab versus placebo over 52 weeks in patients with primary hypercholesterolaemia and mixed dyslipidaemia receiving background lipid-lowering therapy.

These four relevant RCTs, which involved the treatment of almost 3,500 patients, represent a robust evaluation of evolocumab versus ezetimibe and versus placebo in relevant patient populations with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia.

In addition to the relevant RCTs identified in the SLR, a further two studies, OSLER and OSLER-2 (ongoing, randomised, controlled, open-label, long-term extensions of phase 2 and phase 3 studies, respectively) were identified and included in this submission to support long-term evaluation. OSLER-2 included patients enrolled in the four relevant RCTs described above. A non-randomised, non-controlled trial (TAUSSIG) is also included in this submission, which provides additional long-term data in a severe HeFH population.

Clinical effectiveness

Four robust phase 3, randomised controlled trials (RCTs) (LAPLACE-2, RUTHERFORD-2, GAUSS-2, and DESCARTES) demonstrated that evolocumab provided consistent and intensive reductions in LDL-C; up to approximately 72% compared with placebo and up to approximately 46% compared with ezetimibe, in addition to any background lipid-lowering therapies patients were receiving e.g. statins (Table 1-3).

Table 1-3 Treatment differences in mean percent change from baseline in LDL-C in the relevant RCTs

Study	Population	Evolocumab vs. placebo and/or ezetimibe ^a
LAPLACE-2	Patients with primary hypercholesterolaemia and mixed dyslipidaemia treated with background moderate- to high-intensity statin therapy	-69.1% to -71.8% vs. placebo -43.3% to -45.5% vs. ezetimibe
RUTHERFORD-2	Patients with HeFH treated with stable background lipid-lowering therapy (statin ± other lipid-lowering therapy)	-61.3% to -66.2% vs. placebo
GAUSS-2	Patients with primary hypercholesterolaemia and mixed dyslipidaemia with statin intolerance	-38.1% to -39.2% vs. ezetimibe
DESCARTES	Patients with primary hypercholesterolaemia and mixed dyslipidaemia treated with background lipid-lowering therapy	-59.3% vs. placebo
^a Treatment differences in mean percent change from baseline in calculated LDL-C at the mean of weeks 10/12 (LAPLACE-2, RUTHERFORD-2, and GAUSS-2) and at week 52 (DESCARTES) between evolocumab (140 mg Q2W or 420 mg QM) and placebo or ezetimibe, with placebo or ezetimibe as the reference.		
HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol		

Primary hypercholesterolaemia and mixed dyslipidaemia: Results from the relevant RCT (LAPLACE-2) show that in patients receiving background moderate- to high-intensity statins evolocumab significantly reduced LDL-C by an additional 69.1% to 71.8% compared with placebo and 43.3% to 45.5% compared with ezetimibe. Evolocumab was also superior to placebo and to ezetimibe in improving other lipid parameters, including non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), and lipoprotein (a) (Lp[a]). Evolocumab 140 mg every 2 weeks (Q2W) and 420 mg monthly (QM) were clinically equivalent. Pre-specified and post-hoc subgroup analyses show that these reductions in LDL-C are consistent across patient subgroups, including subgroups according to background statin intensity, presence or risk of CVD, and severity of hypercholesterolaemia.

Heterozygous familial hypercholesterolaemia: Results from the relevant RCT (RUTHERFORD-2) show that in patients receiving stable background lipid-lowering therapy (statins ± other lipid-lowering therapies), evolocumab significantly reduced LDL-C by an additional 61.3% to 66.2% compared with placebo. Evolocumab was also superior to placebo in improving other lipid parameters, including non-HDL-C, ApoB, and Lp(a). Evolocumab 140 mg Q2W and 420 mg QM were clinically equivalent. Pre-specified and post-hoc subgroup analyses show that these reductions in LDL-C are consistent across

patient subgroups, including subgroups according to ezetimibe use, background statin intensity, presence or risk of CVD, and severity of hypercholesterolaemia.

Results from an additional ongoing open-label study in patients with severe familial hypercholesterolaemia (homozygous familial hypercholesterolaemia [HoFH] or HeFH) (TAUSSIG) show that in the subset of patients with severe HeFH (mean baseline LDL-C 4.9 mmol/L), evolocumab 420 mg (Q2W or QM) led to sustained reductions from baseline in LDL-C of approximately 50%.

Primary hypercholesterolaemia and mixed dyslipidaemia with statin intolerance:

Results from the relevant RCT (GAUSS-2) show that evolocumab significantly reduced LDL-C by an additional 38.1% to 39.2% compared with ezetimibe. Evolocumab was also superior to ezetimibe in improving other lipid parameters, including non-HDL-C, ApoB, and Lp(a). Evolocumab 140 mg Q2W and 420 mg QM were clinically equivalent. Pre-specified and post-hoc subgroup analyses show that these reductions in LDL-C are consistent across patient subgroups, including subgroups according to lipid-lowering therapy use, presence or risk of CVD, and severity of hypercholesterolaemia

Long-term efficacy: Results from the relevant RCT (DESCARTES) show that in patients receiving background lipid-lowering therapy, evolocumab 420 mg QM led to sustained reductions in LDL-C compared with placebo, with an additional 59.3% reduction at week 52. Evolocumab was also superior to placebo in improving other lipid parameters, including non-HDL-C, ApoB, and Lp(a). Pre-specified and post-hoc subgroup analyses show that these reductions in LDL-C are consistent across patient subgroups, including subgroups according to background lipid-lowering therapy, presence or risk of CVD, and severity of hypercholesterolaemia.

The long-term efficacy of evolocumab is also supported by additional ongoing long-term, randomised, controlled, open-label extension studies (OSLER and OSLER-2) in mixed patient populations. These showed, both individually and in an integrated analysis of both studies, a sustained LDL-C lowering effect of approximately 50% to 60% for evolocumab plus standard of care (SoC) relative to SoC alone for 1 year. This LDL-C lowering effect of evolocumab was maintained for more than 2 years.

Safety and tolerability

Analyses of the safety and tolerability data from the evolocumab studies show that evolocumab has a favourable safety and tolerability profile. In an integrated safety analysis (of 6,026 patients, representing 7,235 patient-years of exposure), as well as across populations and therapeutic settings in individual studies, adverse events were overall balanced between treatment groups. Most adverse events were mild to moderate in severity, with rates of serious adverse events and adverse events leading to treatment discontinuation infrequently reported and generally similar across treatment groups. No safety issues were detected for adverse events of interest associated with other lipid-lowering therapies (i.e. diabetes events, liver events, muscle events) and those that could theoretically be associated with PCSK9 inhibition/LDL-C receptor upregulation (i.e. hepatitis C events). The type and incidence of adverse events observed in patients with LDL-C concentrations < 0.6 mmol/L and < 1.0 mmol/L were generally similar to those observed in patients with LDL-C

concentrations ≥ 1.0 mmol/L. Anti-evolocumab antibodies were infrequent, non-neutralising, and not associated with clinically relevant adverse events. An exploratory safety analysis of recent data from the integrated long-term extension studies showed a significant 53% reduction in 1-year adjudicated CV event rates from 2.18% in the SoC group to 0.95% in the evolocumab plus SoC group (hazard ratio [HR] 0.47, $p = 0.003$). This is in the direction, and of the magnitude, that would be expected given the magnitude of LDL-C lowering associated with evolocumab.

Strengths and limitations of evidence

The clinical evidence base included in this submission includes robust, high-quality evidence (with low risk of bias) demonstrating the consistent and sustained efficacy of evolocumab in lowering LDL-C across a range of patient populations and therapeutic settings, as well as its favourable safety and tolerability profile. The evidence base adequately addresses the decision problem, provides data in relevant patient populations and versus relevant comparators, and is generalisable to patients who will ultimately receive evolocumab in clinical practice in England and Wales.

The current evidence base does not include an assessment of the incidence of CV events as an efficacy outcome (although a CV outcomes study, FOURIER, is ongoing). However, the evidence supporting LDL-C as a therapeutic target and validated surrogate for CV outcomes is substantial and multi-faceted. Further, exploratory safety data from the long-term extension studies show that evolocumab is associated with a reduction in CV events of approximately 50%, which is consistent with that predicted (per CTTC) given the magnitude of its LDL-C lowering.

1.4 Summary of the cost-effectiveness analysis

Type of economic evaluation and justification for the approach used: A *de novo* cost-effectiveness Markov model analysis was developed for the economic evaluation of evolocumab. The economic evaluation was undertaken in accordance with the NICE reference case. A lifetime analysis was performed (cycle length of one year; half-cycle correction used). Costs and outcomes were discounted at 3.5% per annum. Drug costs were taken from the NHS Drug Tariff. The acute and long-term care costs of CV events were based on a retrospective longitudinal observation cohort study using Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) data. Health state utilities were based on NICE Clinical Guideline (CG) 181. Baseline characteristics from the relevant phase 3 evolocumab RCTs were used for the populations under assessment to inform baseline CV risk using Framingham Heart Study and REACH registry risk equations. Baseline CV rates were calibrated based on estimations for patients with and without existing CVD and for patients with HeFH using the CPRD and FH registry data. LDL-C reductions from the relevant phase 3 evolocumab RCTs were used for evolocumab and ezetimibe to model the translation between LDL-C and CV events for the treatment strategies, based on the CTTC meta-analysis for LDL-C reduction and major CV events.

Populations: The following populations have been considered in the context of NICE guidance for whom lipid-lowering therapies would be considered:

- Patients without existing CVD but at high residual risk due to additional risk factors
- Patients with existing CVD at high residual risk due to additional risk factors
- Patients with HeFH

Treatment scenarios: the cost-effectiveness of evolocumab was assessed in the following scenarios for the intervention and comparators within the decision problem.

- **Scenario 1 (combination with statin):** Addition of evolocumab to current high-intensity statin versus addition of ezetimibe to current high-intensity statin.
- **Scenario 2 (monotherapy):** Evolocumab alone versus ezetimibe alone in patients who are either statin-intolerant or contraindicated to statins.
- **Scenario 3 (combination with ezetimibe):** Addition of evolocumab to ezetimibe versus ezetimibe alone in patients who are either statin-intolerant or contraindicated to statins.
- **Scenario 4 (combination with statin and ezetimibe):** addition of evolocumab to current high-intensity statin and ezetimibe versus current high-intensity statin and ezetimibe.

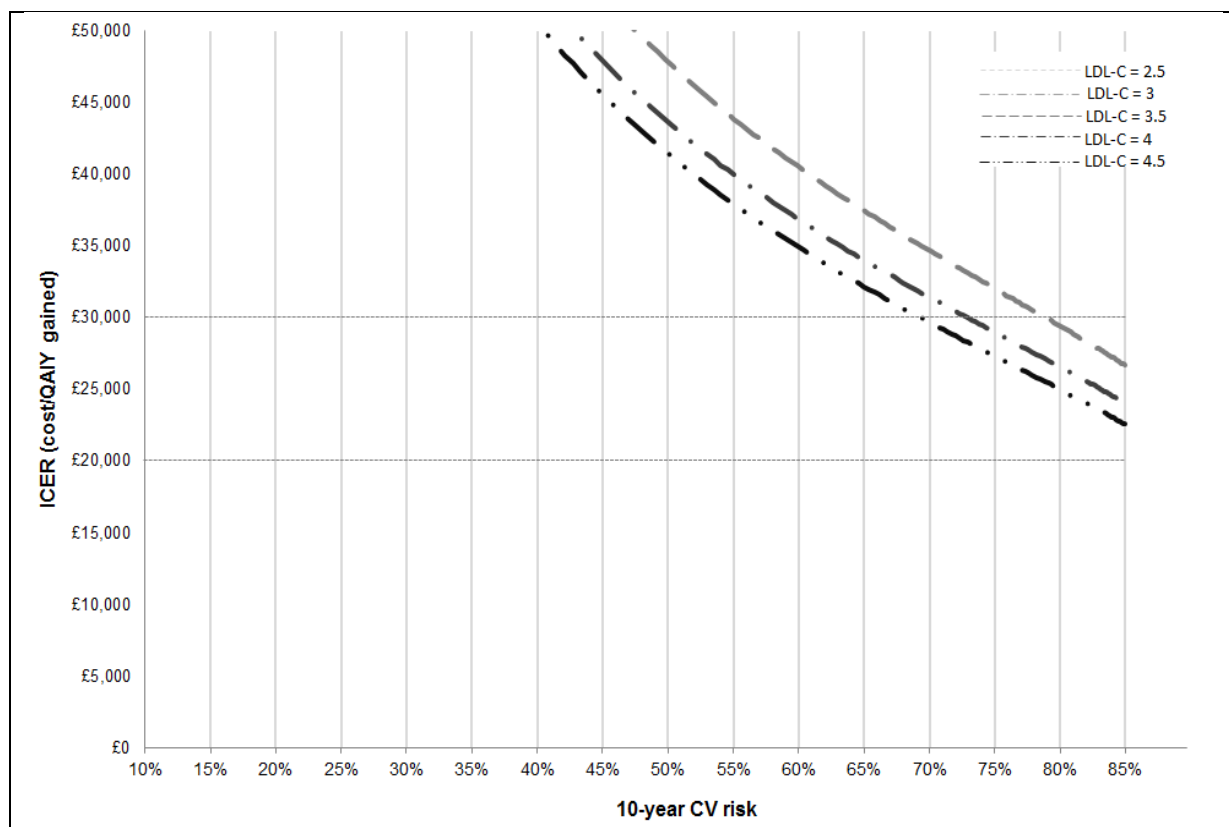
Without existing CVD: Although evolocumab would be beneficial for many patients with existing CVD whose LDL-C remains inadequately controlled by maximally-tolerated doses of statins or who are statin intolerant/contraindicated (per its MA), the priority for use in patients at the highest residual risk. Threshold analyses for various baseline LDL-C levels (2.5 to 4.5mmol/L) were therefore conducted to establish the minimum 10-year CVD risk (measured using a risk assessment tool such as QRISK2) at which treatment with evolocumab in accordance with its MA would be deemed a cost-effective use of NHS resources according to willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained. The minimum absolute 10-year CVD risks required for evolocumab to be cost-effective at these thresholds are presented in Table 1-4 and Figure 1-1.

Table 1-4 Threshold analyses of baseline LDL-C and 10 year CVD risk according to willingness-to-pay thresholds for evolocumab and statin versus ezetimibe and statin

Baseline LDL-C (mmol/L)	10-year CVD risk for £20,000/QALY	10-year CVD risk for £30,000/QALY
2.5	–*	–*
3	–*	–*
3.5	–*	79%
4	–*	73%
4.5	–*	70%

*Not achievable based on threshold analysis for defined willingness-to-pay thresholds
CVD; cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year

Figure 1-1 Threshold analysis of baseline LDL-C and 10-year CVD risk for evolocumab and statin versus ezetimibe and statin



CV, cardiovascular; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year

Existing CVD: Cost-effectiveness analyses for evolocumab compared with ezetimibe in the various treatment scenarios are presented in Table 1-5. Although evolocumab would be beneficial for many patients with existing CVD whose LDL-C remains inadequately controlled by maximally-tolerated doses of statins or who are statin intolerant/contraindicated (per its MA), the priority for use of evolocumab is in patients at the highest residual risk. NICE

CG181 recommends that a risk assessment tool should not be used in patients with existing CVD. Further, currently-available risk assessment tools (e.g. QRISK2 and SCORE) are not intended for use in patients with existing CVD. Therefore, threshold analyses based on 10-year CVD risk as conducted for patients without existing CVD would not be appropriate in the context of current clinical practice and guidelines. To enable the identification of patients at high residual risk due to additional risk factors, various sources of evidence were assessed, i.e. ESC/EAS 2011 guidelines for the management of dyslipidaemias, a targeted literature review of recurrent CVD risk equations, and consultation with UK clinicians. Based on this assessment, the following patient characteristics relevant for identifying patients with existing CVD at high residual risk were identified:

- Patients with type 2 diabetes mellitus and patients with type 1 diabetes mellitus with target organ damage (such as microalbuminuria)
- Patients with moderate to severe CKD (eGFR < 60 mL/min/1.73 m²)
- ≥ 2 vascular beds affected
- CV event in the previous year
- Congestive heart failure
- Atrial fibrillation
- ≥ 2 documented acute ischaemic CV events or revascularisation procedures
- Elevated plasma Lp(a)
- Age (years)
- Male gender

The cost-effectiveness results for evolocumab compared with ezetimibe in the treatment scenarios in patients with existing CVD according to severity of hypercholesterolaemia (baseline LDL-C) and presence of these risk factors are presented in Table 1-6 and Table 1-7

Existing CVD: Deterministic analyses indicate that the incremental cost per quality-adjusted life year (QALY) gained was £[REDACTED] to £[REDACTED] for evolocumab compared with ezetimibe in patients with existing CVD. The cost-effectiveness of evolocumab and ezetimibe in the different scenarios is presented in Table 1-5.

Table 1-5 Incremental cost-effectiveness results: existing CVD

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Scenario 1						
Statin	£17,959	7.28				
Ezetimibe and statin	£20,302	7.62	£2,343	0.34	£6,917	
Evolocumab and statin	[REDACTED]	8.06	[REDACTED]	0.78	[REDACTED]	[REDACTED]
Scenario 2						
No lipid-lowering therapy	£17,542	7.28				
Ezetimibe alone	£20,371	7.52	£2,829	0.23	£12,071	
Evolocumab alone	[REDACTED]	7.94	[REDACTED]	0.66	[REDACTED]	[REDACTED]
Scenario 3						
Ezetimibe alone	£20,371	7.52				
Evolocumab and ezetimibe	[REDACTED]	8.01	[REDACTED]	0.49	[REDACTED]	[REDACTED]
Scenario 4						
Ezetimibe and statin	£20,302	7.62				
Evolocumab, ezetimibe, and statin	[REDACTED]	8.06	[REDACTED]	0.44	[REDACTED]	[REDACTED]
CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Existing CVD at enhanced risk due to additional risk factors (baseline LDL-C 3.5 mmol/L and one other risk factor):

The impact of combining one other risk factor with varying age (+5 and +10 years) and gender (male or female) was assessed for patients with existing CVD (Table 1-6). The grey cells denote patient profiles where the incremental cost per QALY gained is less than £30,000. These results indicate that evolocumab can be considered a cost-effective treatment option in patients with a baseline LDL-C of 3.5 mmol/L and one of the following risk factors, when age and gender are taken into consideration:

- diabetes mellitus
- CV risk factors deemed at equivalent risk to diabetes mellitus:
 - moderate to severe CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²)
 - two or more documented acute ischaemic CV events or revascularisation procedures
 - elevated plasma Lp(a) ≥ 77 mg/dL (≥ 90% centile)
- three vascular beds
- acute coronary syndrome (ACS) in the past 12 months
- other CV conditions that significantly elevate risk of further CV events: atrial fibrillation

Table 1-6 Cost-effectiveness analysis (incremental cost (£) per QALY gained) of evolocumab and statin versus ezetimibe and statin with one additional CV risk factor (Scenario 1)

Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	3VB	ACS
3.5 mmol/L	Cohort	Cohort					
		+5					
		+10					
	Male	Cohort					
		+5					
		+10					
	Female	Cohort					
		+5					
		+10					

ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; PACS, post-acute coronary syndrome; QALY, quality-adjusted life year; SP, secondary prevention; VB, vascular beds

Existing CVD at enhanced risk due to additional risk factors (baseline LDL-C 3.0 mmol/L and two other risk factors):

The impact of combining two of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed for patients with existing CVD (Table 1-7). The grey cells denote patient profiles where the incremental cost per QALY gained is less than £30,000. These results indicate that evolocumab can be considered a cost-effective treatment option in patients with existing CVD, a baseline LDL-C of 3.0 mmol/L, and two of the following risk factors, when age and gender are taken into consideration:

- diabetes mellitus
- CV risk factors deemed at equivalent risk to diabetes mellitus:
 - moderate to severe CKD (eGFR < 60 mL/min/1.73 m²)
 - two or more documented acute ischaemic CV events or revascularisation procedures
 - elevated plasma Lp(a) ≥ 77 mg/dL (≥ 90% centile)
- two or more vascular beds
- ACS in the past 12 months
- other CV conditions that significantly elevate risk of further CV events: heart failure and atrial fibrillation

Table 1-7 Cost-effectiveness analysis (incremental cost (£) per QALY gained) of evolocumab and statin versus ezetimibe and statin with two additional CV risk factors (Scenario 1)

Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB
3.0 mmol/L	Cohort	Cohort							
		+5							
		+10							
	Male	Cohort							
		+5							
		+10							
	Female	Cohort							
		+5							
		+10							
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention; VB, vascular beds									

HeFH: Deterministic analyses indicate that the incremental cost per QALY gained is approximately £[REDACTED] to £[REDACTED] for evolocumab compared with ezetimibe in patients with HeFH. The cost-effectiveness of evolocumab and ezetimibe in the different treatment scenarios is presented in Table 1-8.

Table 1-8 Incremental cost-effectiveness results: HeFH

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Scenario 1						
Statin	£17,244	8.04				
Ezetimibe and statin	£18,697	8.86	£1,453	0.81	£1,791	
Evolocumab and statin	[REDACTED]	10.05	[REDACTED]	2.01	[REDACTED]	[REDACTED]
Scenario 2						
No lipid-lowering therapy	£16,845	8.04				
Ezetimibe alone	£19,005	8.60	£2,161	0.55	£3,913	
Evolocumab alone	[REDACTED]	9.69	[REDACTED]	1.65	[REDACTED]	[REDACTED]
Scenario 3						
Ezetimibe alone	£19,005	8.60				
Evolocumab and ezetimibe	[REDACTED]	9.88	[REDACTED]	1.29	[REDACTED]	[REDACTED]
Scenario 4						
Statin and ezetimibe	£18,697	8.86				
Evolocumab, statin and ezetimibe	[REDACTED]	10.11	[REDACTED]	1.26	[REDACTED]	[REDACTED]
HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

1.5 Conclusion

A third of UK deaths (approximately 500 per day) are attributed to CVD, and preventing premature mortality due to CVD remains a national priority. Elevated low-density lipoprotein cholesterol (LDL-C) plays a critical role in atherosclerotic plaque formation, and is the principal modifiable risk factor for CVD. Evolocumab (Repatha) is an innovative therapy with a novel mechanism of action and convenient two-weekly or monthly subcutaneous self-administration that allows patients at high risk of CV events (e.g. those with existing CVD or HeFH) to attain lowering of LDL-C levels not previously possible. As shown in four robust phase 3 RCTs, evolocumab provided consistent and intensive reductions in LDL-C compared with placebo and ezetimibe, in addition to any background lipid-lowering therapy patients were receiving (e.g. statins). These reductions were consistent regardless of patient population and patient characteristics; evolocumab dosing regimen; and presence and type of background lipid-lowering therapy. Supplementary evidence from ongoing, long-term extension studies show that reductions in LDL-C are maintained for more than 2 years. Evolocumab was also superior to placebo and to ezetimibe in improving other lipid parameters, including non-HDL-C, ApoB, and Lp(a). The robust and long-term effects of evolocumab on LDL-C and other lipids, combined with its favourable safety and tolerability profile, demonstrate that evolocumab represents a major clinical advancement and revolutionary step-change in the management of primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. Evolocumab will, for the first time, enable clinicians to provide high-risk patients who would otherwise remain vulnerable to CV events (because of inadequate LDL-C reduction with existing therapies) with consistent and intensive LDL-C reductions to reduce their risk of major CV events.

Ezetimibe (either in combination with statins or as monotherapy for people who are statin intolerant or contraindicated) is the comparator for evolocumab (either in combination with statins or as monotherapy for people who are statin intolerant or contraindicated) in line with current NICE guidance for patients for whom lipid-lowering therapies would be considered. Evolocumab represents both a clinically- and cost-effective treatment option compared with ezetimibe in adults at high risk of CV events as described below:

- | |
|---|
| 1. Adults with primary hypercholesterolaemia (non-familial) or mixed dyslipidaemia <u>without existing CVD</u> but at high residual risk due to additional risk factors (based on QRISK2 score) according to severity of hypercholesterolaemia |
| 2. Adults with primary hypercholesterolaemia (non-familial) or mixed dyslipidaemia <u>and existing CVD</u> with: <ul style="list-style-type: none">• LDL cholesterol ≥ 3.5 mmol/L (or equivalent non-HDL-cholesterol ≥ 4.3 mmol/L) and at high residual risk due to the presence of <u>one</u> or more of the following:<ul style="list-style-type: none">▪ Diabetes mellitus▪ Moderate to severe chronic kidney disease (eGFR < 60 mL/min/1.73m²)▪ ACS in the past year▪ Progressive CVD evidenced by ≥ 2 documented acute ischaemic CV events or revascularisation procedures▪ 3 vascular beds affected▪ Elevated plasma Lp(a) ≥ 77 mg/dL ($\geq 90\%$ centile)▪ Other CV conditions that significantly elevate risk of further CV events: atrial |

fibrillation

- LDL cholesterol ≥ 3.0 mmol/L (or equivalent non-HDL-cholesterol ≥ 3.8 mmol/L) and at high residual risk due to the presence of two or more of the following:
 - Diabetes mellitus
 - Moderate to severe chronic kidney disease (eGFR < 60 mL/min/1.73m²)
 - ACS in the past year
 - Progressive CVD evidenced by ≥ 2 documented acute ischaemic CV events or revascularisation procedures
 - ≥ 2 vascular beds affected
 - Elevated plasma Lp(a) ≥ 77 mg/dL ($\geq 90\%$ centile)
 - Other CV conditions that significantly elevate risk of further CV events: heart failure and atrial fibrillation

Age and gender should also be taken into consideration.

3. Adults with heterozygous familial hypercholesterolaemia

2 The technology

2.1 *Description of the technology*

UK approved and brand name

Evolocumab (Brand name: Repatha)

Therapeutic class

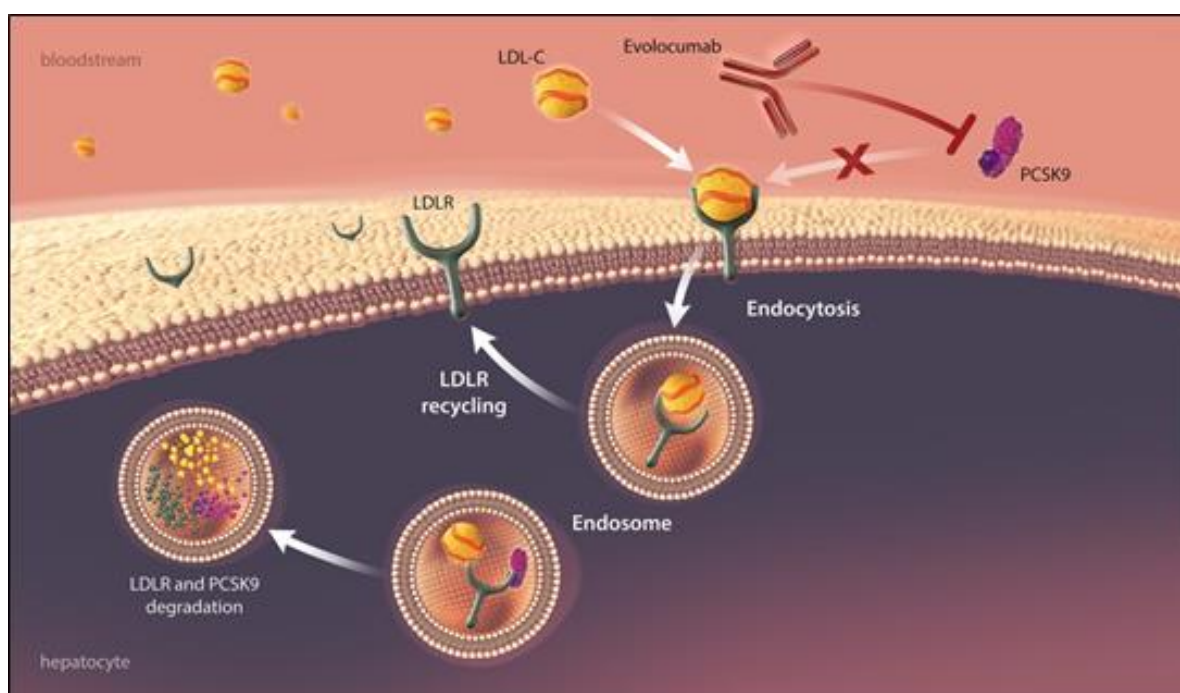
Fully human monoclonal antibody inhibitor of PCSK9.

Mechanism of action

Low-density lipoprotein receptors (LDLRs) regulate the level of plasma LDL-C. Following secretion, PCSK9, a protein that plays an essential role in lipid metabolism, directly binds LDLRs and causes them to be routed for degradation which, in turn, reduces the liver's ability to remove LDL-C from blood and leads to increased levels of circulating LDL-C. Support for targeting PCSK9 comes from gain-of-function mutations identified to be a source of inherited primary hypercholesterolaemia and premature CHD, and loss-of-function mutations which were discovered in families with known hypocholesterolaemia.¹ Population-based genetic epidemiologic studies confirmed that PCSK9 loss-of-function mutation confers lower average LDL-C and is protective against CHD events.¹

Evolocumab is a fully human monoclonal immunoglobulin G2 antibody that binds with high affinity and specificity to human PCSK9 (Figure 2-1). By binding to PCSK9, evolocumab inhibits circulating PCSK9 from binding to LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation, and resulting in increased cell-surface expression of LDLR. Similar to statins (Section 3), evolocumab reduces LDL-C by increasing the levels of LDLR on the hepatic cell surface; however, where statins increase LDLR on the hepatic cell surface by increasing LDLR expression by inhibition of intracellular cholesterol synthesis, evolocumab increases the number of LDLR on hepatic cells by inhibiting downstream destruction of the LDLR by PCSK9. As discussed later in Section 3, LDL-C lowering interventions have been shown to significantly reduce the risk of CV events, irrespective of the type of intervention. Evolocumab represents a novel approach to treating patients with primary hypercholesterolaemia and mixed dyslipidaemia.

Figure 2-1 Mechanism of action of evolocumab



LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.

2.2 Marketing authorisation/CE marking and health technology assessment

Marketing authorisation

An application for MA (centralised process) was made to the European Medicines Agency on 29 August 2014. The Committee for Medicinal Products for Human Use (CHMP) recommended a positive opinion for the MA for evolocumab in the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia on 22 May 2015. The European Commission approved the MA for evolocumab in all European Union Member States on July 21 2015. The anticipated date of availability in the UK is August 2015. Evolocumab is not currently approved outside of the EU; regulatory reviews are ongoing.

Approved indication in primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia:

Evolocumab 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
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated

The effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined.

Before finalising this indication and during the CHMP review of the evolocumab MA application, only one 'major objection' was raised, which regarded the proposed target population. The CHMP expressed concern around the clinical significance of the evolocumab lipid-lowering effects, which it deemed to be uncertain in the absence of a proven CV benefit, and what it deemed to be insufficient data to establish long-term safety (including safety in patients achieving very low LDL-C levels). It suggested, therefore, that the target population should be restricted to patients at high risk of a CV event (Day 120 list of questions). Further to Amgen's response to the list of questions and an oral explanation at Day 180, the CHMP agreed (with a of vote 26 to 6) that a MA could be granted provided that the indication was revised to reinforce the second-line use by adding language related to use after maximally-tolerated statins.

It is noted that there are no special conditions attached to the MA. Please refer to Appendix I for a copy of the Summary of Product Characteristics (SmPC) for evolocumab.

Health technology assessments

Evolocumab will be subject to health technology assessment (HTA) by the Scottish Medicines Consortium (SMC) in accordance with their remit to assess newly licensed medicines. We anticipate submitting a New Product Assessment Form for evolocumab in September to October 2015, and anticipate publication of SMC advice in early 2016 in accordance with their timelines and submission scheduling process.

2.3 Administration and costs of the technology

A brief overview of the administration and costs of evolocumab is provided in Table 2-1.

Table 2-1 Administration and costs of evolocumab^a

	Information
Pharmaceutical formulation	Solution for injection
Acquisition cost (excluding VAT)	NHS list price: £170.10 per 140 mg prefilled pen or syringe
Method of administration	Subcutaneous injection
Doses	140 mg prefilled pen or syringe
Dosing frequency	Primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia One injection (140 mg) Q2W or three injections (420 mg) QM
Average length of a course of treatment	Continuous
Average cost of a course of treatment	• NHS list price: a cost of £4,448.60 for 140 mg Q2W is or £6,123.60 with 420 mg (three injections) QM per patient per year
Dose adjustments	None required
Anticipated care setting	• Secondary care for initiation. Evolocumab is intended for patient self-administration after proper training • Administration of evolocumab can also be performed by an individual who has been trained to administer the product
^a Information on evolocumab for the treatment of HoFH has not been included in this table as it is outside of the scope of this appraisal. HoHF, homozygous familial hypercholesterolaemia; NHS, National Health Service; N/A, not applicable; Q2W, every 2 weeks; QM, monthly; VAT, Value Added Tax	

2.4 Changes in service provision and management

Evolocumab is anticipated to be used in patients who remain at high CV risk despite treatment with conventional lipid-lowering therapy (i.e. statin and/or other lipid-lowering therapies in addition to diet and lifestyle advice). High CV risk patients include patients with or without existing CVD and in whom LDL-C levels remain unacceptably high, and those with confirmed or suspected familial hypercholesterolaemia (identified through clinical assessment or through cascade screening). The high-risk nature of these patients means that they are easily identifiable (e.g. without existing CVD but at high residual risk due to other concomitant conditions such as diabetes) and warrant referral to specialist secondary care lipid clinics or risk review clinics, where their lipid profiles can be rigorously optimised. It is in these secondary care clinics where combinations of lipid-lowering therapies are optimised, drug intolerance (to e.g. statins) can be addressed, and additional investigations or advance treatments can be considered (e.g. family cascade screening in FH, lipoprotein apheresis). Therefore, it is in such secondary care clinics that we anticipate evolocumab (a novel lipid-lowering therapy) will be initiated, followed up, and managed until the point at which it is deemed clinically appropriate to discharge to primary care for ongoing monitoring thereafter. It is anticipated that evolocumab will be commissioned by clinical commissioning groups because the treatment of hypercholesterolaemia and mixed dyslipidaemia (except HoFH) is not currently within the scope of specialised commissioning through NHS England.

No additional tests or investigations for selection of patients appropriate for evolocumab, or any additional monitoring, will be required over and above those which are part of routine clinical practice. Requirements for general ongoing monitoring (secondary and primary care settings) associated with the management of hypercholesterolaemia with lipid-lowering therapies (efficacy and adverse events) are described in Section 5.5. Further, with respect to method of administration, evolocumab is intended for patient self-administration after proper training, as outlined in the SmPC (Appendix I). Evolocumab will be available as a prefilled pen or syringe to facilitate self-administration. Costs associated with patient training to allow self-administration are detailed in Section 5.5. If required, administration of evolocumab can also be performed by an individual who has been trained to administer the product (e.g. a healthcare professional or carer).

No additional infrastructure will be required to support the use of evolocumab. Patient training for self-administration through a healthcare professional (e.g. nurse) will be required at the outset. Further, as specified in the SmPC (Appendix I), no additional concomitant therapies are required to be administered with evolocumab.

2.5 *Innovation*

Evolocumab is an innovative, first-in-class therapy with a novel, targeted mechanism of action and convenient two-weekly or monthly subcutaneous self-administration, without the need for dose adjustment. Four robust phase 3 RCTs demonstrated that evolocumab provided consistent and intensive reductions in LDL-C of up to approximately 72% compared with placebo and up to approximately 46% compared with ezetimibe, in addition to any background lipid-lowering therapies patients were receiving e.g. statins. These reductions were consistent regardless of patient population and patient characteristics (including risk or presence of CVD and severity of hypercholesterolaemia); dosing regimen; and presence and type of background lipid-lowering therapy. Supplementary evidence from ongoing, long-term extension studies showed that this reduction was maintained for more than 2 years. Analyses of the safety and tolerability data from individual studies and an integrated data set of over 6,000 patients (representing 7,235 patient-years of exposure) show that evolocumab has a favourable safety and tolerability profile. The type and incidence of adverse events observed in patients with LDL-C concentrations < 0.6 mmol/L and < 1.0 mmol/L were generally similar to those observed in patients with LDL-C concentrations $\geq$ 1.0 mmol/L. Anti-evolocumab antibodies were infrequent, non-neutralising, and not associated with clinically relevant adverse events. Further, exploratory safety data from the long-term extension studies suggest that evolocumab is associated with a reduction in CV events of approximately 50%, which is consistent with that predicted (per CTTC) given the magnitude of its LDL-C lowering.

The robust and long-term effects of evolocumab on LDL-C and other lipids, combined with its favourable safety and tolerability profile, demonstrate that evolocumab represents a major clinical advancement and revolutionary step-change in the management of primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. Evolocumab will, for the first time, enable clinicians to provide high-risk patients who would otherwise remain vulnerable to CV events (because of inadequate LDL-C reduction with

existing therapies) with consistent and intensive LDL-C reductions to reduce their risk of major CV events.

3 Health condition and position of the technology in the treatment pathway

- CVD is the largest cause of death in the UK; in 2013 a third of all deaths (approximately 192,000 annually or 500 per day) were estimated to be attributable to CVD, including approximately 99,000 due to CHD and 34,000 due to ischaemic stroke. The Department of Health CVD Outcomes Strategy has recognised that England underperforms when compared with similar countries in terms of CV mortality. Preventing premature mortality due to CVD therefore remains a national priority and is a key indicator in the Department of Health NHS Outcomes and Public Health Outcomes Frameworks.
- Non-fatal major CV events can also lead to serious long-term consequences such as functional disability, impaired HRQoL, and increased risk of subsequent CV events.
- CVD also represents a significant economic burden; in 2009, CVD was responsible for 6% (approximately £7 billion of total healthcare expenditure in the UK. Between 2014 and 2020, the (estimated) direct cost of CVD is expected to rise from approximately £10 billion per year to approximately £12 billion per year, underlying the importance of making available new cost-effective therapeutic options to reduce the incidence and long-term costs of CVD.
- The risk of a CV event is a composite of modifiable and non-modifiable risk factors. Elevated LDL-C plays a critical role in atherosclerotic plaque formation, and is the principal modifiable risk factor for CVD. FH, a hereditary condition, leads to life-long markedly elevated LDL-C levels. Additional risk factors for CV events include increased age, male gender, smoking, existing CVD, diabetes mellitus and chronic kidney disease.
- The evidence supporting LDL-C as a therapeutic target and surrogate for CV outcomes is robust and multi-faceted (epidemiological studies, studies of genetic variants, and interventional studies with LDL-C-lowering therapies). A meta-analysis of 26 interventional studies (169,138 individuals with a median follow-up 4.9 years) conducted by the CTTC showed that for every 1 mmol/L reduction in LDL-C the annual risk of major CV events was reduced by 22%, with a continued benefit observed even with low LDL-C levels (< 2.0 mmol/L).
- Interventions to achieve LDL-C control in patients with elevated LDL-C and in those with high CV risk are prescribed to reduce the risk of CV events, and have been shown to significantly reduce the risk of CV events irrespective of the type of intervention.
- Following lifestyle changes, statins are considered the cornerstone of therapy to reduce LDL-C levels; however, the maximum dose of high-intensity statin licensed in the UK achieves a maximal LDL-C reduction of up to 55%. For patients with elevated LDL-C levels despite treatment with statins, ezetimibe and other lipid-lowering therapies may be additionally prescribed, but their potency is limited, with LDL-C reductions in the order of 10% to 20%.
- Existing treatment options adequately reduce LDL-C levels in most patients; however, there remains a cohort of high-risk patients (e.g. patients with non-familial hypercholesterolaemia at high residual risk due to presence of additional risk factors, and patients with HeFH) for whom existing treatment options are inadequate and who remain particularly vulnerable to CV events. These patients have a substantial unmet medical need.
- Although evolocumab would be beneficial for many patients whose LDL-C remains

inadequately controlled by maximally-tolerated doses of statins or who are statin intolerant/contraindicated (per its anticipated MA), the priority for use of evolocumab is in those patients who are at the highest residual risk and are most vulnerable to CV events, where evolocumab represents both a clinically- and cost-effective treatment option for the NHS. These include:

- Patients without existing CVD but at high residual risk due to additional risk factors (based on QRISK2 score)
- Patients with existing CVD at high residual risk due to additional risk factors (e.g. diabetes mellitus or CKD)
- Patients with HeFH

Overview of the disease/condition

Hyperlipidaemia is the heterogeneous group of disorders characterised by an excess of lipids (i.e. cholesterol, phospholipids, triglycerides) in the bloodstream. Primary hyperlipidaemia is usually due to genetic causes (monogenetic or polygenetic) and environmental factors, such as diet and lifestyle, whilst primary non-familial hyperlipidaemia is hyperlipidaemia that is not due to a specific genetic disorder (although there are polygenetic influences). Mixed dyslipidaemia is generally defined as elevated LDL-C and high triglycerides and/or low HDL-C. Finally hypercholesterolaemia, a type of hyperlipidaemia, specifically refers to the presence of high levels of cholesterol, including LDL-C, in the blood.

The risk of a CV event is a composite of modifiable and non-modifiable risk factors. Elevated LDL-C, the primary component of total cholesterol, plays a critical role in atherosclerotic plaque formation, and is the principal modifiable risk factor for CV events.² CVD is a general term that includes CHD, vascular diseases of the brain, and diseases of blood vessels. Atherosclerotic CV events include myocardial infarction (MI) and unstable angina (collectively referred to as CHD), IS and transient ischaemic attacks (TIAs), and peripheral arterial disease.³⁻⁶ FH, a hereditary condition, may lead to life-long markedly elevated LDL-C levels.^{11,12} In addition to elevated LDL-C, other important risk factors for CV events include existing CVD, diabetes mellitus, and CKD.²

Elevated LDL-C: Elevated LDL-C is a principle driver of CV risk.⁷⁻¹⁰ Large-scale, epidemiological studies have demonstrated a direct relationship between LDL-C levels and the rate of new-onset CHD and CHD events, including mortality.^{7,8,10,11} Data from the Munster Heart Study (PROCAM) in Germany, which prospectively followed 4,849 men aged 40 to 65 years for at least 8 years, showed that higher LDL-C was the most important modifiable risk factor for severe coronary events, including MI and cardiac mortality.⁸

Familial hypercholesterolaemia: FH is a hereditary condition caused by various genetic mutations that lead to life-long markedly elevated LDL-C levels resulting in a 20-fold increased lifetime risk for premature CVD.^{12,13} In FH, elevated LDL-C leads to atherosclerotic plaque formation in the coronary arteries and proximal aorta at an early age and, over time, this prolonged exposure to elevated LDL-C renders affected individuals extremely vulnerable to the consequences of severe atherosclerotic disease, such as MI and stroke.¹⁴⁻¹⁶ It is estimated that one in every three patients with FH has CHD.¹⁷ Compared with non-FH hyperlipidaemic patients off lipid-lowering therapy, individuals with FH had 13-fold and 10-

fold higher risks of CHD in relation to being off and on lipid-lowering therapy, respectively (adjusted odds ratios [ORs] off lipid-lowering therapy 13.2, 95% confidence interval [CI] 10.0, 17.4; OR on lipid-lowering therapy 10.3, 95% CI 7.8, 13.8).¹⁷

Diagnosis of FH is typically made based on lipid levels and patient age, as well as family history. Early diagnosis and treatment can improve life expectancy in patients with FH.¹⁸ Unfortunately, many patients with FH are never diagnosed with the condition, and many are diagnosed only after their first CHD event. There are two variants of FH: patients who have inherited the gene for FH from one parent are classified as having HeFH and patients who have inherited the gene from both parents are classified as having HoFH. HoFH is an extremely rare condition affecting approximately 1 in 1 million individuals and is not part of the current appraisal, and so will not be discussed in any further detail.^{12,19,20} LDL-C levels in patients with HeFH are typically 2- to 3-fold higher than normal (approximately 5 to 10 mmol/L).^{21,22} In the UK, HeFH has an estimated prevalence of 1 in 500 people.^{20,23} Based on a population of 56 million in England and Wales as measured in the most recent UK census (2011), this translates to approximately 112,000 affected individuals with HeFH.²⁴

Existing CVD: Data from the multinational REduction of Atherothrombosis for Continued Health (REACH) registry show that patients with a history of an ischaemic event at baseline were at higher risk for ischaemic events (including a composite endpoint of CV-related mortality, MI, and stroke) during the study compared with patients without a history of ischaemic events (HR 1.71; 95% CI 1.57, 1.85; $p < 0.001$).²⁵ Event rates were highest in those who experienced an ischaemic event within 1 year of study enrolment. Thus, one of the strongest predictors of future ischaemic risk is a recent history of ischaemic events.²⁵ Another analysis based on data from the REACH registry showed that significant risk predictors of recurrent CV events and CV mortality in patients with existing CVD include the number of vascular beds affected, occurrence of a CV event in the previous year, HF, and atrial fibrillation.²⁶ Depending on gender and clinical outcome, survivors of an MI have a chance of illness and death that is 1.5 to 15 times higher than the general population. Among men and women 65 years of age or older who survive a first MI, 22% will experience a recurrent MI or fatal CHD event and 5% to 8% will experience a stroke within 5 years of the initial MI.⁴

Diabetes mellitus: Diabetes mellitus is an independent risk factor for CVD and is associated with a higher risk of CVD, particularly in women.² CVD is the major cause of both morbidity and mortality in patients with diabetes.² Data from the National Diabetes Audit show that in 2012 to 2013 in England and Wales, patients with diabetes had a 139% additional risk of unstable angina, 94% additional risk of MI, and 63% additional risk of stroke over a 1-year follow-up period compared with people without diabetes.²⁷ These data also show that in 2013, people with diabetes in England and Wales were 34% more likely to die than people without diabetes.²⁷ Furthermore, in patients with existing CVD, diabetes mellitus significantly increased the risk of further CV events and CV mortality.²⁶

CKD: Decreasing glomerular filtration rate (GFR) is independently associated with CVD, and CKD is widely acknowledged as a CHD-risk equivalent.² It is estimated in NICE guidelines that approximately 7,000 excess strokes and 12,000 excess MIs occurred in individuals with CKD in England in 2009 to 2010 relative to age- and gender-matched controls.²⁸ Most

patients with stage 3 to 5 CKD have mixed dyslipidaemia with a highly atherogenic lipid profile.²

In addition to those risk factors described above, other risk factors for CVD include: ^{2,11,29-34}

- increased age
- male gender
- other markers of hypercholesterolaemia and dyslipidaemia, e.g.
 - elevated levels of total cholesterol, very low-density lipoprotein cholesterol, Lp(a), non-HDL-C (used to estimate the total number of atherogenic particles e.g. LDL-C and very low-density lipoprotein cholesterol in the blood), and ApoB
 - low levels of low HDL-C and apolipoprotein A1 (ApoA1)
 - abnormal ApoB/ApoA1 and total cholesterol/HDL-C ratios
- smoking
- hypertension
- physical inactivity and increased body mass index (BMI)
- family history of CHD

Effects of CVD on patients, carers, and society

CVD is the largest cause of death in the UK.³⁵ Although age-standardised UK mortality rates from CVD have fallen over recent years, the mortality burden associated with CVD remains substantial.³⁶ In the UK, CHD and stroke accounted for the first and third most common causes of premature mortality in 2013, respectively.³⁷ In total, a third of all deaths in the UK in 2013 (approximately 192,000 annually or 500 per day) were estimated to be attributable to CVD, including approximately 99,000 due to CHD and 34,000 due to IS.³⁷ The Department of Health CVD Outcomes Strategy (2013) recognised that England underperforms when compared with similar countries in terms of CV mortality.³⁵ Preventing premature mortality due to CVD therefore remains a national priority area and is a key indicator in the Department of Health's NHS Outcomes Framework (2015-2016) and Public Health Outcomes Framework (2013-2016).^{38,39} With an ageing population and current levels of obesity, without improvements in CV prevention, previous improvements in CV mortality will not be sustained.³⁵

Non-fatal major CV events can lead to serious long-term consequences such as functional disability, impaired HRQoL, and increased risk of subsequent CV events.^{4,40,41} A survey conducted to assess HRQoL of stable patients with CHD showed that HRQoL in patients with CHD is lower than that of the general population, with those having a history of CV events or diabetes experiencing the greatest decrements in HRQoL.⁴¹ Having a history of stroke or experiencing a recurrent CV event were significant predictors of reduced HRQoL.⁴¹ Survivors of CV events may also require support from informal caregivers, which can lead to a detrimental impact on the quality of life of individuals providing such support.⁴²

CVD represents not only a substantial patient burden, but also a considerable direct cost to society that is increasing over time. In 2009, CVD was responsible for 6% (approximately £7 billion) of total healthcare expenditure in the UK, of which CHD accounted for approximately £1.5 billion.⁴³ Two key drivers of this expenditure are hospitalisations and CVD-related procedures (such as revascularisation), representing 54% of direct costs associated with

CVD and 56% of direct costs associated with CHD.⁴³ Per-patient costs associated with CV events (revascularisation, MI, IS, unstable angina, and TIA) are substantial and range from £1,570 to £6,000 in the first 6 months following the event, and up to approximately £1,000 annually thereafter.⁴⁴ Between 2014 and 2020, the total healthcare expenditure on CVD in the UK is estimated to rise from approximately £10 billion per year to approximately £12 billion per year,⁴⁵ underlying the importance of making available new therapeutic options to reduce the incidence and long-term costs of CVD.

Aims of lipid-lowering therapies

The evidence supporting LDL-C as a therapeutic target and surrogate for CV outcomes comes from epidemiological studies, genetic variants (both gain-of-function and loss-of-function), and interventional studies with LDL-C-lowering therapies.^{8,46-59} A meta-analysis of 26 statin trials (169,138 individuals with a median follow-up of 4.9 years) conducted by the CTTC showed that for every 1 mmol/L reduction in LDL-C, the annual risk of major CV events was reduced by 22%, with a continued benefit observed even with low LDL-C levels (< 2.0 mmol/L).⁴⁷ To date, no lower limit for LDL-C reduction and the associated reduction in CV risk has been identified.

Interventions to achieve LDL-C control in patients with elevated LDL-C and in those with high CV risk are prescribed to reduce the risk of CV events. Lowering LDL-C levels through lipid-lowering therapy has been shown to reduce the risk of CV events irrespective of the type of intervention, as noted in NICE technology appraisal (TA) 132.⁶⁰⁻⁶⁴ A log-linear relationship between LDL-C and CV risk exists with the risk of CHD reduced by approximately 1% for every 1% reduction in LDL-C.⁶⁵ This log-linear relationship was independent of the method by which LDL-C was lowered (i.e. by lifestyle modifications, drug treatment, or other therapy).^{60,61} Multiple meta-analyses have demonstrated that LDL-C lowering with non-statin therapies is also associated with reductions in CV events, including CHD mortality.^{63,66-70} A meta-analysis of 58 trials (including 148,321 patients) of lipid-lowering therapies showed that a reduction in LDL-C of 1.0 mmol/L reduced the risk of CHD events by up to 36% over 6 or more years of treatment, regardless of initial CV risk.⁷⁰ Another meta-analysis specifically assessed the relationship between LDL-C and CHD risk using data from 81,859 patients enrolled in nine trials of non-statin treatments (bile acid sequestrants, surgery, and diet) and 10 statin trials over 5 years of treatment. The analysis showed that larger reductions in LDL-C were associated with greater reductions in CHD risk. A one-to-one relationship between LDL-C lowering and CHD and stroke reduction was observed over 5 years of treatment, with no difference between the statin and non-statin trials.⁶³ Results from the large, multinational IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) show that, in patients with a recent history of ACS, ezetimibe added to simvastatin further lowered LDL-C and significantly reduced the occurrence of a composite endpoint of CV death, MI, unstable angina requiring hospitalisation, coronary revascularisation, or stroke compared with statin alone ($p = 0.016$).⁶⁴ IMPROVE-IT further confirms the relationship between LDL-C reduction and the reduction in risk of CV events, and demonstrates the incremental benefit of adding a non-statin lipid-lowering therapy to a statin.

Description and limitations of current treatment options

Management of primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia comprises a combination of lifestyle interventions (e.g. diet modification and weight loss, smoking cessation, and alcohol reduction) and lipid-lowering therapies including statins, ezetimibe, bile acid sequestrants, nicotinic acid, fibrates, and, in exceptional circumstances, LDL apheresis. A list of lipid-lowering therapies licensed for use in the UK and listed on the British National Formulary is provided in Appendix II.

Statins

Statins provide an effective first-line treatment option for lowering LDL-C levels by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, a key mediator in the production of cholesterol in the liver. Statins are considered the cornerstone of therapy to reduce LDL-C levels, and are generally the most frequently used first-line therapy for high-risk patients. Statins can be dosed at different intensities, which offer differing magnitudes of LDL-C reduction (Table 3-1). Recent studies have shown that more intensive statin therapy (and, consequently, greater LDL-C reduction leading to lower LDL-C levels) is more effective at reducing CV events than less intensive statin therapy.⁷¹ However, on average, the maximum dose of high-intensity statin licensed in the UK achieves a maximal LDL-C reduction of up to 55% (Table 3-1). Moreover, the bulk of LDL-C reduction occurs with the initial selected statin dose;^{72,73} doubling the statin dose results in only a 6% incremental reduction in LDL-C levels on average.^{70,74-76}

Table 3-1 Grouping of statins by intensity of LDL-C reduction based on NICE clinical guideline 181 (Lipid modification: cardiovascular risk assessment and modification of blood lipids for the primary and secondary prevention of cardiovascular disease)

Statin	Total percent reduction in LDL-C				
Dose (mg/day)	5	10	20	40	80
Fluvastatin	–	–	21% ^a	27% ^a	33% ^b
Pravastatin	–	20% ^a	24% ^a	29% ^a	–
Simvastatin	–	27% ^a	32% ^b	37% ^b	42% ^{c,d}
Atorvastatin	–	37% ^b	43% ^c	49% ^c	55% ^c
Rosuvastatin	38% ^b	43% ^c	48% ^c	53% ^c	–

References: NICE, 2014⁷⁷ Appendix A: Grouping of statins.

Note: Percent reductions are total reductions for each statin agent and dose; reductions are not additive when statin doses are increased.

^a20% to 30%: low intensity. ^b31% to 40%: medium intensity. ^cAbove 40%: high intensity. ^dAdvice from the MHRA: there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80 mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of CV complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MHRA, Medicines and Healthcare Products Regulatory Agency; NICE, National Institute for Health and Care Excellence

Further, a subset of patients with hypercholesterolaemia (approximately 10% to 20%) is statin intolerant and develop signs or symptoms associated with statin use, including muscle-related symptoms (e.g. myalgia) that can lead to partial or complete intolerability.⁷⁸ Statin dose titration will often be accompanied by an increase in these muscle-related adverse events.⁷² Such adverse events could lead to treatment discontinuation or dose reduction, thereby limiting the ability of statins to lower LDL-C and prevent major CV events.⁷⁹ Statins also have well-documented drug-drug interactions, and thus in patients receiving certain medications (e.g. fibrates and cyclosporine), statin use may be contraindicated or not clinically appropriate.⁸⁰⁻⁸²

Ezetimibe

Ezetimibe selectively blocks cholesterol absorption in the intestine, and is licensed for use in combination with statins for patients with total cholesterol or LDL-C not adequately controlled by statins alone at their maximally-tolerated dose. The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE), and IMPROVE-IT studies demonstrated significant reductions in LDL-C levels with statin plus ezetimibe combination therapy compared with a statin alone.^{64,83} However, these incremental reductions are modest (e.g. 17% in the ENHANCE study)⁸³ and are accompanied by a correspondingly modest reduction in CV events as shown in the IMPROVE-IT study in which the 7-year composite CV event rate primary endpoint for ezetimibe/statin versus statin monotherapy was 0.94 ($p = 0.016$).⁶⁴ Ezetimibe is also licensed for use as a monotherapy in patients for whom statins are not tolerated or contraindicated, but offers similar modest reductions in LDL-C (17% to 22%).⁸⁴

Additional pharmacological lipid-lowering therapies

Additional lipid-lowering therapies (bile acid sequestrants, fibrates, and nicotinic acid) are also available alone or in combination with statins, but are similarly associated with highly limited LDL-C reductions, as well as various adverse effects (Table 3-2).

Table 3-2 Details of additional lipid-lowering therapies

Lipid-lowering therapy	Percent reduction in LDL-C	Adverse effects
Bile acid sequestrants ²	18% to 25%	GI distress, constipation, decreased absorption of other drugs
Fibrates ⁸⁵	5% to 20% ^a	Dyspepsia, gallstones, myopathy, unexplained non-CHD deaths in WHO study
Nicotinic acid ²	15% to 18%	Flushing, hyperglycaemia, hyperuricaemia (or gout), upper GI distress, hepatotoxicity
^a Effect may be increased in patients with elevated triglycerides.		
CHD, coronary heart disease; GI, gastrointestinal; LDL-C, low-density lipoprotein cholesterol; WHO, World Health Organization		

LDL apheresis

LDL apheresis is a regular process similar to haemodialysis that involves extracting LDL-C from circulating blood over a period of 2 to 4 hours. In some exceptional cases, patients with severe HeFH (Table 3-3) may require apheresis, although this does not offer a long-term solution for patients because the reduction in LDL-C is transient, and LDL-C begins to reaccumulate after each apheresis session. Additionally, apheresis costs are substantial, with an estimated annual cost of between £26,000 to £62,000 for treatment every 1 to 2 weeks (based on a cost of £1,000 to £1,200 per session^{78,79}), and the treatment is performed at hospitals or specialised centres (of which there are only 6 in England and Wales) due to the type and cost of equipment required. Apheresis is also burdensome for patients, and often requires extended travel time due to the limited number of centres, in addition to the long duration of the procedure, which requires substantial time away from work and social activities.^{21,86,87} 'Market research data showed that patients undergoing apheresis felt that an effective new therapy that would avoid or reduce the need for apheresis would improve their QoL.⁸⁸

Unmet need in LDL-C reduction

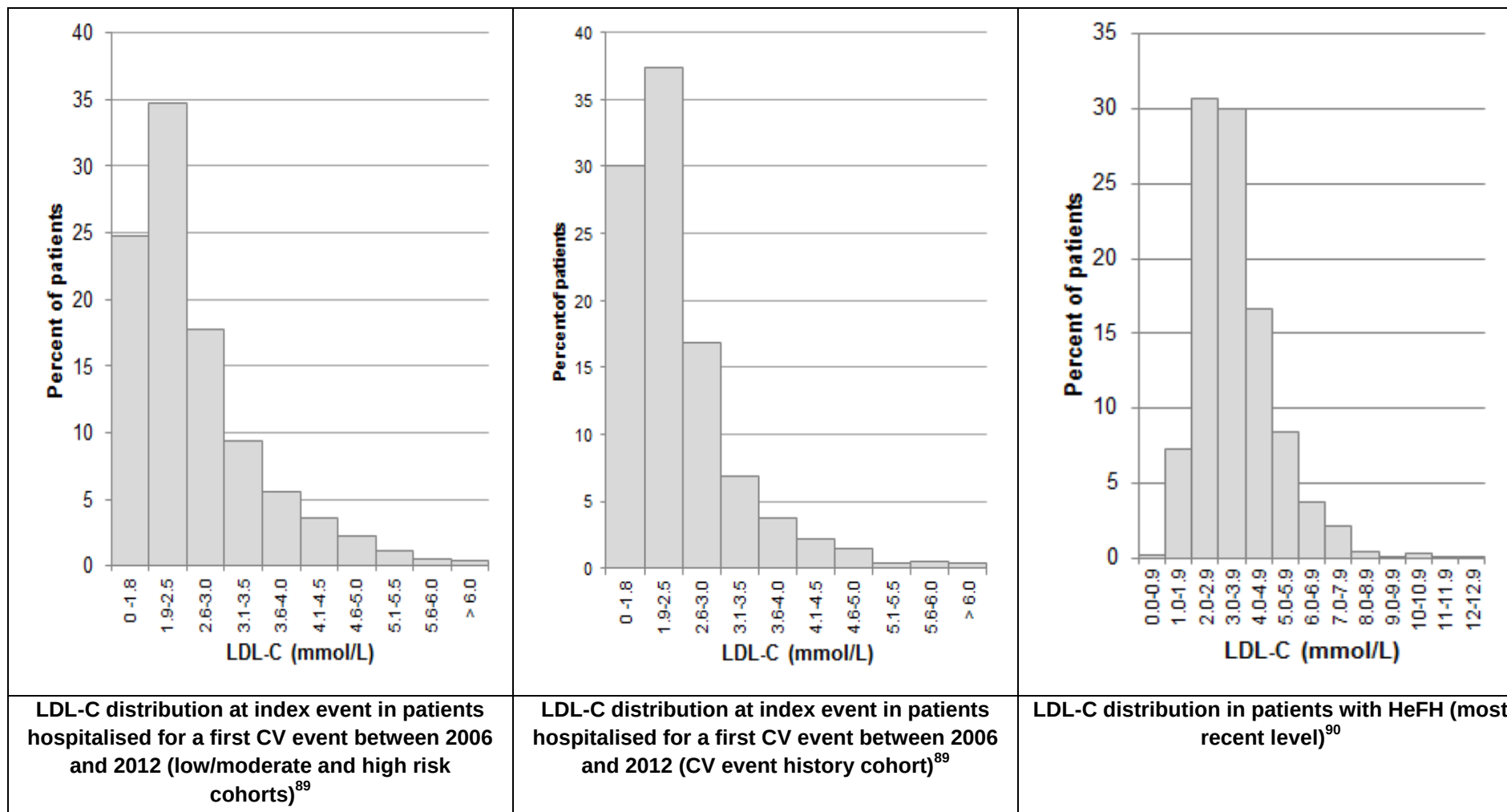
Data from a retrospective study of over 20,000 patients in the CPRD hospitalised for a first CV event between 2006 and 2012 were used to assess LDL-C distribution patterns.⁸⁹ The study population consisted of a cohort of patients who were alive and observable in both the CPRD and hospital episode statistics (HES) data as of January 1, 2005, and were hospitalised for a first CV event between January 2006 and March 2012 (end of HES observation period) i.e. all patients had a CV event at the study index date. Patient cohorts were retrospectively classified as CV low/moderate risk, CV high risk, and CV event history. In patients across the low/moderate and high risk cohorts, 23% of patients treated with high-intensity statins ($\pm$ other lipid-lowering therapies) had LDL-C levels > 3.0 mmol/L at the time of the index event, despite their lipid-lowering therapy. Similarly, 17% of patients in the CV event history cohort treated with high-intensity statins ($\pm$ other lipid-lowering therapies) had LDL-C levels > 3.0 mmol/L at the time of the index event, despite their lipid-lowering therapy.

Further, data from the National Audit of Familial Hypercholesterolaemia show that 62% of patients with diagnosed HeFH in the UK have elevated LDL-C levels > 3.0 mmol/L (median 3.3 mmol/L, minimum 0.8 mmol/L to maximum 12.7 mmol/L), despite wide availability of lipid-lowering therapies.⁹⁰

An overview of LDL-C distribution patterns in patients based on the UK CPRD study and data from the National Audit of Familial Hypercholesterolaemia described above is provided in Figure 3-1.

Existing treatment options adequately reduce LDL-C levels in most patients; however, there remains a cohort of high-risk patients (e.g. patients with non-familial hypercholesterolaemia at high residual risk due to presence of additional risk factors, and patients with HeFH) for whom existing treatment options are inadequate and who remain particularly vulnerable to CV events. These patients have a substantial unmet medical need.

Figure 3-1 LDL-C distribution patterns in the UK



Note: Estimates for LDL-C levels in HeFH adapted from National Audit of Familial Hypercholesterolaemia National Report 2010.⁹⁰

CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol

Summary of clinical guidelines, guidance and the UK treatment pathway

NICE CG and TA guidance

Seven current NICE CGs and one TA providing guidance on lipid modification therapy for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia were identified (Appendix II). CG181, CG71, and TA132 are most relevant to this appraisal (because all others refer to, or are superseded by, this guidance):

- CG181 provides specific recommendations on lipid-lowering therapy for the primary and secondary prevention of CVD.⁷⁷
- CG71 provides specific recommendations on management of patients with HeFH, including lipid-lowering therapy.⁹¹
- TA132 provides guidance about the use of ezetimibe for the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial).⁶²

An overview of the UK treatment pathway based on these guidelines and TA guidance is provided in Figure 3-2, with detailed recommendations provided in Table 3-3.

Primary prevention: CG181 recommends use of a risk assessment tool (QRESEARCH Cardiovascular Risk Algorithm; QRISK2) to assess CVD risk in patients up to and including age 84 years for primary prevention. Atorvastatin 20 mg is recommended for patients who have a $\geq 10\%$ 10-year risk of developing CVD assessed using the QRISK2 assessment tool. A risk assessment tool should not be used in patients with type 1 diabetes mellitus or CKD (eGFR < 60 mL/min/1.73 m² and/or albuminuria).

Secondary prevention: CG181 specifies that a risk assessment tool should not be used in patients with existing CVD. When lipid-lowering therapy is required, high-intensity statin therapy (e.g. atorvastatin 80 mg) is the recommended first-line treatment.

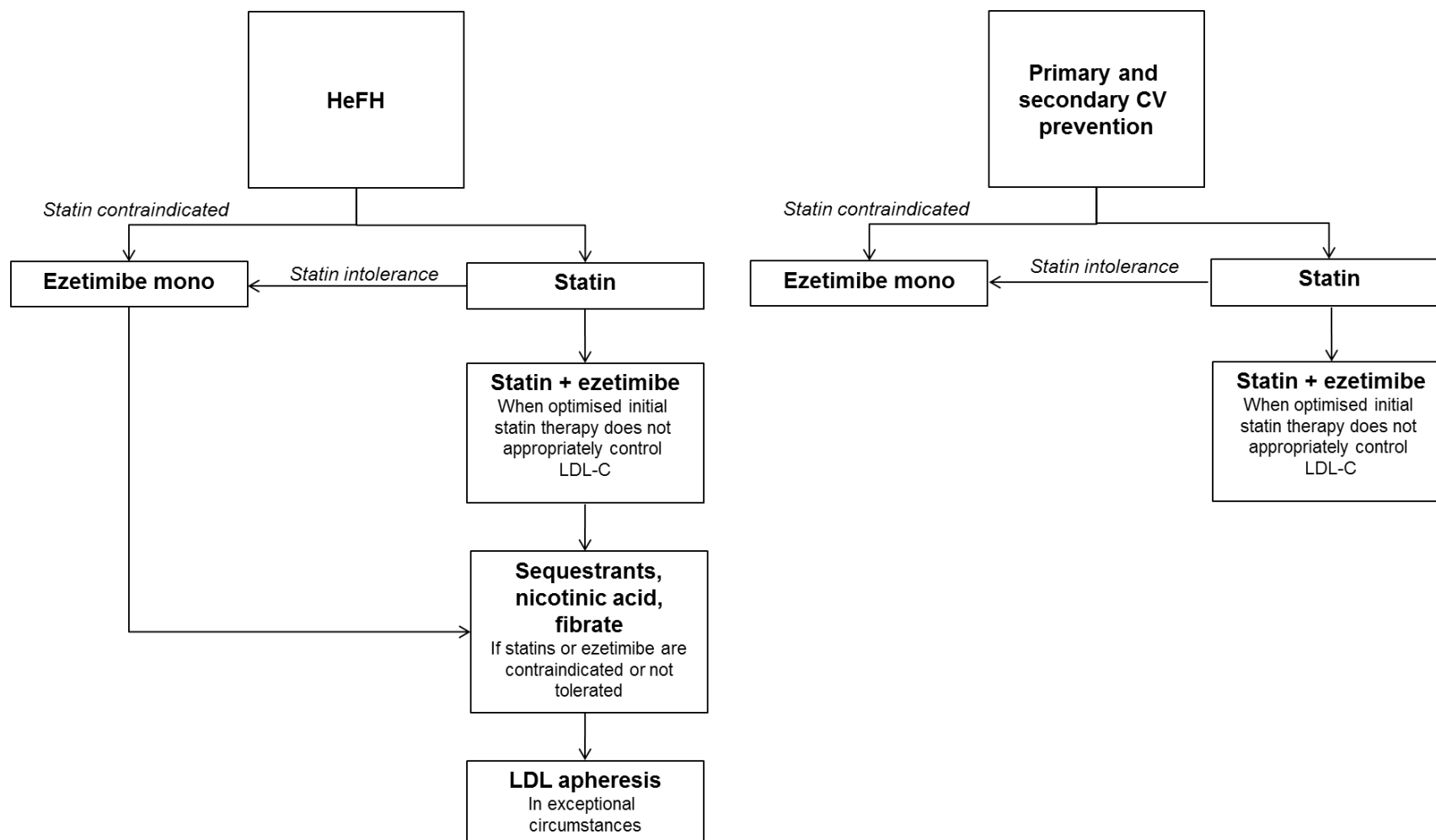
Familial hypercholesterolaemia: CG71 specifies that risk estimation tools should not be used given this patient population is already at high risk of premature CVD. Therefore, appropriate control of cholesterol should be based on individualised risk assessment by a clinician. Lipid-lowering therapy is recommended with high-intensity statins as a first-line treatment. Patients with FH are deemed very high risk if they have established CHD, a family history of CHD or two or more other CV risk factors (e.g. male gender, current smoker, hypertension, and diabetes).

Statin intolerance: CG71 and TA132 define statin intolerance as the presence of clinically significant adverse effects (e.g. myalgia or alterations of liver function tests) that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. CG181 specifies that statin intolerance should be defined clinically as the inability to tolerate any dose of three different statins.⁹²

Ezetimibe and other lipid-modifying therapies: TA132 provides guidance recommending ezetimibe as an option in patients (familial and non-familial hypercholesterolaemia) achieving inadequate LDL-C reduction with statins. Ezetimibe is recommended for use as combination treatment with statins, or monotherapy in patients with contraindications or intolerance to statins. CG71 recommends that patients with HeFH may further receive

alternative lipid-lowering therapies (bile acid sequestrants, nicotinic acid, and fibrates) as later line treatment options and, in exceptional circumstances, LDL apheresis.

Figure 3-2 Summary of current UK clinical pathway of care for lipid-lowering therapy for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia based on NICE clinical guidelines and technology appraisal guidance



CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; mono, monotherapy; NICE, National Institute for Health and Care Excellence

Table 3-3 Summary of the most relevant NICE clinical guidelines and technology appraisal guidance on lipid modification therapy for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia

Selected relevant clinical guideline recommendations and technology appraisal guidance
NICE CG181, July 2014. Lipid modification: cardiovascular risk assessment and modification of blood lipids for the primary and secondary prevention of cardiovascular disease⁷⁷ <u>Primary prevention</u> • Use the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years • Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a $\geq 10\%$ 10-year risk of developing CVD assessed using the QRISK2 assessment tool <u>Secondary prevention</u> • Do not use a risk assessment tool for patients with pre-existing CVD • Start statin treatment in patients with CVD with atorvastatin 80 mg • Use a lower dose of atorvastatin if any of the following apply: potential drug interactions, high risk of adverse events, or patient preference <u>Type 1 or type 2 diabetes and CKD</u> • Do not use a risk assessment tool to assess CVD risk in patients with type 1 diabetes or patients with an $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ and/or albuminuria • Consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes; start treatment for adults with type 1 diabetes with atorvastatin 20 mg • Offer atorvastatin 20 mg for the primary prevention of CVD to patients with diabetes mellitus type 2 who have a $\geq 10\%$ 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool • Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to patients with CKD <u>Follow-up of people receiving statin treatment</u> • Measure total cholesterol, HDL-C, and non-HDL-C in all patients who have started high-intensity statin treatment at 3 months of treatment and aim for a greater than 40% reduction in non-HDL-C. If a $> 40\%$ reduction in non-HDL-C is not achieved: discuss adherence and timing of dose, optimise adherence to diet and lifestyle measures, consider increasing dose if started with less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score, or using clinical judgement <u>Other lipid-modifying therapies</u> • Do not routinely offer fibrates, nicotinic acid, or bile acid sequestrants, alone or in combination with statins for the prevention of CVD to any of the following: patients who are being treated for primary prevention, patients who are being treated for secondary prevention, patients with CKD, patients with type 1

Selected relevant clinical guideline recommendations and technology appraisal guidance
diabetes, and patients with type 2 diabetes • Patients with primary hypercholesterolaemia should be considered for treatment with ezetimibe in line with NICE TA132 (see below)
NICE CG71, August 2008. Identification and management of familial hypercholesterolaemia ⁹¹
<u>Risk assessment</u> • CHD risk estimation tools such as those based on the Framingham algorithm should not be used because patients with FH are already at a high risk of premature coronary heart disease <u>Statins</u> • Statins should be the initial treatment for all adults with FH • Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of > 50% from baseline (that is, LDL-C concentration before treatment) • The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of > 50% from baseline (that is, LDL-C concentration before treatment) <u>Ezetimibe</u> • Recommendations for use in this population in line with NICE TA132 (see below) <u>Other lipid-modifying therapies</u> • Adults with FH and intolerance to or contraindications for statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration of treatment with either a bile acid sequestrant (resin), nicotinic acid, or a fibrate to reduce their LDL-C concentration <u>LDL apheresis</u> • In exceptional instances (such as when there is progressive, symptomatic CHD despite maximally-tolerated lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of patients with HeFH
NICE TA132 guidance, November 2007. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial hypercholesterolaemia)⁶²
• Ezetimibe monotherapy is recommended as an option for the treatment of adults with primary hypercholesterolaemia (heterozygous familial or non-familial) who: ▪ would otherwise be initiated on statin therapy, but who are unable to do so because of contraindications to initial statin therapy; OR ▪ are intolerant to statin therapy^a • Ezetimibe is recommended as an option in combination with statin therapy for patients initiated on statin therapy in whom: ▪ serum total or LDL-C concentration is not appropriately controlled^b after dose titration of statin therapy or due to statin intolerance^a; AND

Selected relevant clinical guideline recommendations and technology appraisal guidance
▪when consideration is being given to changing from the initial statin therapy to an alternative statin
^aStatin intolerance is defined as presence of clinically significant adverse effects (e.g. new-onset muscle pain, significant GI disturbance or alterations of liver function tests) from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. ^bAppropriate control of LDL-C based on individualised risk assessment in accordance with national guidance. CG, clinical guideline; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; QRISK2, QRESEARCH Cardiovascular Risk Algorithm; TA, technology appraisal

Additional UK relevant guidelines

Other available relevant UK guidelines and recommendations published by the Scottish Intercollegiate Guidelines Network, Joint British Societies, and HEART-UK LDL Apheresis Working Group are generally consistent with the guidance issued by NICE with respect to use of statins as a cornerstone lipid-lowering therapy for prevention of CVD in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. There are some minor differences with respect to definition patient populations requiring lipid-lowering therapy, and recommendations about specific lipid-lowering therapies. See Appendix II for further details.

ESC and EAS Guidelines

The ESC and EAS issued guidelines for the management of dyslipidaemias in 2011.² These guidelines recommend the assessment of total CVD risk and stratify patients into 4 risk groups (low, moderate, high and very high) based on clinical characteristics (Table 3-4). Patients classified as very high risk and high risk include those with existing CVD, diabetes mellitus (all type 2 and type 1 patients with target organ damage), moderate to severe CKD, and markedly increased individual risk factors such as familial dyslipidaemias. Patients with a 10-year risk of fatal CV events using the Systemic Coronary Risk Estimation (SCORE) above defined thresholds are also considered very high risk ($\geq 5\%$) and high risk ($\geq 5\%$ and $< 10\%$). The ESC/EAS guidelines recognise that patients at very high risk and high risk should receive immediate drug intervention when LDL-C levels are > 1.8 mmol/L and > 2.5 mmol/L, respectively.

Table 3-4 ESC/EAS risk categories

ESC/EAS risk level	Characteristics
Very high risk	• Documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous MI, ACS, coronary revascularisation (PCI or CABG) and other arterial revascularisation procedures, ischaemic stroke, PAD • Patients with type 2 diabetes mellitus and patients with type 1 diabetes mellitus with target organ damage (such as microalbuminuria) • Patients with moderate to severe CKD (eGFR < 60 mL/min/1.73 m²) • A calculated 10-year risk SCORE $\geq 10\%$ for fatal CVD
High risk	• Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension • A calculated SCORE $\geq 5\%$ and $< 10\%$ for 10-year risk for fatal CVD
Moderate risk	• Subjects are considered to be at moderate risk when their SCORE is $\geq 1\%$ and, $< 5\%$ over 10 years. • Many middle-aged subjects belong to this risk category. • This risk is further modulated by a family history of premature CAD, abdominal obesity, physical activity pattern, HDL-C, TG, hsCRP, Lp(a), fibrinogen, homocysteine, ApoB, and social class
Low risk	• The low risk category applies to individuals with SCORE $< 1\%$
References: ESC/EAS guidelines for the management of dyslipidaemias 2011 ²	

ESC/EAS risk level	Characteristics
ACS, acute coronary syndrome; ApoB, apolipoprotein B; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; eGFR, glomerular filtration rate; ESC, European Society of Cardiology; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a); MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SCORE, Systemic COronary Risk Estimation; TG, triglycerides	

Issues relating to current clinical practice, including any variations or uncertainty about established practice

As described earlier in this section, CV risk is a composite of modifiable and non-modifiable risk factors. Consequently, all current CGs for the prevention of CVD recommend the assessment of total CV risk (e.g. using QRISK2 or SCORE) in clinical practice. Patients with existing CVD are routinely deemed to be at high risk, and therefore undergo closer clinical management to reduce the risk of a recurrent CV event. In the UK, NICE guidelines recommend that CVD risk assessment tools should not be used in patients with existing CVD, as well as those with other clinical conditions which are routinely deemed to place patients at high CV risk (e.g. diabetes mellitus, CKD and FH). This approach is consistent with the ESC/EAS guidelines where patients with existing CVD, diabetes mellitus or moderate to severe CKD are automatically deemed to be very high risk (Table 3-4). Furthermore, risk predictions models are not generally used by clinicians to support their overall assessment of CV risk. Therefore, absolute CV risks (e.g. 10-year risk of > X% of a recurrent fatal or non-fatal CV event) are not used as a starting rule for the management of hypercholesterolaemia with lipid-lowering therapies in these specific populations. Instead, high-risk patients, for example, those with existing CVD and in whom LDL-C levels remain unacceptably high are managed closely to optimise lipid profiles given the contribution of hypercholesterolaemia to overall CV risk. This is an important consideration for the clinical- and cost-effectiveness assessment of evolocumab within its anticipated MA in patients with existing CVD or HeFH for the purposes of this appraisal.

Proposed positioning of evolocumab within the treatment pathway and patient populations

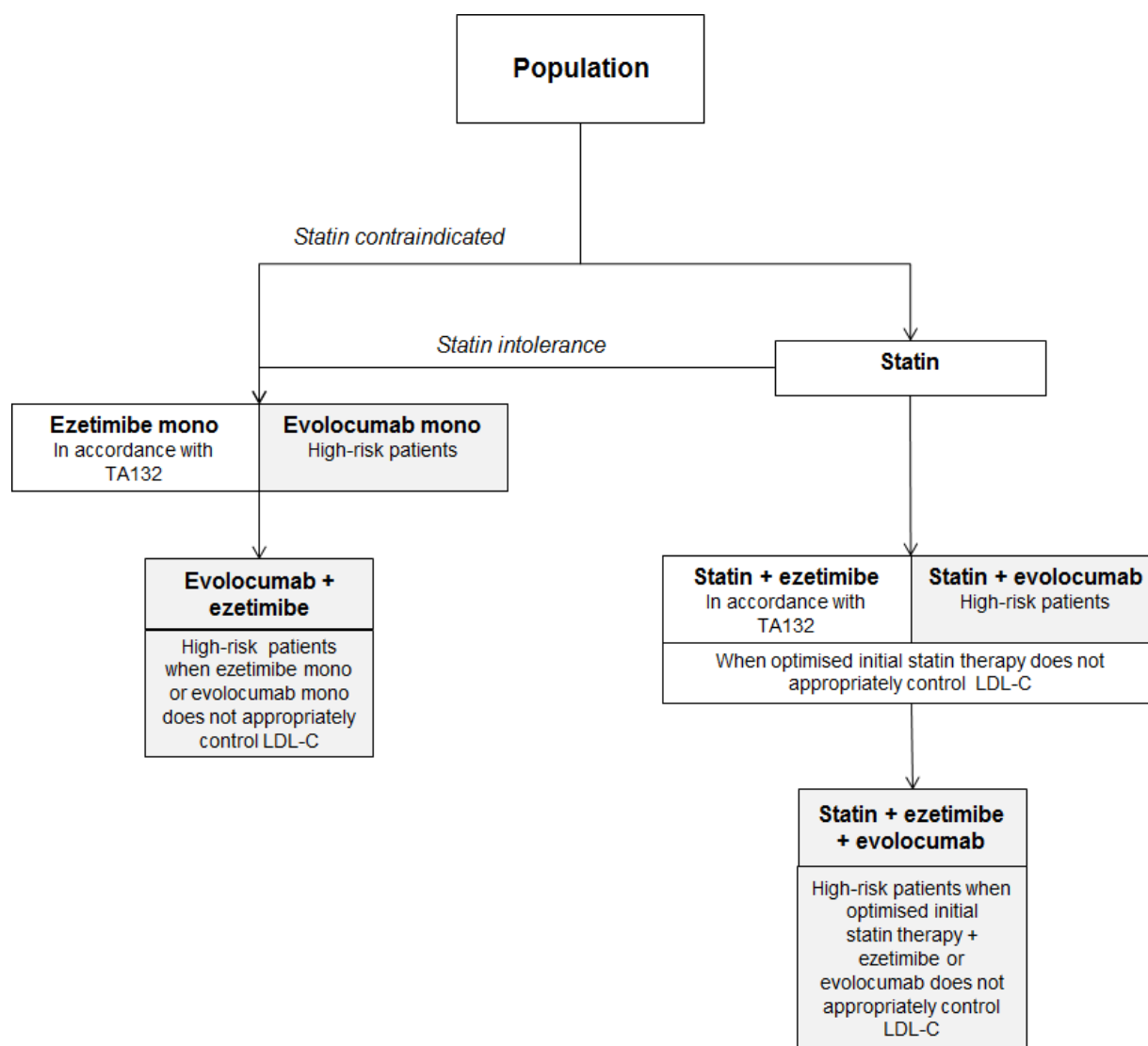
Although evolocumab would be beneficial for many patients whose LDL-C remains inadequately controlled by maximally-tolerated doses of statins or who are statin intolerant/contraindicated (per its anticipated MA), the priority for use of evolocumab is in those patients who are at the highest residual risk and are most vulnerable to CV events, where evolocumab represents both a clinically- and cost-effective treatment option for the NHS. These include:

- Patients without existing CVD but at high residual risk due to additional risk factors (based on QRISK2 score)
- Patients with existing CVD at high residual risk due to additional risk factors (e.g. diabetes mellitus or CKD)
- Patients with HeFH

The subgroup of patients that is contraindicated or intolerant to statins is considered within these patient populations.

A summary of the proposed place in the treatment pathway for evolocumab in these populations is provided in Figure 3-3.

Figure 3-3 Proposed place of evolocumab in the treatment pathway



LDL-C, low-density lipoprotein cholesterol; mono, monotherapy; TA, technology appraisal

Overview of positioning of evolocumab in patients without existing CVD but at high residual risk

QRISK2 is recommended by NICE as a risk assessment tool for patients without existing CVD who are ≤ 84 years of age (Table 3-3). It is recognised that NICE CG181 does not recommend risk assessment for patients without existing CVD but with type 1 diabetes or CKD (eGFR < 60 mL/min/1.73 m² and/or albuminuria) before initiating treatment with statins.

It is proposed that evolocumab is positioned as a treatment option for patients without existing CVD but at high residual risk due to additional risk factors (based on QRISK2 score) according to severity of hypercholesterolaemia.

Overview of positioning of evolocumab in patients with existing CVD at high residual risk due to additional risk factors

NICE CG181 recommends that a risk assessment tool should not be used in patients with existing CVD. Further, currently-available risk scores (e.g. QRISK2 and SCORE) are not intended for use in patients with existing CVD. Therefore, in order to identify patients with existing CVD at high residual risk due to additional risk factors, various sources of evidence were assessed:

- ESC/EAS 2011 guidelines for the management of dyslipidaemias
- a targeted literature review of recurrent CVD risk equations
- consultation with UK clinicians

ESC/EAS guidelines: The ESC/EAS guidelines classify patients with existing CVD, patients with diabetes mellitus, patients with moderate to severe CKD, and patients with a calculated 10-year risk SCORE for fatal CVD $\geq 10\%$, as being at 'very high' CV risk (Table 3-4). It is reasonable to assume therefore that patients with existing CVD and either moderate to severe CKD or diabetes mellitus will be at high residual risk of future events. The 10-year risk SCORE is not intended for use in patients with existing CVD, and risk estimation is not recommended for patients with existing CVD in NICE CGs (e.g. CG181), so 10-year risk SCORE $\geq 10\%$ was discounted as a relevant patient characteristic for defining patients with existing CVD at high residual risk.

Risk equations for recurrent events: Of the four risk equation publications identified,^{26,93-95} a publication based on the REACH registry was deemed to be the most relevant as it assessed CV risk using a broad definition of CV events.²⁶ Data from the REACH registry highlighted several additional patient characteristics that were significant predictors of recurrent CV events (both fatal and non-fatal) including age, male gender, diabetes mellitus, number of vascular beds affected, atrial fibrillation, and congestive HF. Other factors were also found to significantly impact risk of recurrent CV events, but were either modifiable patient characteristics (current smoker and BMI < 20 kg/m²) or not clinical patient characteristics (statin use, aspirin use, geographic location) and were consequently discounted as relevant characteristics for defining patients with existing CVD at high residual risk.

Expert UK clinical opinion: UK clinical experts were used to validate the risk factors assessed as being relevant for identifying patients with existing CVD at high residual risk based on ESC/EAS guidelines and data from the REACH registry. In addition, this expert opinion suggested that presence of progressive CVD (evidenced by two or more documented acute ischaemic CV events or revascularisation procedures) is a highly clinically relevant risk factor and should be used as an additional characteristic to define patients with existing CVD at high residual risk. Clinicians suggested that patients with progressive CVD had a risk of recurrent events equivalent to or greater than the risk associated with presence of diabetes mellitus. Further, clinicians highlighted the importance of high levels of Lp(a) as a relevant identifier of patients with existing CVD at high residual risk, though no threshold was specified by the clinicians. A ESC/EAS current opinion publication relating to Lp(a) as a CV risk factor³⁴ highlights the Copenhagen City Heart Study, which showed that multifactorially adjusted HRs for MI for elevated Lp(a) levels were as high as 1.9 (95% CI 1.2, 3.0) for the 90th–95th centile (77–117 mg/dL), and 2.6 (95% CI 1.6, 4.1) for levels > 95th centile (> 117 mg/dL), respectively, versus levels < 22nd centile (trend $p < 0.001$).^{96,97}

A summary of patient characteristics relevant for identifying patients with existing CVD at high residual risk due to additional risk factors is provided in Table 3-5.

Table 3-5 Patient characteristics relevant for identifying patients with existing CVD at high residual risk due to additional risk factors

Source	Risk factor
ESC/EAS guidelines for the management of dyslipidaemias 2011 ² <i>Patients classified as very high risk</i>	• Patients with type 2 diabetes mellitus and patients with type 1 diabetes mellitus with target organ damage (such as microalbuminuria) • Patients with moderate to severe CKD (eGFR < 60 mL/min/1.73 m²)
REACH registry ²⁶ <i>Risk factors for recurrent CV events^a</i>	• Age (years) • Male gender • Diabetes mellitus • 2 or 3 vascular beds affected (1 referrent) • CV^a event in previous year • Congestive heart failure • Atrial fibrillation
Expert UK clinical opinion <i>Additional clinically relevant risk factors for recurrent CV events</i>	• ≥ 2 documented acute ischaemic CV events or revascularisation procedures • High Lp(a)
^a MI, cerebrovascular disease, or CV mortality. CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; Lp(a), lipoprotein (a); MI, myocardial infarction	

Overview of positioning of evolocumab in patients with HeFH

It is proposed that evolocumab is positioned as a treatment option in all patients with HeFH given that these patients have lifelong exposure to elevated LDL-C which renders affected individuals extremely vulnerable to the consequences of severe atherosclerotic disease, such as MI and stroke (Section 3).

Detailed positioning of evolocumab in high-risk patients

Based on the above, and where evolocumab is both clinically- and cost-effective, it is proposed that evolocumab is positioned as a treatment option specifically in the following patient populations at high CV risk as described below:

1. Adults with primary hypercholesterolaemia (non-familial) or mixed dyslipidaemia without existing CVD but at high residual risk due to additional risk factors (based on QRISK2 score) according to severity of hypercholesterolaemia
2. Adults with primary hypercholesterolaemia (non-familial) or mixed dyslipidaemia <u>and existing CVD</u> with: • LDL cholesterol ≥ 3.5 mmol/L (or equivalent non-HDL-cholesterol ≥ 4.3 mmol/L) and at high residual risk due to the presence of one or more of the following: ▪ Diabetes mellitus ▪ Moderate to severe chronic kidney disease (eGFR $< 60\text{mL/min/1.73m}^2$) ▪ ACS in the past year ▪ Progressive CVD evidenced by ≥ 2 documented acute ischaemic CV events or revascularisation procedures ▪ 3 vascular beds affected ▪ Elevated plasma Lp(a) ≥ 77 mg/dL ($\geq 90\%$ centile) ▪ Other CV conditions that significantly elevate risk of further CV events: atrial fibrillation • LDL cholesterol ≥ 3.0 mmol/L (or equivalent non-HDL-cholesterol ≥ 3.8 mmol/L) and at high residual risk due to the presence of <u>two</u> or more of the following: ▪ Diabetes mellitus ▪ Moderate to severe chronic kidney disease (eGFR $< 60\text{mL/min/1.73m}^2$) ▪ ACS in the past year ▪ Progressive CVD evidenced by ≥ 2 documented acute ischaemic CV events or revascularisation procedures ▪ ≥ 2 vascular beds affected ▪ Elevated plasma Lp(a) ≥ 77 mg/dL ($\geq 90\%$ centile) ▪ Other CV conditions that significantly elevate risk of further CV events: heart failure and atrial fibrillation Age and gender should also be taken into consideration.
3. Adults with heterozygous familial hypercholesterolaemia

Life expectancy of patients with the disease

Although there are no specific data on absolute life expectancy of patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia, the key consequence of this condition (i.e. CVD) leads to substantial premature mortality. In England and Wales in 2012, more than 35,000 premature deaths (deaths in people < 75 years of age) were caused by CVD, of which approximately 20,000 were caused by CHD.⁹⁸ It is estimated that the typical CV event shortens a person's life by 17 years.⁹⁹

4 Clinical effectiveness

- A SLR identified four high quality (low risk of bias) relevant RCTs, involving the treatment of almost 3,500 patients and representing a robust evaluation of evolocumab versus ezetimibe and versus placebo in relevant patient populations.
- In these four RCTs, evolocumab 140 mg Q2W and 420 mg QM provided clinically-equivalent, consistent and intensive reductions of up to approximately 72% compared with placebo and up to approximately 46% compared with ezetimibe, in addition to any background lipid-lowering therapies patients were receiving (e.g. statins).
 - Evolocumab reduced LDL-C by an additional 69.1% to 71.8% relative to placebo and 43.3% to 45.5% relative to ezetimibe at the mean of weeks 10/12 in LAPLACE-2 (patients with primary hypercholesterolaemia and mixed dyslipidaemia receiving background moderate- to high-intensity statin therapy).
 - Evolocumab reduced LDL-C by an additional 61.3% to 66.2% relative to placebo at the mean of weeks 10/12 in RUTHERFORD-2 (patients with HeFH receiving stable background lipid-lowering therapy [statin ± other lipid lowering therapies]).
 - Evolocumab reduced LDL-C by an additional 38.1% to 39.2% relative to ezetimibe at the mean of weeks 10/12 in GAUSS-2 (patients with primary hypercholesterolaemia and mixed dyslipidaemia with statin intolerance).
 - Evolocumab reduced LDL-C by an additional 59.3% relative to placebo at week 52 weeks in DESCARTES (patients with primary hypercholesterolaemia and mixed dyslipidaemia receiving stable background lipid-lowering therapy).
- Pre-specified and post-hoc subgroup analyses show that these reductions in LDL-C are consistent across patient subgroups, including subgroups according to presence or risk of CVD and severity of hypercholesterolaemia.
- Evolocumab was also superior to placebo and to ezetimibe in improving other lipid parameters, including non-HDL-C, ApoB, and Lp(a).
- Supplementary evidence from ongoing, long-term extension studies (OSLER and OSLER-2) show that reductions in LDL-C are maintained for more than 2 years.
- Analyses of the safety and tolerability data from the evolocumab studies show that evolocumab has a favourable safety and tolerability profile. In an integrated safety analysis (of 6,026 patients, representing 7,235 patient-years of exposure), as well as across populations and therapeutic settings in individual studies, adverse events were overall balanced between treatment groups. Most adverse events were mild to moderate in severity, with serious adverse events and adverse events leading to treatment discontinuation infrequently reported and generally similar across treatment groups.
- The type and incidence of adverse events observed in patients with LDL-C concentrations < 0.6 mmol/L and < 1.0 mmol/L were generally similar to those observed in patients with LDL-C concentrations ≥ 1.0 mmol/L.
- Anti-evolocumab antibodies were infrequent, non-neutralising, and not associated with clinically relevant adverse events.

- An exploratory safety analysis of recent data from the integrated long-term extension studies showed a significant 53% reduction in 1-year adjudicated CV event rates from 2.18% in the SoC group to 0.95% in the evolocumab plus SoC group (HR: 0.47, $p = 0.003$). This is in the direction, and of the magnitude, that would be expected given the magnitude of LDL-C lowering associated with evolocumab.
- The robust and long-term effects of evolocumab on LDL-C and other lipids, combined with its favourable safety and tolerability profile, demonstrate that evolocumab represents a significant medical advance, and a revolutionary step-change in the management of primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. Evolocumab will, for the first time, enable clinicians to provide high-risk patients who would otherwise remain vulnerable to CV events (because of inadequate LDL-C reduction with existing therapies) with consistent and intensive LDL-C reductions to reduce their risk of major CV events.

4.1 Identification and selection of relevant studies

A broad SLR was conducted to identify and summarise evidence available from RCTs reporting on the efficacy and safety of evolocumab and a range of other lipid-lowering therapies for the management of primary hypercholesterolaemia (familial and non-familial). Additional exclusion criteria were applied to this broad review to further align the results with the decision problem outlined in the appraisal scope, and to identify studies most relevant for inclusion in this submission, as detailed below.

Search strategy

Search strategies were developed for the review specifically for each database and the keywords adapted according to the configuration of each database. Searches were not limited by date, language, or publication status (published, unpublished, in press, and in progress).

The following databases were searched for relevant studies from inception to March 2015:

- MEDLINE (OvidSP): 1946 to March 2015 Week 2
- MEDLINE In-Process Citations & Daily Update (OvidSP): up to 13 March 2015
- EMBASE (OvidSP): 1974 to 13 March 2015
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 3/March 2015
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 2/February 2015
- Database of Abstracts of Reviews of Effects (DARE) (Wiley): Issue 1/January 2015
- HTA Database (Wiley): Issue 1/January 2015.

Where appropriate, objectively-derived methodological filters were included to restrict the searches to RCTs and limit the searches to studies in humans.

Supplementary searches were undertaken for the following trials registers from inception to March 2015:

- NIH ClinicalTrials.gov (<http://www.clinicaltrials.gov/>): up to 17 March 2015

- Current Controlled Trials (mRCT) (<http://www.controlled-trials.com/>): up to 6 October 2014 (this resource ceased being available during 2014)
- PharmNetBund (<http://pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm>): up to 17 March 2015
- EU Clinical Trials Register (EUCTR) (<https://www.clinicaltrialsregister.eu/ctr-search/search>): up to 17 March 2015
- WHO International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictip/en/>): up to 17 March 2015
- Health Canada Trials Database (<http://ctdb-bdec.hc-sc.gc.ca/ctdb-bdec/index-eng.jsp>): up to 17 March 2015
- Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au/TrialSearch.aspx>): up to 17 March 2015
- Merck clinical trials database (<http://www.merck.com/clinical-trials/search.html>): up to 17 March 2015
- Sanofi clinical study result ([http://en.sanofi.com/rd/clinical trials/our commitments/clinical study results.aspx](http://en.sanofi.com/rd/clinical%20trials/our%20commitments/clinical%20study%20results.aspx)): up to 17 March 2015.

Further supplementary searches were undertaken in relevant conference abstracts from 2011 to present:

- European Atherosclerosis Society Congress
 - 2011 <http://www.sciencedirect.com/science/journal/15675688/12/1>
 - 2012 <http://www.kenes.com/eas2012/abstracts/Search.htm>
 - 2013 <http://w3.kenes-group.com/apps/eas2013/abstracts/Search.htm>
 - 2014 <http://www.sciencedirect.com/science/journal/00219150/235>
- European Society of Cardiology Congress 2011, 2012, 2013, 2014
<http://spo.escardio.org/abstract-book/search.aspx>
- American College of Cardiology
 - 2011 <http://www.abstractsonline.com/EPPosterViewer/Home.aspx?Mkey=79E691F3-9BF2-4C60-B958-A23D68B60921>
 - 2012 <http://www.abstractsonline.com/EPPosterViewer/Home.aspx?Mkey=86D3D797-1DEA-4B4D-A5C5-A402B3E95F8C>
 - 2013 <http://www.sciencedirect.com/science/journal/07351097/61/10/supp/S>
 - 2014 <http://www.sciencedirect.com/science/journal/07351097/63/12/supp/S>
- American Heart Association Annual Scientific Sessions 2011, 2012, 2013, 2014
<http://circ.ahajournals.org/search>.

All search strategies are provided in Appendix III.

Study selection

Broad systematic literature review

For the SLR, study inclusion was not limited by language or publication date, and included completed Amgen studies that are not yet published. Studies were included in the review if they fulfilled the inclusion and exclusion criteria outlined in Table 4-1.

Table 4-1 Inclusion and exclusion criteria for the broad clinical efficacy/safety systematic literature review

	Inclusion criteria	Exclusion criteria
Population	• Studies in adults (≥ 18 years old) with primary hypercholesterolaemia (including familial and non-familial) who are candidates for treatment of elevated lipid levels (hyperlipidaemia) and consequent reduction in CV events. For patients with HoFH, studies including patients ≥ 12 years old were also included • Where available, data were identified and reported for two specific groups of patients: ▪ Patients whose condition is not adequately controlled or is unlikely to be adequately controlled (according to European lipid targets) with a statin alone ▪ Patients in whom a statin is considered inappropriate or is only tolerated at low dose/intensity. • Data relevant to the following subgroups were identified: ▪ Patients with HeFH; patients with HoFH; patients with IHD, CVD, or PAD; and patients with diabetes mellitus type 2 • Data were also recorded for subgroups defined by gender, age (< 65, ≥ 65 years), and race (white, non-white) where reported	• Studies including patients with organ transplantations and infectious diseases (e.g. HIV) were excluded. In addition, studies including patients with significant heart failure (NYHA grade III-IV) or significant renal dysfunction (Stage 4-5), which are considered to be major confounding comorbidities, were also excluded
Intervention	• Evolocumab used in combination with moderate- or high-dose statins where cholesterol is insufficiently controlled with statin therapy alone and as monotherapy (in for example statin-intolerant patients). The following doses of evolocumab evaluated will be eligible for inclusion: ▪ 140 mg SC Q2W (1 prefilled AI/pen injection) ▪ 420 mg SC QM (3 prefilled AI/pen injections or 1 personal injector injection)	• Studies that do not include either the included intervention or comparator agents as one of their treatment arms
Comparators ^a	<u>Patients whose condition is not adequately controlled with a statin alone</u> • Alternative moderate- to high-intensity statin monotherapies (daily dose lowers LDL-C on average, by approximately $\geq 30\%$): atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin • Or alternatively, statins in combination with any of the following alternative lipid-lowering therapies such as: other alternative PCSK9 inhibitor monotherapies; cholesterol absorption inhibitors; nicotinic acids; fibrates; cholesteryl ester transfer proteins; and lomitapide, mipomersen, and apheresis (for HoFH) <u>Patients in whom a statin is considered inappropriate or is not tolerated</u> • No treatment/placebo; other alternative PCSK9 inhibitor monotherapies; cholesterol absorption inhibitors; bile acid resins; fibrates; cholesteryl ester transfer proteins; and lomitapide, mipomersen, and apheresis	

	Inclusion criteria	Exclusion criteria
	(for HoFH)	
Outcomes	<u>Clinical outcomes</u> • Overall survival; incidence of CV death; incidence of non-CV death; incidence of fatal and non-fatal CV events (composite and individual outcomes) e.g. CV death, MI, ischaemic stroke, TIA, hospitalisation for unstable angina, hospitalisation for worsening heart failure, symptomatic PAD, CHD and coronary revascularisation; time to fatal or non-fatal CV events (composite and individual outcomes) <u>Lipid-related outcomes (absolute values and change from baseline):</u> • LDL-C; triglycerides; HDL-C; VLDL-C; total cholesterol; total cholesterol/ HDL-C ratio; non-HDL-C; ApoB; ApoB/ApoA1 ratio; Lp(a); and incidence of apheresis (HoFH only). <u>Safety outcomes</u> • Incidence of treatment-related adverse events (any event, serious events, and specific individual events such as hepatic events, gastrointestinal events, headaches, muscle-related events, etc.) <u>Patient-reported outcomes (absolute values and change from baseline)</u> • HRQoL	• RCTs that do not assess one of the included outcomes
Study design	RCTs (including randomised dose finding and formulation studies with either a control or active control arm) were eligible for inclusion, if they were of ≥ 12 weeks' duration. This reflects regulatory guidance on the minimum duration of studies to demonstrate the lipid-lowering effects of investigational agents. It is also in line with previous recommendations included in NICE TA132 (ezetimibe for the treatment of hypercholesterolaemia). This STA reported that trials of shorter duration were considered 'unlikely to inform on survival, CVD events, adverse events or HRQoL' and were also 'excluded to allow for the tachyphylaxis effects'.	• Non-randomised studies • Studies < 12 weeks' duration or with < 10 participants per arm • Pre-clinical, phase 1, and animal studies
Language	Searches were not limited by language.	N/A

^aA more detailed list of specific comparator agents is provided in Appendix III.

AI, autoinjector; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; HIV, human immunodeficiency virus; HoFH, homozygous familial hypercholesterolaemia; HRQoL, health-related quality of life; IHD, ischaemic heart disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); MI, myocardial infarction; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; QM, monthly; RCT, randomised controlled trial; SC, subcutaneous; STA, single technology appraisal; TIA, transient ischaemic attack; VLDL-C, very low-density lipoprotein cholesterol

Alignment of the SLR with the decision problem

To address the information needs of the decision problem as outlined in the final scope for this appraisal, additional exclusion criteria were applied in a second stage of screening to further align the SLR with the decision problem, and to identify all relevant RCTs that could potentially be used for data synthesis in the absence of sufficient head-to-head data to address the information needs of the decision problem. These additional exclusion criteria included:

- study not in a population relevant to the decision problem (e.g. HoFH, Japanese population)
- study assessed neither relevant intervention nor relevant comparator defined in the decision problem
 - evolocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe
 - ezetimibe in combination with a statin (when optimised statin therapy does not appropriately control LDL-C) or ezetimibe alone (when statins are contraindicated or not tolerated)
- study did not include outcome defined in the decision problem
 - plasma lipid and lipoprotein levels, including LDL-C, non-HDL-C, ApoB, and Lp(a)
 - requirement of procedures including LDL apheresis and revascularisation
 - fatal and non-fatal cardiovascular events
 - mortality
 - adverse effects of treatment
 - HRQoL.

All publications excluded at this second stage of the screening process were documented along with the reasons for exclusion (Appendix III). The remaining publications were considered as potentially relevant for data synthesis.

Identification of studies most relevant for inclusion in the submission

In a third and final filtration step to identify RCTs most relevant for inclusion in this submission, further exclusion criteria were applied:

- exclusion of studies that did not assess evolocumab
- exclusion of phase 2 studies if an equivalent phase 3 study in the same population had been conducted.

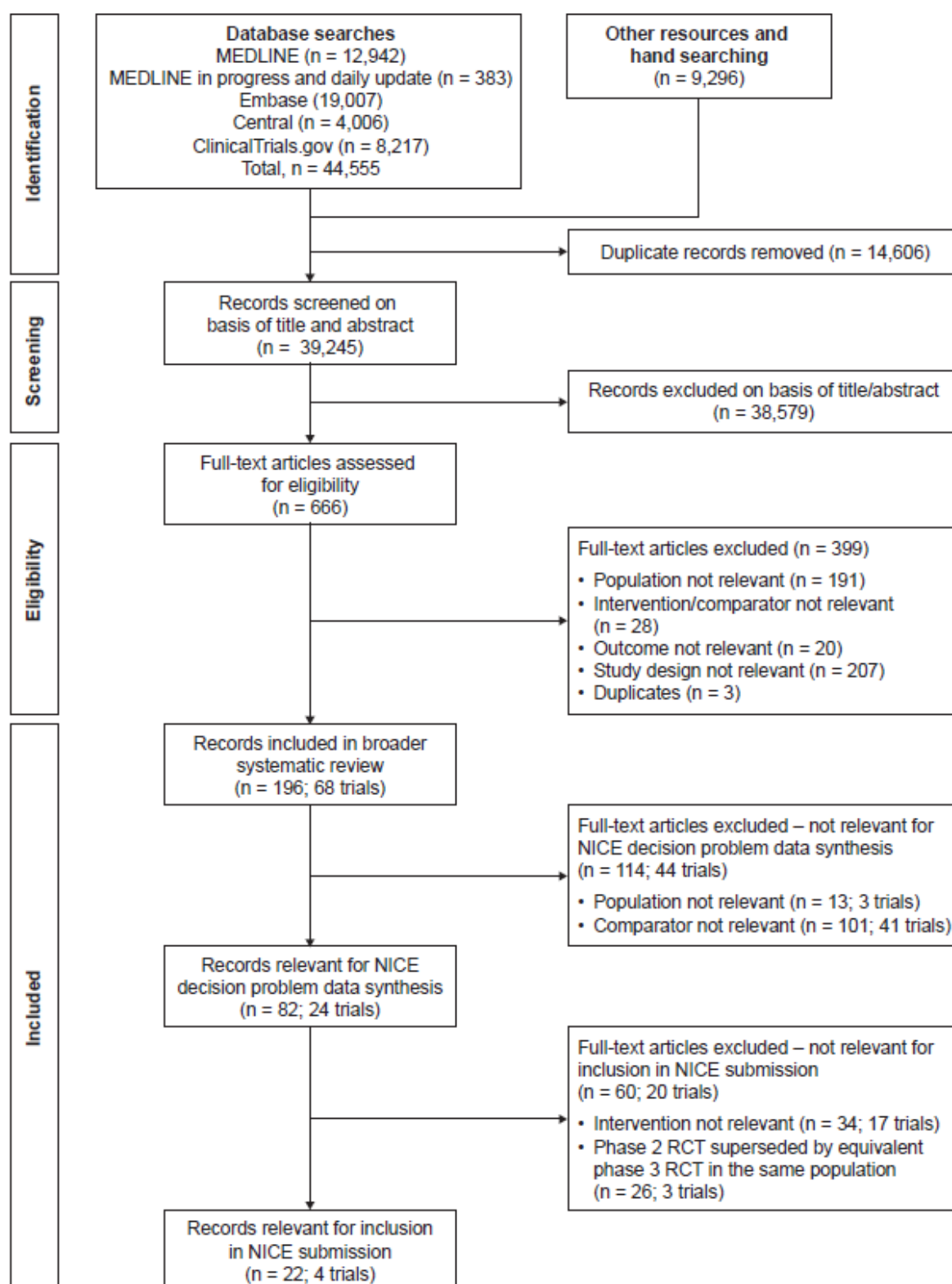
All publications excluded at this third stage of the screening process were documented along with the reasons for exclusion (Appendix III).

Study selection results

196 publications reporting data for 68 studies were included in the broad SLR. When additional exclusion criteria were applied in a second stage of screening to further align the SLR with the decision problem and to identify all relevant RCTs that could potentially be used for additional data synthesis, 82 publications reporting data for 24 studies were identified. Finally, following application of further exclusion criteria to identify RCTs most relevant for inclusion in this submission, 22 publications reporting 4 studies were identified. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow

diagram providing a summary of the searching, screening, and assessment process is provided in Figure 4-1

Figure 4-1 PRISMA flow diagram for the clinical efficacy/safety SLR



NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SLR, systematic literature review

4.2 *List of relevant randomised controlled trials*

The SLR identified four Amgen-sponsored relevant phase 3 RCTs assessing the efficacy and safety of evolocumab, reported in 22 publications.

Two of these studies provide direct head-to-head evidence for relevant interventions versus relevant comparators as defined in the decision problem:

- LAPLACE-2: evolocumab (plus background statin therapy) versus ezetimibe (plus background statin therapy) in patients with primary hypercholesterolaemia and mixed dyslipidaemia
- GAUSS-2: evolocumab monotherapy versus ezetimibe monotherapy in statin-intolerant patients with primary hypercholesterolaemia and mixed dyslipidaemia.

Two of these studies were placebo-controlled studies, with prespecified stratification factor and covariate subgroup analyses providing comparative data for relevant interventions versus relevant comparators as defined in the decision problem:

- RUTHERFORD-2: evolocumab (plus stable background lipid-lowering therapy [statin ± other lipid-lowering therapy]) versus placebo (plus stable background lipid-lowering therapy [statin ± other lipid-lowering therapy]) in patients with HeFH
- DESCARTES: evolocumab (plus background lipid-lowering therapy) versus placebo (plus background lipid-lowering therapy) in patients with primary hypercholesterolaemia and mixed dyslipidaemia.

A brief overview of the relevant RCTs is provided in Table 4-2.

Table 4-2 List of relevant RCTs

Study (Acronym)	Population	Intervention	Comparator	Primary study reference
20110115 (LAPLACE-2)	Patients with primary hypercholesterolaemia and mixed dyslipidaemia treated with background moderate- to high-intensity statin therapy	•Evolocumab 420 mg QM SC + Placebo OD oral •Evolocumab 140 mg Q2W SC+ Placebo OD oral	•Placebo QM SC + Placebo OD oral •Placebo Q2W SC + Placebo OD oral •Ezetimibe 10 mg OD oral + Placebo QM SC (atorvastatin cohorts only) • Ezetimibe 10 mg OD oral + Placebo Q2W SC (atorvastatin cohorts only)	Robinson et al, 2014 ¹⁰⁰ and CSR ¹⁰¹
20110117 (RUTHERFORD-2)	Patients with HeFH treated with stable background lipid-lowering therapy (statin ± other lipid-lowering therapy)	•Evolocumab 420 mg QM SC •Evolocumab 140 mg Q2W SC	•Placebo QM SC •Placebo Q2W SC	Raal et al, 2015 ¹⁰² and CSR ¹⁰³
20110116 (GAUSS-2)	Patients with primary hypercholesterolaemia and mixed dyslipidaemia with statin intolerance	•Evolocumab 140 mg Q2W SC + Placebo OD oral •Evolocumab 420 mg QM SC + Placebo OD oral	• Ezetimibe 10 mg OD oral + Placebo Q2W SC •Ezetimibe 10 mg OD oral + Placebo QM SC	Stroes et al, 2014 ¹⁰⁴ and CSR ¹⁰⁵
20110109 (DESCARTES)	Patients with primary hypercholesterolaemia and mixed dyslipidaemia treated with background lipid-lowering therapy	•Evolocumab 420 mg QM SC	•Placebo QM SC	Blom et al, 2014 ¹⁰⁶ and CSR ¹⁰⁷
CSR, clinical study report; HeFH, heterozygous familial hypercholesterolaemia; OD, once daily, Q2W, every 2 weeks; QM, monthly; RCT, randomised controlled trial; SC, subcutaneous				

Although excluded from the SLR due to the mixed patient populations enrolled in them, interim results from two ongoing, long-term, extension studies (OSLER and OSLER-2) are also reported in this submission to provide additional evidence on the long-term effects of treatment with evolocumab for up to an additional 124 weeks of follow-up. OSLER is an ongoing, phase 2, multicentre, randomised, controlled, open-label, 5-year extension study that enrolled patients who completed a range of phase 2 RCTs, and represents the longest PCSK9 study to date. OSLER-2 is an ongoing, phase 3, multicentre, randomised, controlled, open-label, 2-year extension study that enrolled patients who completed a range of phase 3 RCTs, including all of the relevant RCTs defined in Table 4-2. In both extension studies, patients were randomly assigned to receive evolocumab plus SoC (based on local guidelines and which may include other lipid-lowering therapy) or SoC alone during the first year. Patients randomised to evolocumab plus SoC received evolocumab 420 mg QM (OSLER) or 140 mg Q2W or 420 mg QM at patients' choice (OSLER-2). An overview of the design and methodology of OSLER and OSLER-2 is provided in Appendix IV.

4.3 *Summary of methodology of the relevant randomised controlled trials*

The relevant RCTs were international, multicentre, phase 3 RCTs of 12 weeks' (LAPLACE-2, RUTHERFORD-2, and GAUSS-2) and 52 weeks' (DESCARTES) duration involving the treatment of almost 3,500 patients.

LAPLACE-2 was a 12-week RCT designed to evaluate the efficacy and safety of evolocumab compared with placebo or ezetimibe, when administered in combination with moderate- to high-intensity statin therapy in patients with primary hypercholesterolaemia and mixed dyslipidaemia. Prior to randomisation, patients entered a screening period to determine eligibility, which included a requirement for LDL-C ≥ 2.1 mmol/L (if taking an intensive statin at screening), ≥ 2.6 mmol/L (if taking a non-intensive statin at screening), or ≥ 4.5 mmol/L (if not taking a statin at screening). During screening, SC administration of placebo was performed to confirm tolerability of SC administration prior to randomisation. After the screening period, eligible patients were randomised to one of five open-label statin cohorts (atorvastatin 10 mg or 80 mg, rosuvastatin 5 mg or 40 mg, or simvastatin 40 mg) for a 4-week lipid stabilisation period. After the lipid-stabilisation period, patients within the atorvastatin cohorts were randomised to one of six treatment groups: placebo Q2W plus ezetimibe OD, placebo Q2W plus placebo OD, evolocumab 140 mg Q2W plus placebo OD, placebo QM plus ezetimibe OD, placebo QM plus placebo OD, evolocumab 420 mg QM plus placebo OD, while continuing background statin therapy. Patients who received rosuvastatin or simvastatin were randomised into one of four treatment groups: placebo Q2W, evolocumab 140 mg Q2W, placebo QM, or evolocumab 420 mg QM, while continuing background statin therapy. Patients were asked to maintain a stable diet and exercise regimen throughout LAPLACE-2.

RUTHERFORD-2 was a 12-week RCT designed to evaluate the efficacy and safety of evolocumab compared with placebo in patients with HeFH (as per Simon Broome criteria) who did not achieve adequate LDL-C control (i.e. LDL-C levels ≥ 2.6 mmol/L) after receiving a stable dose of an approved statin $\pm$ stable dose(s) of allowed lipid-regulating drugs for ≥ 4 weeks before LDL-C screening. Prior to randomisation, patients entered a screening period during which SC administration of placebo was performed to confirm tolerability of SC

administration. Patients who completed the screening period and met final eligibility criteria were randomised into 4 treatment groups: placebo Q2W, evolocumab 140 mg Q2W, placebo QM, and evolocumab 420 mg QM, while continuing background lipid-lowering therapy. Patients were asked to maintain a stable diet and exercise regimen throughout RUTHERFORD-2.

GAUSS-2 was a 12-week RCT designed to evaluate the efficacy and safety of evolocumab compared with ezetimibe in patients with primary hypercholesterolaemia and mixed dyslipidaemia unable to tolerate any statins or a statin dose high enough to control their LDL-C levels. Statin intolerance was defined as present in patients who had tried two or more statins and were unable to tolerate any statin dose or an increase in dose above a total weekly maximum dose because of intolerable myopathy, with symptoms resolving or improving with statin discontinuation or dose reduction. Prior to randomisation, patients entered a screening period during which SC administration of placebo was performed to confirm tolerability of SC administration prior to randomisation. Depending on a patient's risk category (based on NCEP adult treatment panel [ATP] III treatment goals), patients must have had LDL-C levels at screening ranging from ≥ 2.6 mmol/L (patients with CHD or CHD risk equivalent) to ≥ 4.9 mmol/L (patients without diagnosed CHD or CHD risk equivalent, with no additional risk factors). Patients who completed the screening period and met final eligibility criteria were randomised into 4 treatment groups: ezetimibe plus placebo Q2W, evolocumab 140 mg Q2W plus placebo OD, ezetimibe plus placebo QM, and evolocumab 420 mg QM plus placebo OD. Patients were asked to maintain a stable diet and exercise regimen throughout GAUSS-2.

DESCARTES was a 52-week RCT designed to evaluate the long-term efficacy and safety of evolocumab compared with placebo, when added to background lipid-lowering therapy in patients with primary hypercholesterolaemia and mixed dyslipidaemia. Eligible patients with screening LDL-C values ≥ 1.9 mmol/L were instructed to follow the NCEP ATP III Therapeutic Lifestyle Changes diet and were assigned to one of the following four background lipid-lowering therapies for a 4-week stabilisation period based on their screening LDL-C levels and its distance from the goal stipulated by NCEP ATP III risk category. These background therapies were diet, diet plus atorvastatin 10 mg, diet plus atorvastatin 80 mg, or diet plus atorvastatin 80 mg plus ezetimibe. At the end of the 4-week stabilisation period, patients who still exceeded the NCEP ATP III risk category LDL-C goal underwent background therapy up-titration to the next therapy level and entered an additional 4-week stabilisation period after which study eligibility based on LDL-C was reassessed. A maximum of two up-titrations were permitted. Patients who were on maximal background therapy were eligible if their LDL-C was ≥ 2.0 mmol/L at the end of the stabilisation period. Patients on maximal background therapy whose LDL-C was < 2.0 mmol/L at the end of the stabilisation period could undergo a single background therapy down-titration to diet plus atorvastatin 80 mg and enter an additional 4-week lipid stabilisation period, after which study eligibility based on a final LDL-C blood draw was reassessed. Patients whose eligibility was confirmed were randomised into two treatment groups: placebo QM and evolocumab 420 mg QM, while continuing background lipid-lowering therapy. Patients were asked to maintain a stable diet and exercise regimen throughout DESCARTES.

The determination of efficacy in each study was based on changes in LDL-C and other lipid parameters at select time points. In the relevant RCTs of 12 weeks' duration (RUTHERFORD-2, LAPLACE-2, and GAUSS-2), the co-primary endpoints were the percent change in LDL-C from baseline at week 12, to address regulatory precedence, and the mean percent change in LDL-C from baseline at the mean of weeks 10 and 12. The rationale for assessing LDL-C at the mean of weeks 10 and 12 is that it represents the average between peak and trough levels for the QM dose. At week 12, the LDL-C lowering effect begins returning toward baseline due to clearance of the antibody and ongoing hepatic PCSK9 production. Obtaining LDL-C levels at weeks 10 and 12 provides a time-averaged efficacy estimate between peak and trough effects. In addition, the week 10/12 data is helpful to clinicians since they won't necessarily time lipid draws to the dosing cycle.

In DESCARTES, the primary endpoint was the percent change in LDL-C from baseline at week 52.

Analyses of LDL-C in the relevant RCTs utilised ultracentrifugation LDL-C, a reflexive approach, and calculated LDL-C. Ultracentrifugation LDL-C values were used to achieve the most rigorous and accurate LDL-C assessment possible, but are not widely available or routinely used in clinical practice. Ultracentrifugation LDL-C was used as the primary analysis method in DESCARTES. A reflexive testing approach was evaluated to assess whether calculated LDL-C concentrations could be used in place of ultracentrifugation LDL-C concentrations in the primary analysis. For analyses of the relevant RCTs of 12 weeks' duration (RUTHERFORD-2, LAPLACE-2, GAUSS-2), a reflexive approach was used as the primary analysis method, where the calculated LDL-C was employed unless the calculated LDL-C was < 1.0 mmol/L or triglycerides were > 4.5 mmol/L, in which case ultracentrifugation LDL-C was determined and utilised. This approach was chosen to provide a robust, conservative, and accurate assessment of LDL-C in the rigorous environment of a controlled clinical study. Data were also evaluated using calculated LDL-C because this method of LDL-C measurement is widely available and is the predominant way in which LDL-C is assessed in clinical practice.

A summary of key aspects of trial methodology including trial design, eligibility criteria, study settings and locations, study drugs and concomitant medications, and outcome measures is provided in Table 4-3, Table 4-4, and Table 4-5.

Table 4-3 Summary of locations, design and trial drugs in the relevant RCTs

	20110115 (LAPLACE-2)	20110117 (RUTHERFORD-2)	20110116 (GAUSS-2)	20110109 (DESCARTES)
Location	Multicentred (198 sites) worldwide in countries such as Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Netherlands, Russia, Spain, Sweden, Switzerland, UK, USA.	Multicentred (39 sites) worldwide in countries such as Canada, Netherlands, South Africa, Spain, USA, Germany, UK, Norway, Sweden, France, Switzerland, Australia, New Zealand, Hong Kong.	Multicentred (51 sites) worldwide in countries such as Australia, Belgium, Canada, Denmark, France, Spain, Germany, Netherlands, Poland, China, Switzerland, South Africa, UK, USA.	Multicentred (88 sites) worldwide in countries such as Australia, Belgium, Canada, Denmark, Hungary, Czech Republic, South Africa, USA.
Trial design	•Phase 3, parallel-group RCT •Duration of 12 weeks •Double-blind (patients, caregivers, and outcome assessors blinded) •Computer randomisation (statin without ezetimibe ratio 2:2:1:1 and with ezetimibe ratio 2:2:1:1:1:1) •Allocation concealed using IVRS to assign a randomisation number and group to the patient •Stratified by entry statin therapy (no statin use vs. non-intensive statin use vs. intensive statin use) and simvastatin contraindicated therapy usage for first randomisation	•Phase 3, parallel-group RCT •Duration of 12 weeks •Double-blind (patients, caregivers, and outcome assessors blinded) •Computer randomisation (2:2:1:1 ratio) •Allocation concealed using IVRS to assign a randomisation number and group to the patient •Stratified by screening LDL-C level (< 4.2 mmol/L vs. ≥ 4.2 mmol/L) and ezetimibe use at baseline (yes vs. no)	•Phase 3, parallel-group RCT •Duration of 12 weeks •Double-blind (patients, caregivers, and outcome assessors blinded) •Computer randomisation (2:2:1:1 ratio) •Allocation concealed using IVRS to assign a randomisation number and group to the patient •Stratified by screening LDL-C level (< 4.7 mmol/L vs. ≥ 4.7 mmol/L) and baseline statin use (yes vs. no)	•Phase 3, parallel-group RCT •Duration of 52 weeks •Double-blind (patients, caregivers, and outcome assessors blinded) •Computer randomisation (2:1 ratio) •Allocation concealed using IVRS to assign a randomisation number and group to the patient •Stratified by background lipid-modifying therapy

	20110115 (LAPLACE-2)	20110117 (RUTHERFORD-2)	20110116 (GAUSS-2)	20110109 (DESCARTES)
Settings and locations where the data were collected	Secondary care/hospital setting	Secondary care/hospital setting	Secondary care/hospital setting	Secondary care/hospital setting
Trial drugs, interventions and comparators, and permitted and disallowed concomitant medication	<u>Trial drugs</u> •Evolocumab 420 mg QM SC + Placebo OD oral (n = 562 randomised) •Evolocumab 140 mg Q2W SC+ Placebo OD oral (n = 557 randomised) •Placebo QM SC + Placebo OD oral (n = 278 randomised) •Ezetimibe 10 mg OD oral + Placebo QM SC (n = 109 randomised) •Ezetimibe 10 mg OD oral + Placebo Q2W SC (n = 112 randomised) •Placebo Q2W SC + Placebo OD oral (n = 281 randomised) <u>Permitted and disallowed concomitant medication</u> Investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except: •Prescription lipid-regulating	<u>Trial drugs</u> •Evolocumab 420 mg QM SC (n = 110 randomised) •Evolocumab 140 mg Q2W SC (n = 111 randomised) •Placebo QM SC (n = 55 randomised) •Placebo Q2W SC (n = 55 randomised) <u>Permitted and disallowed concomitant medication</u> Investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except: •Prescription lipid-regulating medications, such as regulatory approved niacin, fibrates (or derivatives), bile-acid sequestering resins, statins, or ezetimibe outside of what has been provided as background therapy •Red yeast rice, niacin > 200 mg per day, omega-3 fatty	<u>Trial drugs</u> •Evolocumab 140 mg Q2W SC + Placebo OD oral (n = 103 randomised) •Evolocumab 420 mg QM SC + Placebo OD oral (n = 102 randomised) •Ezetimibe 10 mg OD oral + Placebo Q2W SC (n = 51 randomised) •Ezetimibe 10 mg OD oral + Placebo QM SC (n = 51 randomised) <u>Permitted and disallowed concomitant medication</u> Investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except: •Prescription lipid-regulating medications (such as non-study ezetimibe, fibrates, and fibrate derivatives) other than statins, bile-acid sequestering resin, or stanols and stanols	<u>Trial drugs</u> •Evolocumab 420 mg QM SC (n = 602 randomised) •Placebo QM SC (n = 303 randomised) <u>Permitted and disallowed concomitant medication</u> Investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except: •Prescription lipid-regulating medications (e.g. fibrates and fibrate derivatives, and bile-acid sequestering resin) other than protocol assigned statins or ezetimibe •Red yeast rice, niacin > 200 mg/day •Other drugs that significantly affect lipid metabolism •Prescribed amphetamines (or derivatives), and weight loss medications

	20110115 (LAPLACE-2)	20110117 (RUTHERFORD-2)	20110116 (GAUSS-2)	20110109 (DESCARTES)
	medications, such as regulatory approved niacin, fibrates (and derivatives), and bile-acid sequestering resins. In addition, statins or ezetimibe outside of what has been provided as background therapy are also excluded • Red yeast rice, niacin > 200 mg per day, omega-3 fatty acid > 1000 mg/day • Other drugs that significantly affects lipid metabolism • Prescribed amphetamines (or derivatives), and weight loss medications • Colchicine	acid > 1000 mg/day • Other drugs that significantly affect lipid metabolism • Prescribed amphetamines (or derivatives) and weight loss medications • Medications or foods that are known potent inhibitors of CYP3A are not recommended	esters • Red yeast rice, niacin > 200 mg/day • Other drugs that significantly affect lipid metabolism • Prescribed amphetamines (or derivatives), and weight loss medications • Medications or foods that are known potent inhibitors of CYP3A are not recommended	• Medications or foods that are known potent inhibitors of CYP3A are not recommended • Antiarrhythmic medications are not recommended
References: LAPLACE-2 study design/rationale publication,¹⁰⁰ primary study publication,¹⁰⁸ study protocol,¹⁰⁹ and CSR¹⁰¹; RUTHERFORD-2 primary study publication,¹⁰² study protocol,¹¹⁰ and CSR¹⁰³; GAUSS-2 rationale/design publication,¹¹¹ primary study publication,¹⁰⁴ study protocol,¹¹² and CSR¹⁰⁵; DESCARTES primary study publication,¹⁰⁶ study protocol,¹¹³ and CSR.¹⁰⁷ CYP3A, cytochrome P450 3A; CSR, clinical study report; IVRS, interactive voice/web response system; LDL-C, low-density lipoprotein cholesterol; OD, once daily; Q2W, every 2 weeks; QM, monthly; RCT, randomised controlled trial; SC, subcutaneous				

Table 4-4 Summary of eligibility criteria in the relevant RCTS

Study (Acronym)	Inclusion criteria	Major exclusion criteria ^a
20110115 (LAPLACE-2)	• Informed consent • Male or female ≥ 18 to ≤ 80 years of age • Fasting LDL-C ≥ 2.1 mmol/L (taking an intensive statin at screening), ≥ 2.6 mmol/L (taking a non-intensive statin at screening), or ≥ 4.5 mmol/L (not taking a statin at screening) at screening • Fasting TG ≤ 4.5 mmol/L at screening • Negative pregnancy test, AST and ALT ≤ 2 times ULN, CK $\leq 3 \times$ ULN as determined by central laboratory at the end of the lipid stabilisation period	• Use of other lipid-lowering therapy other than statin or ezetimibe in previous 6 weeks • NYHA class III/IV HF or LVEF $< 30\%$ • Uncontrolled cardiac arrhythmia within 3 months • MI, UA, PCI, CABG, or stroke within 6 months • Planned cardiac surgery or revascularisation • Type 1 diabetes or newly diagnosed or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction
20110117 (RUTHERFORD-2)	• Informed consent • Male or female ≥ 18 to ≤ 80 years of age • Diagnosis of HeFH by Simon Broome criteria • On a stable dose of an approved statin $\pm$ other allowed lipid-lowering therapy (e.g. ezetimibe, resins, stanols, or niacin) for ≥ 4 weeks before screening and, in the opinion of the investigator, not requiring up titration • Fasting LDL-C ≥ 2.6 mmol/L at screening • Fasting TG ≤ 4.5 mmol/L at screening	• HoFH • LDL or plasma apheresis within 4 months • NYHA class III/IV HF or LVEF $< 30\%$ • Uncontrolled cardiac arrhythmia within 3 months • MI, UA, PCI, CABG, or stroke within 3 months • Planned cardiac surgery or revascularisation • Type 1 diabetes or newly diagnosed or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction

Study (Acronym)	Inclusion criteria	Major exclusion criteria ^a
20110116 (GAUSS-2)	• Informed consent • Male or female ≥ 18 to ≤ 80 years of age • No or low-dose statin at baseline • Fasting LDL-C at screening based on NCEP ATP III risk category goals ▪ LDL-C ≥ 2.6 mmol/L for those with CHD or CHD risk equivalents ▪ LDL-C ≥ 3.4 mmol/L for patients without diagnosed CHD or risk equivalent but with ≥ 2 risk factors ▪ LDL-C ≥ 4.1 mmol/L for patients without diagnosed CHD or risk equivalent but with 1 risk factor ▪ LDL-C ≥ 4.9 mmol/L for patients without diagnosed CHD or risk equivalent and no risk factors • Statin intolerant (history of intolerance to ≥ 2 statins) ▪ Inability to tolerate any dose or increase above a maximum dose^b because of intolerable muscle-related side effects; AND ▪ Symptoms resolved or improved when statin dose was decreased or discontinued • Stable lipid-lowering therapy for ≥ 4 weeks before screening if on statin and/or bile acid sequestrant and/or stanol; if on ezetimibe at screening, ezetimibe must be discontinued for ≥ 4 weeks before LDL-C screening • Fasting TG ≤ 4.5 mmol/L at screening	• NYHA class III/IV HF or LVEF $< 30\%$ • Uncontrolled cardiac arrhythmia in the prior 3 months • MI, UA, PCI, CABG, or stroke within 3 months • Planned cardiac surgery or revascularisation • Type 1 or 2 diabetes or newly diagnosed or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction

Study (Acronym)	Inclusion criteria	Major exclusion criteria ^a
20110109 (DESCARTES)	• Informed consent • Male or female ≥ 18 to ≤ 75 years of age • Fasting LDL-C ≥ 2.0 mmol/L and fasting TG ≤ 4.5 mmol/L at screening • Fasting LDL-C after 4-week lipid stabilisation period with one of four background lipid-lowering therapy regimens based on NCEP ATP III risk category goals ▪ LDL-C ≥ 2.0 mmol/L and < 2.6 mmol/L for those with CHD or CHD risk equivalents; ▪ LDL-C ≥ 2.0 mmol/L and < 3.4 mmol/L in patients without CHD or risk equivalent; ▪ OR for patients on maximal background lipid-lowering therapy (diet + atorvastatin 80 mg + ezetimibe), LDL-C ≥ 2.0 mmol/L	• CHD or CHD risk equivalent and not receiving statin with LDL-C at screening ≤ 2.6 mmol/L • NYHA class II/III/IV HF or LVEF < 30% • Uncontrolled cardiac arrhythmia within 3 months prior to randomisation • MI, UA, PCI, CABG, or stroke within 3 months prior to randomisation • Planned cardiac surgery or revascularisation • Type 1 diabetes or newly diagnosed or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction
References: LAPLACE-2 study design/rationale publication,¹⁰⁰ primary study publication,¹⁰⁸ study protocol,¹⁰⁹ and CSR¹⁰¹; RUTHERFORD-2 primary study publication,¹⁰² study protocol,¹¹⁰ and CSR¹⁰³; GAUSS-2 rationale/design publication,¹¹¹ primary study publication,¹⁰⁴ study protocol,¹¹² and CSR¹⁰⁵; DESCARTES primary study publication,¹⁰⁶ study protocol,¹¹³ and CSR.¹⁰⁷ ^aSee Appendix IV for full list of exclusion criteria. ^bAtorvastatin ≤ 70 mg, simvastatin ≤ 140 mg, pravastatin ≤ 140 mg, rosuvastatin ≤ 35 mg, lovastatin ≤ 140 mg, fluvastatin ≤ 280 mg, and 7 times the smallest available tablet size for other statins. ALT, alanine transaminase; AST, aspartate transaminase; ATP, adult treatment panel; CABG, coronary artery bypass graft; CHD, coronary heart disease; CK, creatine kinase; CSR, clinical study report; GI, gastrointestinal; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NCEP, National Cholesterol Education Program; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TG, triglycerides; UA, unstable angina; ULN, upper limit of normal		

Table 4-5 Summary of outcome measures and pre-planned subgroups in the relevant RCTs

20110115 (LAPLACE-2)	20110117 (RUTHERFORD-2)	20110116 (GAUSS-2)	20110109 (DESCARTES)
Primary outcomes (including scoring methods and timings of assessments)^a			
•Percent change from baseline in LDL-C at week 12 •Percent change from baseline in LDL-C at the mean of weeks 10/12			•Percent change from baseline in LDL-C at week 52
Secondary/tertiary outcomes (including scoring methods and timings of assessments)^a			
<u>Co-secondary endpoints at week 12 and the mean of weeks 10/12</u> •Tier 1 endpoints ▪Absolute change from baseline in LDL-C ▪Percent change from baseline in non-HDL-C, ApoB, TC/HDL-C ratio, and ApoB/ApoA1 ratio •Tier 2 endpoints ▪Percent of patients with LDL-C < 1.8 mmol/L ▪Percent change from baseline in Lp(a), TG, VLDL-C, and HDL-C <u>Tertiary endpoints</u> •Percent change from baseline in ApoA1 at week 12 and the mean of weeks 10 and 12	<u>Co-secondary endpoints at week 12 and the mean of weeks 10/12</u> •Tier 1 endpoints ▪Absolute change from baseline in LDL-C ▪Percent of patients with LDL-C < 1.8 mmol/L ▪Percent change from baseline in non-HDL-C, ApoB, TC/HDL-C ratio, and ApoB/ApoA1 ratio •Tier 2 endpoints ▪Percent change from baseline in Lp(a), TG, VLDL-C, and HDL-C <u>Tertiary endpoints</u> •Percent change from baseline in ApoA1 at week 12 and the mean of weeks 10 and 12	<u>Co-secondary endpoints at week 12 and the mean of weeks 10/12</u> •Tier 1 endpoints ▪Absolute change from baseline in LDL-C ▪Percent of patients with LDL-C < 1.8 mmol/L ▪Percent change from baseline in non-HDL-C, ApoB, TC/HDL-C ratio, and ApoB/ApoA1 ratio •Tier 2 endpoints ▪Percent change from baseline in Lp(a), TG, VLDL-C, and HDL-C <u>Tertiary endpoints</u> •Percent change from baseline in ApoA1 at week 12 and the mean of weeks 10 and 12	<u>Secondary efficacy endpoints (hypothesis testing)</u> •Tier 1 endpoints ▪Percent change from baseline in LDL-C at week 12 ▪Absolute change from baseline in LDL-C at week 52 ▪Percent of patients with LDL-C < 1.8 mmol/L at week 52 ▪Percent change from baseline in TC, non-HDL-C, ApoB, TC/HDL-C ratio, and ApoB/ApoA1 ratio at week 52 ▪Percent change from baseline in TC at week 12 •Tier 2 endpoints ▪Percent change from baseline in Lp(a), TG, HDL-C, and VLDL-C at week 52 <u>Secondary efficacy endpoint (estimation)</u> ▪Percent change from week 12 in

20110115 (LAPLACE-2)	20110117 (RUTHERFORD-2)	20110116 (GAUSS-2)	20110109 (DESCARTES)
			LDL-C at week 52 <u>Tertiary endpoints</u> Percent change from baseline in ApoA1 at week 52
Pre-planned subgroups^b			
<u>Stratification factors</u> • Entry statin therapy • Simvastatin contraindicated therapy usage for first randomisation <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2 , region, family history of premature CHD, baseline PCSK9, baseline TG, and NCEP high risk	<u>Stratification factors</u> • Screening LDL-C < 4.2 mmol/L vs. ≥ 4.2 mmol/L • Ezetimibe use at baseline <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2 , region, family history of premature CHD, baseline PCSK9, baseline TG, NCEP high risk, HeFH status, and background lipid-modifying therapy	<u>Stratification factors</u> • Screening LDL-C < 4.7 mmol/L vs. ≥ 4.7 mmol/L • Baseline statin use <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2 , region, family history of premature CHD, baseline PCSK9, baseline TG, NCEP high risk, intolerance to statin, and background lipid-modifying therapy	<u>Stratification factors</u> • Background lipid-lowering therapy <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2 , region, family history of premature CHD, baseline PCSK9, baseline TG, and NCEP high risk
References: LAPLACE-2 study design/rationale publication, ¹⁰⁰ primary study publication, ¹⁰⁸ study protocol, ¹⁰⁹ and CSR ¹⁰¹ ; RUTHERFORD-2 primary study publication, ¹⁰² study protocol, ¹¹⁰ and CSR ¹⁰³ ; GAUSS-2 rationale/design publication, ¹¹¹ primary study publication, ¹⁰⁴ study protocol, ¹¹² and CSR ¹⁰⁵ ; DESCARTES primary study publication, ¹⁰⁶ study protocol, ¹¹³ and CSR. ¹⁰⁷ ^a LDL-C was assessed via ultracentrifugation, a reflexive approach where calculated LDL-C (via the Friedwald formula) was employed unless the calculated LDL-C was < 1.0 mmol/L or triglycerides were > 4.5 mmol/L, in which case ultracentrifugation LDL-C was determined and utilised, and by calculated assessment alone in each of the relevant RCTs. The primary analysis method was ultracentrifugation in DESCARTES and in the other relevant RCTs the primary analysis method was the reflexive approach. ^b See Section 4.8 for detailed definitions of prespecified stratification factor and baseline covariate subgroups. ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; CHD, coronary heart disease; CSR, clinical study report; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); NCEP, National Cholesterol Education Program; non-HDL-C, non-high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomised controlled trial; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol			

4.4 *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

An overview of the primary hypothesis, statistical tests used in the primary analysis, power of the trial (including description of sample size calculation with rationale and assumptions), and data management for each of the relevant RCTs is provided in Table 4-6.

Table 4-6 Statistical analyses in the relevant RCTs

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
20110115 (LAPLACE-2)			
Primary statistical hypothesis: Within each randomised statin treatment group and SC IP dose frequency, the null hypothesis was that there was no difference in the coprimary endpoints between evolocumab and placebo or ezetimibe, and the alternative hypothesis was that a mean difference did exist.	<u>General principles</u> - Efficacy and safety analyses were performed on the FAS, which includes all subjects randomised to IP who have received ≥ 1 dose of IP (i.e. a modified ITT approach). - Analyses were performed separately by each statin dose cohort and dose frequency (Q2W and QM). The superiority of evolocumab to either placebo or ezetimibe was assessed for all efficacy endpoints. - No multiplicity adjustments were made between the statin cohorts and IP dose frequencies. Multiplicity adjustments due to multiple endpoints (coprimary and cosecondary efficacy endpoints) within each dose frequency are described in the CSR. - For all analyses related to LDL-C, a reflexive approach was used as the primary analysis method, where the calculated LDL-C was employed unless the calculated LDL-C was < 1.0 mmol/L or TGs were > 4.5 mmol/L, in which case UC LDL-C was determined and utilised. <u>Analysis of coprimary endpoints</u> - To assess the coprimary endpoints, a repeated measures linear effects model was used within each dose frequency (i.e. Q2W or QM) and statin cohort to compare the efficacy of evolocumab with ezetimibe or placebo. The repeated measures model included terms for treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit. Missing values were not imputed when the repeated measures linear effects model	- The planned total sample size was 1,700 patients randomised into 5 statin dose cohorts. Within each statin dose cohort and dose frequency (either Q2W or QM), 100 patients were planned to be randomised to evolocumab and 50 patients were planned to be randomised to placebo. Furthermore, for the atorvastatin dose cohorts, 50 patients were planned to be randomised to receive ezetimibe within each dosing frequency. - For the atorvastatin dose cohorts, the overall familywise error rate of 0.05 was allocated to be 0.01 and 0.04 for the comparisons of evolocumab against each control arm (placebo or ezetimibe) within each dose frequency (Q2W or QM). It was anticipated that the treatment effect would be attenuated due to the following assumptions: - Approximately 15% of patients randomised in the primary study phase would end IP early but would remain on study. - Approximately 5% of patients randomised in the primary study phase would end the study early. - After accounting for treatment attenuation	- The Medidata Rave 5.6.4 database (Medidata Solutions Inc., New York, New York, USA), which includes an electronic data capture system, was used for this study. - Data quality checks were applied using manual and electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained. The final database was transferred to Amgen. - Information regarding each administered dose of SC IP was recorded on the IP

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	was used. <u>Analyses of cosecondary endpoints</u> - The statistical model and testing of the tier 1 cosecondary efficacy endpoints were similar to the primary analysis of the co-primary endpoint. - Analyses of the tier 2 cosecondary efficacy endpoints used the same analysis model as the tier 1 endpoints, with the exception of achievement of LDL-C < 1.8 mmol/L, which was analysed using the CMH test adjusted by the stratification factors. <u>Analyses of tertiary endpoints</u> - Analysis of the tertiary endpoints was similar to the primary analysis of the coprimary endpoints, though no multiplicity adjustment was applied.	and assuming 10% of randomised patients would not receive any IP in the primary study phase, the sample size provided approximately 96% power in testing the superiority of each evolocumab dosing regimen over ezetimibe at week 12. The sample size calculation was performed using a two-sided t-test with a 0.04 significance level, an attenuated treatment effect of 16.5% reduction in LDL-C and an attenuated common SD of 23%.	administration eCRF.
20110117 (RUTHERFORD-2)			
Primary statistical hypothesis: Within each dose frequency, the null hypothesis was that there was no difference in the coprimary endpoints between evolocumab and placebo, and the alternative	<u>General principles</u> - Efficacy and safety analyses was performed on FAS, which includes all patients randomised to IP who have received ≥ 1 dose of IP (i.e. a modified ITT approach). - Analyses were performed separately by each dose frequency (Q2W and QM). The superiority of evolocumab compared with placebo was assessed for all efficacy endpoints. - No multiplicity adjustments were made between the dose frequencies (Q2W and QM). Multiplicity adjustments due to multiple endpoints (coprimary and cosecondary efficacy endpoints) within each dose frequency are described in the CSR.	- The planned total sample size was 300 patients (100 evolocumab Q2W, 100 evolocumab QM, 50 placebo Q2W, and 50 placebo QM). - The power calculation was derived assuming a true treatment effect of evolocumab (Q2W or QM) over placebo in the percent reduction of LDL-C of at least 20% at week 12, with a common SD of 20%. It was anticipated that the treatment effect would be attenuated due to the following assumptions: - Approximately 15% of randomised patients	- The Medidata Rave 5.4 database (Medidata Solutions Inc., New York, New York, USA), which includes an electronic data capture system, was used for this study. - Data quality checks were applied using manual and electronic

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
hypothesis was that a mean difference did exist.	- For all analyses related to LDL-C, a reflexive approach was used as the primary analysis method, where the calculated LDL-C was employed unless the calculated LDL-C was < 1.0 mmol/L or TG were > 4.5 mmol/L, in which case UC LDL-C was determined and utilised. <u>Analysis of coprimary endpoints</u> - To assess the co-primary endpoints, a repeated measures linear effects model was used within each dose frequency (i.e. Q2W or QM) to compare the efficacy of evolocumab with placebo. The repeated measures model included terms for treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit. Missing values were not imputed when the repeated measures linear effects model was used. <u>Analyses of cosecondary endpoints</u> - The statistical model and testing of the tier 1 cosecondary endpoints was similar to the primary analysis of the coprimary endpoints, with the exception of achievement of LDL-C < 1.8 mmol/L was analysed using the CMH test adjusted by the stratification factors. - Analyses of the tier 2 cosecondary endpoints used the same analysis model as the tier 1 endpoints. <u>Analyses of tertiary endpoints</u> - Analysis of the tertiary endpoints was similar to the primary analysis of the coprimary endpoints, though no multiplicity adjustment was applied.	would end IP early but remain on study. - Approximately 5% of randomised patients would end the study early. - After accounting for treatment attenuation and assuming 2% of randomised patients would not receive any IP, the sample size provided approximately 98% power in testing the superiority of each evolocumab dosing regimen over its respective placebo at week 12. The sample size calculation was performed using a two-sided t-test with a 0.05 significance level for each test (evolocumab Q2W vs. placebo Q2W and evolocumab QM vs. placebo QM), an attenuated treatment effect of 16.5% reduction in LDL-C, and an attenuated common SD of 23%.	verification methods. An audit trail to support data query resolution and any modification to the data was maintained. The final database was transferred to Amgen. Information regarding each administered dose was recorded on the IP administration eCRF.

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
20110116 (GAUSS-2)			
Primary statistical hypothesis: Within each dose frequency, the null hypothesis was that there is no difference in the coprimary endpoints between evolocumab and ezetimibe, and the alternative hypothesis is that a difference does exist.	<u>General principles</u> - Efficacy and safety analyses was performed on FAS, which includes all patients randomised to IP who have received ≥ 1 dose of IP (i.e. a modified ITT approach). - Analyses were performed separately by each statin dose cohort and dose frequency (Q2W and QM). The superiority of evolocumab to ezetimibe was assessed for all efficacy endpoints. - No multiplicity adjustments were made between the dose frequencies (Q2W and QM). Multiplicity adjustments due to multiple endpoints (coprimary and cosecondary efficacy endpoints) within each dose frequency are described in the CSR. - For all analyses related to LDL-C, a reflexive approach was used as the primary analysis method, where the calculated LDL-C was employed unless the calculated LDL-C was < 1.0 mmol/L or TG were > 4.5 mmol/L, in which case UC LDL-C was determined and utilised. <u>Analysis of primary endpoints</u> - To assess the co-primary endpoints, a repeated measures linear effects model was used within each dose frequency (i.e. Q2W or QM) to compare the efficacy of evolocumab with ezetimibe. The repeated measures model included terms for treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit. Missing values were not imputed when the repeated measures linear effects model was used.	- The planned total sample size was 300 patients (100 evolocumab Q2W, 100 evolocumab QM, 50 ezetimibe Q2W, 50 ezetimibe QM). It was anticipated that the treatment effect would be attenuated due to the following assumptions: - Approximately 15% of randomised patients would end IP early but would remain on study. - Approximately 5% of randomised patients would end the study early. - After accounting for treatment attenuation and assuming 2% of randomised patients would not receive any IP, the sample size provided approximately 98% power in testing the superiority of each evolocumab dosing regimen over ezetimibe for week 12. The sample size calculation was performed using a 2-sided t-test with a 0.05 significance level for each test (evolocumab Q2W vs. ezetimibe and evolocumab QM vs. ezetimibe), an attenuated treatment effect of 16.5% reduction in LDL-C, and an attenuated common SD of 23%.	- The Medidata Rave 5.6.4 database (Medidata Solutions Inc., New York, New York, USA), which includes an electronic data capture system, was used for this study. - Data quality checks were applied using manual and electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained. The final database was transferred to Amgen. - Information regarding each administered dose of SC IP was recorded on the IP administration

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	<u>Analyses of cosecondary endpoints:</u> - The statistical model and testing of the tier 1 cosecondary endpoints were similar to the primary analysis of the co-primary endpoints, with the exception of achievement of LDL-C < 1.8 mmol/L, which was analysed using the CMH test adjusted by the stratification factors. - Analyses of the tier 2 cosecondary endpoints used the same analysis model as the tier 1 endpoints. <u>Analyses of tertiary endpoints</u> - Analysis of the tertiary endpoints was similar to the primary analysis of the co-primary endpoints, though no multiplicity adjustment was applied.		eCRF.
20110109 (DESCARTES)			
Primary statistical hypothesis: The null hypothesis was that there is no difference in the primary endpoint between evolocumab and placebo, and the alternative hypothesis is that a difference does exist.	<u>General principles</u> - Efficacy and safety analyses were performed on the FAS, which includes all patients randomised to IP who have received ≥ 1 dose of IP (i.e. a modified ITT approach). - The superiority of evolocumab compared with placebo was assessed for all efficacy endpoints. - Multiplicity adjustments due to multiple endpoints (primary and secondary efficacy endpoints) are described in the CSR. - All primary and secondary endpoint analyses of LDL-C in this study used UC LDL-C as the primary analysis method (if available). <u>Analysis of the primary endpoint</u> - For the primary endpoint, evolocumab QM was evaluated by comparing the treatment effect with that of placebo SC QM. The analysis used a repeated measures linear effects model,	- The planned total sample size was 900 patients (600 randomised to evolocumab 420 mg QM and 300 randomised to placebo QM). This sample size provided sufficient power to determine whether there was a treatment effect of evolocumab compared with placebo at week 52. - The power calculation was derived by assuming a true treatment effect of evolocumab QM over placebo in the percent reduction of LDL-C of at least 20%, with a common SD of 20%. - It was anticipated that the treatment effect would be attenuated due to the following assumptions: - Approximately 20% of patients within the	- The Medidata Rave 5.6.4 database (Medidata Solutions Inc., New York, New York, USA), which includes an electronic data capture system, was used for this study. - Data quality checks were applied using manual and electronic verification methods. An audit trail to support data

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	including terms for treatment group, stratification factor (background therapy group), scheduled visit and the interaction of treatment with scheduled visit. Missing values were not imputed for the repeated measures analysis. <u>Analyses of secondary endpoints (hypothesis testing)</u> - Analyses of the tier 1 and tier 2 secondary efficacy hypothesis testing endpoints were similar to the primary analysis of the primary endpoint, with the exception of achievement of LDL-C < 1.8 mmol/L which was analysed using the CMH test adjusted by the stratification factors. <u>Analyses of tertiary efficacy endpoints</u> - Analyses of tertiary efficacy endpoints were similar to the primary analysis of the primary endpoint, though no multiplicity adjustment was applied.	evolocumab and placebo treatment groups would end IP early but would remain on study. - Approximately 10% of patients within the evolocumab and placebo treatment groups would end the study early. - After accounting for treatment attenuation, and assuming 2% of randomised patients did not receive any IP, the sample size would provide > 99% power to test the study hypothesis. The sample size calculation was performed using a 2-sided t-test with a 0.05 significance level, an attenuated treatment effect of 15.0% reduction in LDL-C and an attenuated common SD of 23.3%.	query resolution and any modification to the data was maintained. The final database was transferred to Amgen. Information regarding each administered dose of SC IP was recorded on the IP administration eCRF.
References: LAPLACE-2 study design/rationale publication,¹⁰⁰ primary study publication,¹⁰⁸ study protocol,¹⁰⁹ and CSR¹⁰¹; RUTHERFORD-2 primary study publication,¹⁰² study protocol,¹¹⁰ CSR¹⁰³; GAUSS-2 rationale/design publication,¹¹¹ primary study publication,¹⁰⁴ study protocol,¹¹² and CSR¹⁰⁵; DESCARTES primary study publication,¹⁰⁶ study protocol,¹¹³ and CSR.¹⁰⁷ ANCOVA, analysis of covariance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CSR, clinical study report; eCRF, electronic case report form; FAS, full analysis set; IP, investigational product; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly; SC, subcutaneous; SD, standard deviation; TG, triglycerides; UC, ultracentrifugation			

4.5 *Participant flow in the relevant randomised controlled trials*

CONSORT participant flow diagrams

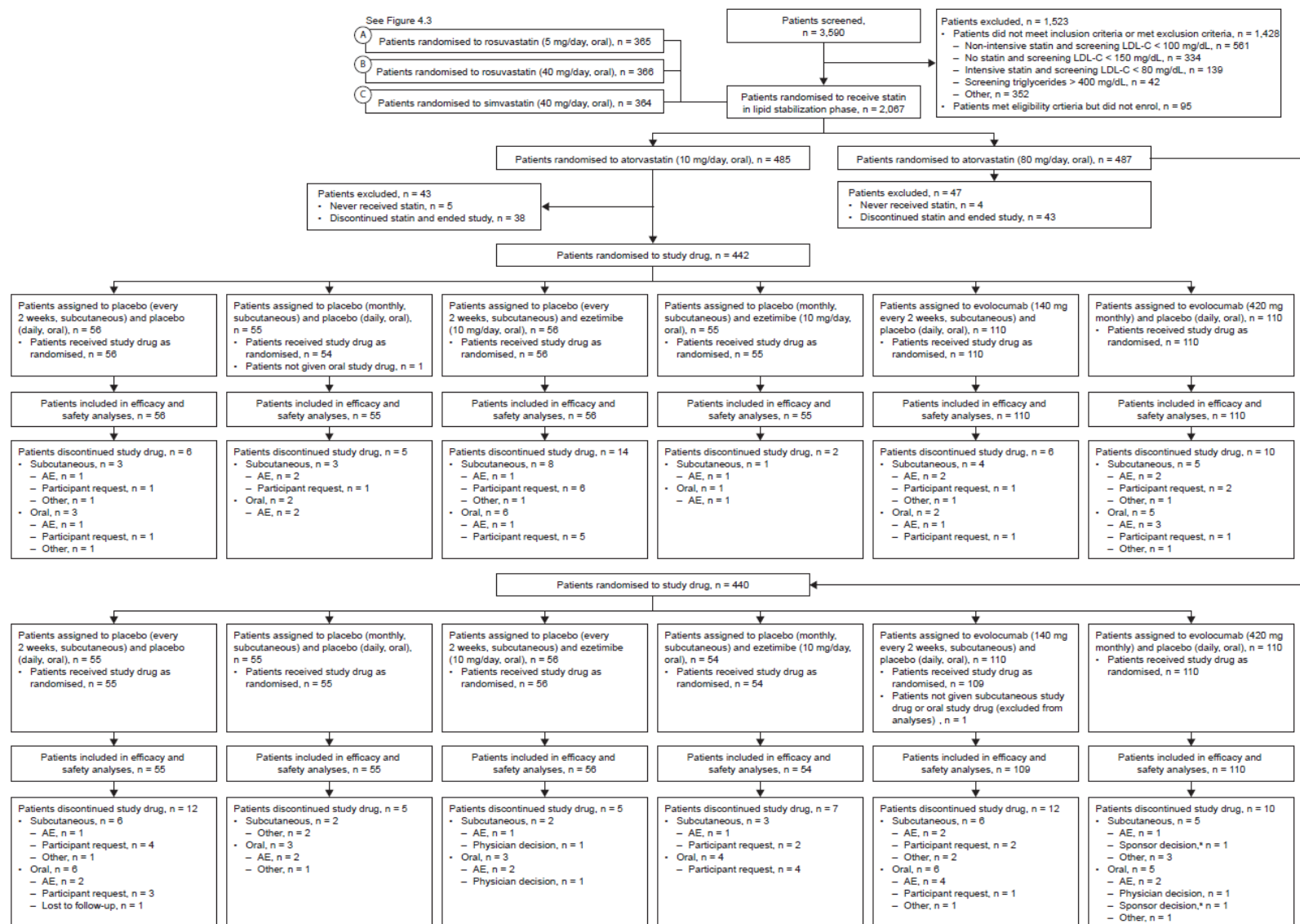
Consort participant flow diagrams are provided for each of the relevant RCTs below:

- LAPLACE-2 (Figure 4-2 and Figure 4-3)
- RUTHERFORD-2 (Figure 4-4)
- GAUSS-2 (Figure 4-5)
- DESCARTES (Figure 4-6).

An overview of baseline characteristics and baseline/screening/study entry and post-baseline/on-study lipid-lowering therapy use are provided for each of the relevant RCTs in Table 4-7 (LAPLACE-2) and Table 4-8 (RUTHERFORD-2, GAUSS-2, and DESCARTES). Characteristics were generally well-balanced across treatment groups.

More detailed information on patient disposition, baseline characteristics, and lipid-lowering therapy use is available in the CSRs of each of the relevant RCTs.

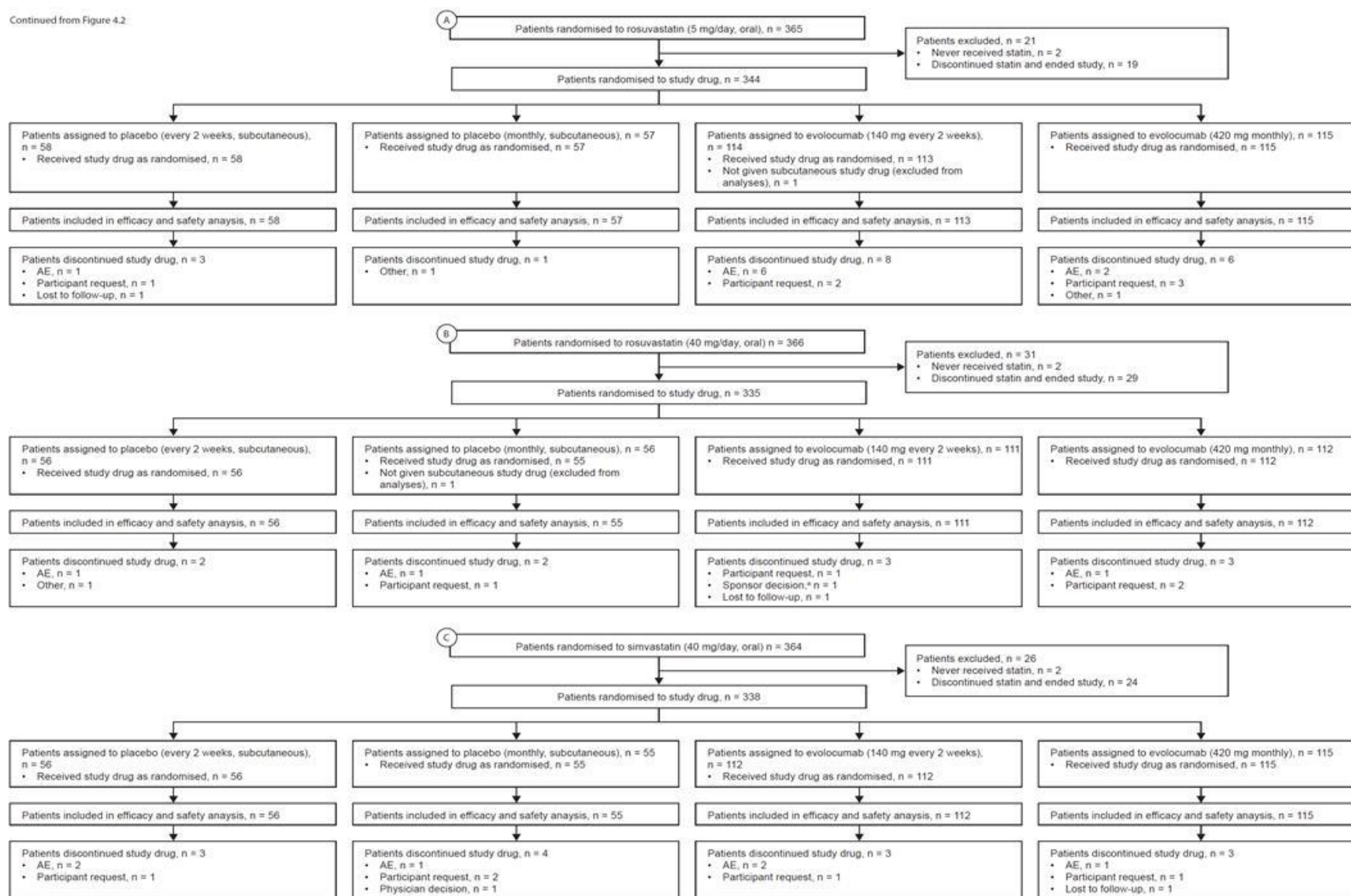
Figure 4-2 CONSORT participant flow diagram for LAPLACE-2 (atorvastatin cohorts)



References: Adapted from the LAPLACE-2 primary study publication.¹⁰⁸ *Sponsor decision because of other reason. AE, adverse event; CONSORT, Consolidated Standards of Reporting Trials; LDL-C, low-density lipoprotein cholesterol

Figure 4-3 CONSORT participant flow diagram for LAPLACE-2 (rosuvastatin and simvastatin cohorts)

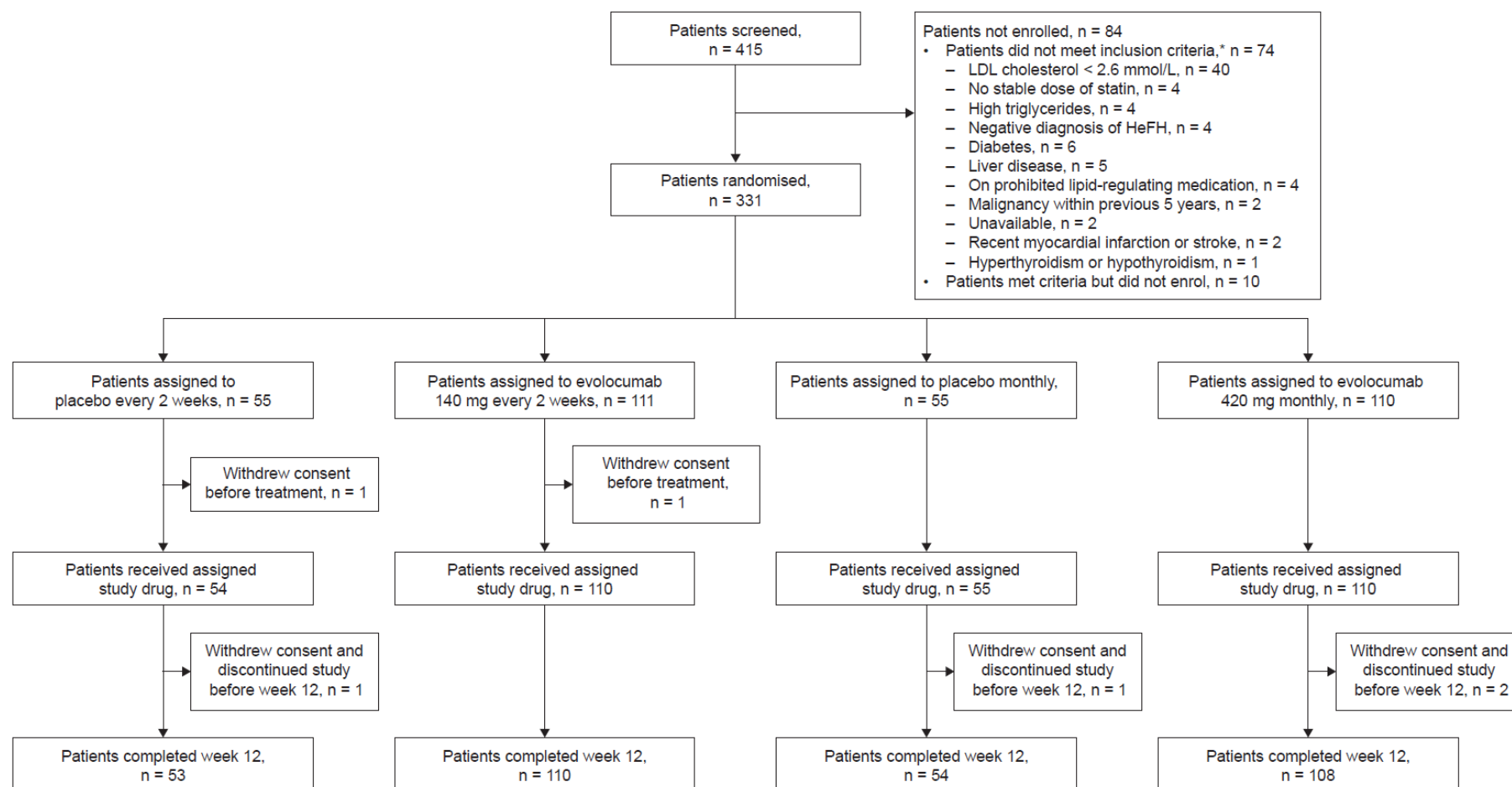
Continued from Figure 4.2



References: Adapted from the LAPLACE-2 primary study publication.¹⁰⁸ ^aPatient removed due to eligibility deviation (participation in previous evolocumab study); AE, adverse event; CONSORT, Consolidated Standards of Reporting Trials

Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

Figure 4-4 CONSORT participant flow diagram for RUTHERFORD-2



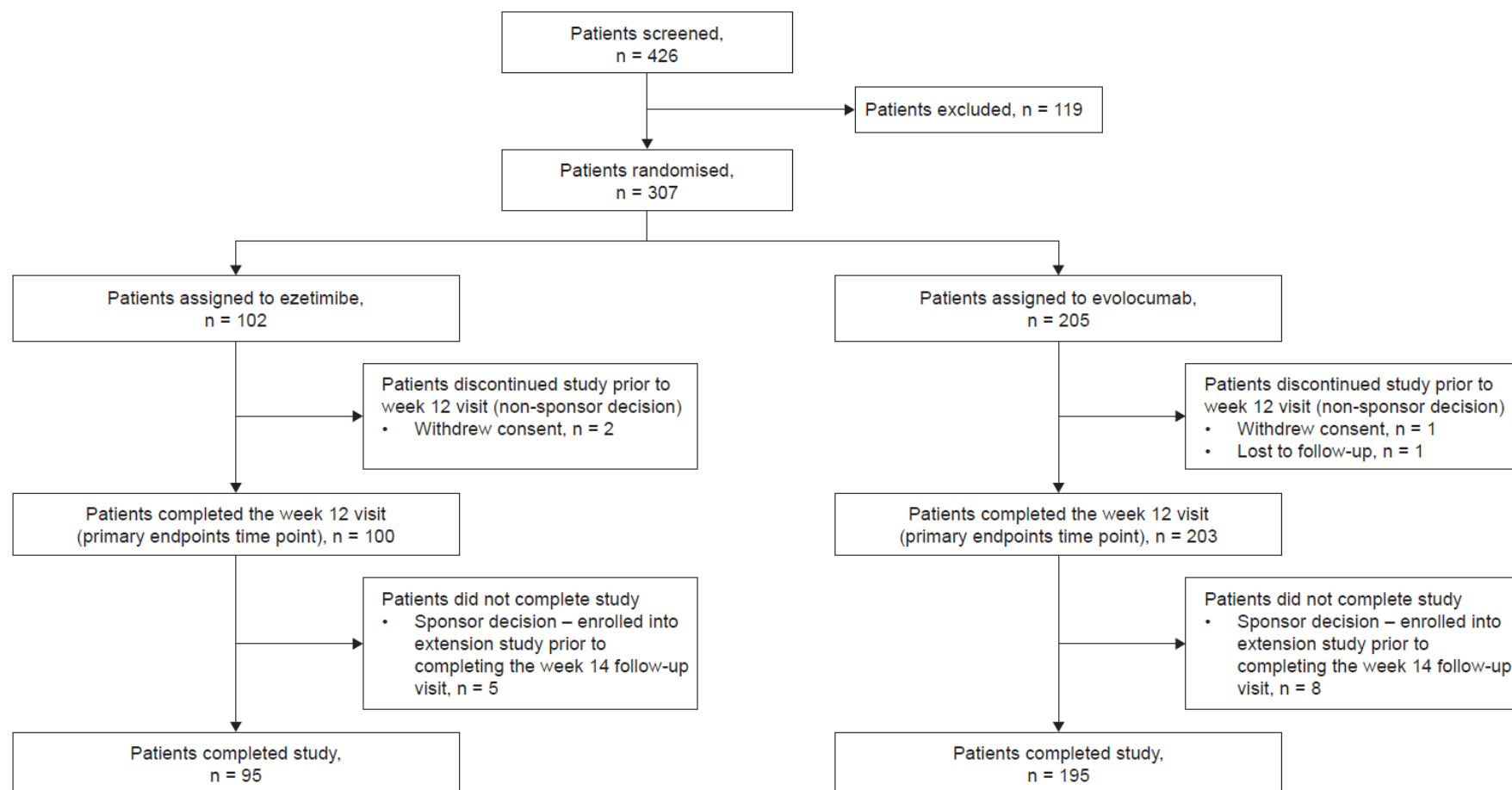
References: Adapted from the RUTHERFORD-2 primary study publication.¹¹⁴

*Participants could be excluded at screening for several reasons.

Note: An error in the original study publication for patients not meeting inclusion criteria due to hyperthyroidism or hypothyroidism has been corrected (n=1 instead of n=11). See RUTHERFORD-2 CSR¹⁰³ Table 14-3.1.2.

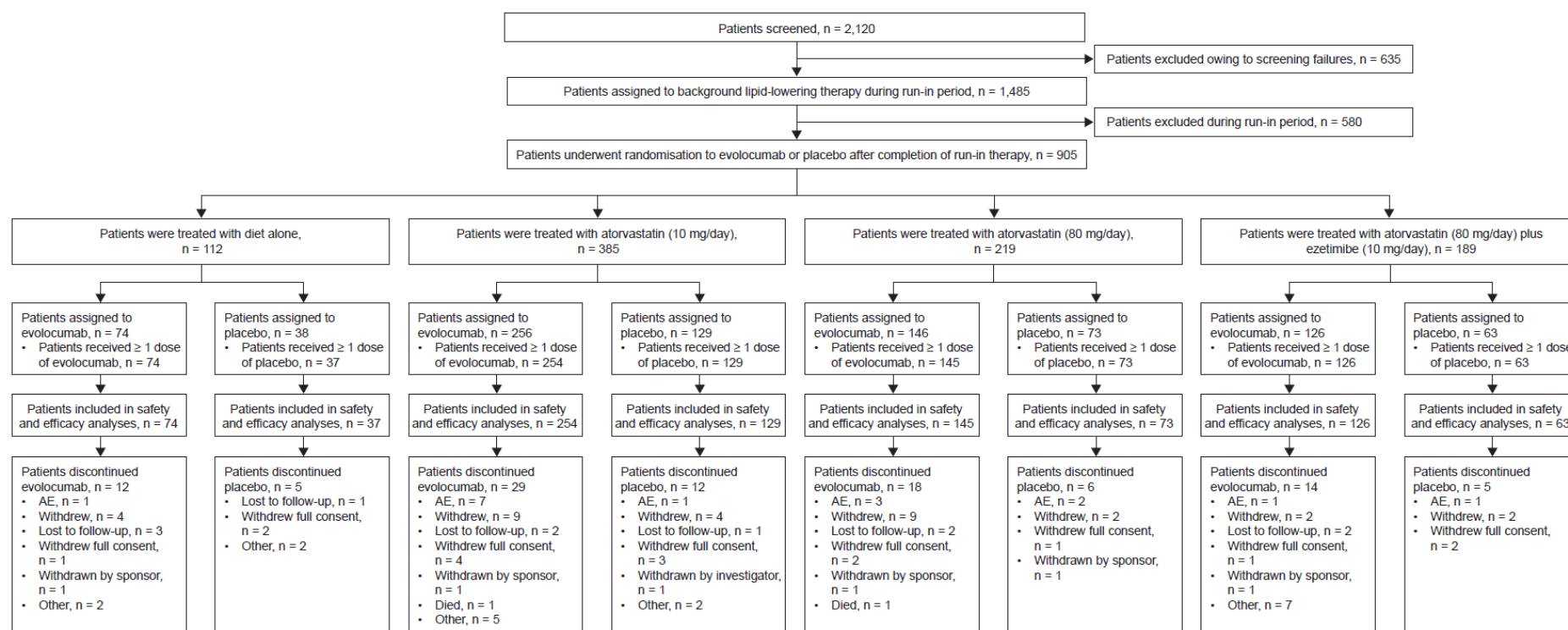
CONSORT, Consolidated Standards of Reporting Trials; CSR, clinical study report; LDL, low-density lipoprotein

Figure 4-5 CONSORT participant flow diagram for GAUSS-2



References: Adapted from the GAUSS-2 primary study publication.¹⁰⁴
CONSORT, Consolidated Standards of Reporting Trials

Figure 4-6 CONSORT participant flow diagram for DESCARTES



References: DESCARTES primary study publication.¹⁰⁶

AE, adverse event; CONSORT, Consolidated Standards of Reporting Trials

Table 4-7 Baseline characteristics and lipid-lowering medication use in LAPLACE-2 (FAS)

	PBO + any statin without EZE		PBO + any atorvastatin with EZE		EvoMab + any statin	
	Q2W (N = 281)	QM (N = 277)	PBO Q2W (N = 112)	PBO QM (N = 109)	140 mg Q2W (N = 555)	420 mg QM (N = 562)
Demographics						
Age, years (SD)	60 (10)	60 (11)	61 (10)	61 (9)	59 (10)	60 (10)
Male, n (%)	147 (52)	144 (52)	59 (53)	53 (49)	317 (57)	308 (55)
Race, n (%)						
White	263 (94)	268 (97)	106 (95)	98 (90)	515 (93)	532 (95)
Black	9 (3)	7 (3)	4 (4)	6 (6)	28 (5)	21 (4)
Asian	6 (2)	0 (0)	2 (2)	4 (4)	7 (1)	6 (1)
Other	3 (1)	2 (1)	0 (0)	1 (1)	5 (1)	3 (1)
Lipid parameters						
LDL-C, mean mmol/L ^a	2.7	2.9	2.9	2.7	2.8	2.9
ApoB, mean g/L	0.9	0.9	0.9	0.9	0.9	0.9
Lp(a), median nmol/L	35.0	34.0	33.0	38.0	33.0	34.5
ApoA1, mean g/L	1.5	1.5	1.5	1.5	1.5	1.5
HDL-C, mean mmol/L	1.4	1.5	1.3	1.4	1.4	1.4
Non-HDL-C, mean mmol/L	3.4	3.5	3.6	3.5	3.5	3.6
Free PSCK9, mean nmol/L	4.8	5.0	5.1	4.6	5.0	4.9
CHD characteristics, n (%)						
Coronary artery disease	62 (22)	61 (22)	19 (17)	19 (17)	129 (23)	137 (24)
Cerebrovascular or peripheral arterial disease	22 (8)	33 (12)	14 (13)	5 (5)	63 (11)	61 (11)
CV risk factors, n (%)						
Current smoking	38 (14)	45 (16)	21 (19)	16 (15)	92 (17)	79 (14)

	PBO + any statin without EZE		PBO + any atorvastatin with EZE		EvoMab + any statin	
	Q2W (N = 281)	QM (N = 277)	PBO Q2W (N = 112)	PBO QM (N = 109)	140 mg Q2W (N = 555)	420 mg QM (N = 562)
Diabetes mellitus type 2	31 (11)	43 (16)	16 (14)	28 (26)	103 (19)	72 (13)
Hypertension	158 (56)	152 (55)	62 (55)	62 (57)	338 (61)	312 (56)
Family history premature CHD	59 (21)	54 (20)	24 (21)	20 (18)	99 (18)	127 (23)
Low HDL-C	87 (31)	76 (27)	38 (34)	34 (31)	161 (29)	135 (24)
≥ 2 risk factors	114 (41)	110 (40)	51 (46)	48 (44)	235 (42)	214 (38)
NCEP risk categories, n (%)						
High	99 (35)	114 (41)	44 (39)	44 (40)	231 (42)	208 (37)
Moderately high	38 (14)	23 (8)	11 (10)	13 (12)	56 (10)	73 (13)
Moderate	80 (29)	76 (27)	31 (28)	31 (28)	162 (29)	153 (27)
Low	64 (23)	64 (23)	26 (23)	21 (19)	106 (19)	128 (23)
Lipid-lowering therapy at study entry (%)^b						
Statins	184 (66)	193 (70)	80 (71)	68 (62)	394 (71)	391 (70)
Bile acid sequestrants	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nicotinic acid	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ezetimibe	21 (8)	28 (10)	12 (11)	6 (6)	43 (8)	50 (9)
Concomitant lipid-lowering therapy use post-baseline (%)^c						
Any	27 (10)	19 (7)	7 (6)	9 (8)	72 (13)	27 (5)
Statins	17 (6)	5 (2)	6 (5)	4 (4)	48 (9)	9 (2)
Bile acid sequestrants	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nicotinic acid	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Ezetimibe	2 (1)	2 (1)	1 (1)	1 (1)	5 (1)	0 (0)
References: LAPLACE-2 CSR ¹⁰¹ Tables 9-3, 9-4, 14-2.4.7, 14-2.5.2, 14-4.41.21, 14-4.41.28, 14-8.8.8 and 14-8.8.9.						
Note: Data presented by randomised IP treatment groups across statin cohorts for brevity, details of baseline characteristics for randomised IP treatment arms within each						

	PBO + any statin without EZE		PBO + any atorvastatin with EZE		EvoMab + any statin	
	Q2W (N = 281)	QM (N = 277)	PBO Q2W (N = 112)	PBO QM (N = 109)	140 mg Q2W (N = 555)	420 mg QM (N = 562)
individual statin cohort are available in the primary study publication supplementary appendix and CSR. ^aCalculated LDL-C. ^bPrior to randomisation to statins and IP. ^cOther than study-dispensed statins or IP. ApoA1, apolipoprotein A1, ApoB, apolipoprotein B; CHD, coronary heart disease; CSR, clinical study report; CV, cardiovascular; EvoMab, evolocumab; EZE, ezetimibe; FAS, full analysis set; HDL-C, high-density lipoprotein cholesterol; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); NCEP, National Cholesterol Education Program; non-HDL-C, non-high-density lipoprotein cholesterol; PAD, peripheral arterial disease; PBO, placebo; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; QM, monthly; SD, standard deviation						

Table 4-8 Baseline characteristics and lipid-lowering medication use in RUTHERFORD-2, GAUSS-2, and DESCARTES (FAS)

	RUTHERFORD-2				GAUSS-2				DESCARTES	
	PBO Q2W (N = 54)	EvoMab 140 mg Q2W (N = 110)	PBO QM (N = 55)	EvoMab 420 mg QM (N = 110)	PBO Q2W + EZE 10 mg OD (N = 51)	EvoMab 140 mg Q2W + placebo OD (N = 103)	PBO QM + EZE 10 mg OD (N = 51)	EvoMab 420 mg QM + placebo OD (N = 102)	PBO QM (N = 302)	EvoMab QM (N = 599)
Demographics										
Age, years (SD)	51 (14)	53 (12)	47 (12)	52 (12)	62 (10)	61 (10)	60 (9)	63 (10)	57 (10)	56 (11)
Male, n (%)	29 (54)	66 (60)	31 (56)	64 (58)	24 (47)	57 (55)	29 (57)	56 (55)	140 (47)	290 (48)
Race, n (%)										
White	50 (93)	99 (90)	49 (89)	98 (89)	49 (96)	94 (91)	46 (90)	98 (96)	248 (82)	476(80)
Black	1 (2)	1 (1)	0 (0)	1 (1)	0 (0)	3 (3)	1 (2)	3 (3)	23 (8)	41 (7)
Asian	1 (2)	3 (4)	3 (6)	8 (7)	1 (2)	5 (5)	3 (6)	1 (1)	16 (5)	53 (9)
Other	2 (4)	6 (6)	3 (6)	3 (3)	1 (2)	0(0)	1 (2)	0(0)	15 (5)	29 (5)
Simon Broome diagnosis										
Definite	45 (83)	85 (77)	43 (78)	84 (76)	NR	NR	NR	NR	NR	NR
Possible	9 (17)	25 (23)	12 (22)	26 (24)	NR	NR	NR	NR	NR	NR
Lipid parameters										
LDL-C, mean mmol/L ^a	3.9	4.2	3.9	4.0	5.0	5.1	5.1	5.0	2.6	2.6
ApoB, mean g/L	1.1	1.2	1.1	1.1	1.4	1.4	1.4	1.3	0.9	0.9
Lp(a), median nmol/L	44.0	77.5	87.0	61.0	56.5	39.0	26.0	31.0	40.0	38.0
ApoA1, mean g/L	1.5	1.4	1.3	1.4	1.5	1.5	1.4	1.5	1.6	1.5
HDL-C, mean mmol/L	1.4	1.3	1.3	1.3	1.4	1.3	1.2	1.4	1.4	1.4

	RUTHERFORD-2				GAUSS-2				DESCARTES	
	PBO Q2W (N = 54)	EvoMab 140 mg Q2W (N = 110)	PBO QM (N = 55)	EvoMab 420 mg QM (N = 110)	PBO Q2W + EZE 10 mg OD (N = 51)	EvoMab 140 mg Q2W + placebo OD (N = 103)	PBO QM + EZE 10 mg OD (N = 51)	EvoMab 420 mg QM + placebo OD (N = 102)	PBO QM (N = 302)	EvoMab QM (N = 599)
Non-HDL-C, mean mmol/L	4.5	4.9	4.5	4.6	6.0	5.9	6.0	5.8	3.2	3.2
Free PSCK9, mean nmol/L	6.0	6.4	6.1	6.1	4.4	4.0	4.1	3.7	6.7	6.6
CHD characteristics, n (%)										
Coronary artery disease	16 (30)	38 (35)	10 (18)	39 (36)	16 (31)	30 (29)	12 (24)	32 (31)	42 (14)	94 (16)
Cerebrovascular disease or PAD	11 (20)	18 (16)	7 (13)	20 (18)	11 (22)	11 (11)	8 (16)	19 (19)	11 (4)	26 (4)
CV risk factors, n (%)										
Current smoking	4 (7)	18 (16)	13 (24)	17 (16)	5 (10)	12 (12)	4 (8)	3 (3)	48 (16)	87 (15)
Type 2 diabetes	4 (7)	5 (5)	5 (9)	10 (9)	11 (22)	20 (19)	16 (31)	15 (15)	42 (14)	62 (10)
Hypertension	19 (35)	34 (31)	17 (31)	37 (34)	30 (59)	57 (55)	38 (75)	56 (55)	149 (49)	289 (48)
Family history of premature CHD	30 (56)	64 (58)	37 (67)	62 (56)	10 (20)	31 (30)	22 (43)	36 (35)	66 (22)	142 (24)
Low HDL-C	13 (24)	42 (38)	20 (36)	37 (34)	18 (35)	37 (36)	18 (35)	29 (28)	98 (33)	180 (30)
≥ 2 risk factors	20 (37)	52 (47)	27 (49)	49 (45)	20 (39)	54 (52)	35 (69)	38 (37)	128 (42)	224 (37)

	RUTHERFORD-2				GAUSS-2				DESCARTES	
	PBO Q2W (N = 54)	EvoMab 140 mg Q2W (N = 110)	PBO QM (N = 55)	EvoMab 420 mg QM (N = 110)	PBO Q2W + EZE 10 mg OD (N = 51)	EvoMab 140 mg Q2W + placebo OD (N = 103)	PBO QM + EZE 10 mg OD (N = 51)	EvoMab 420 mg QM + placebo OD (N = 102)	PBO QM (N = 302)	EvoMab QM (N = 599)
NCEP risk categories, n (%)										
High	22 (41)	49 (45)	20 (37)	51 (46)	32 (63)	51 (50)	32 (63)	58 (57)	79 (26)	156 (26)
Moderately high	0 (0)	7 (6)	4 (7)	8 (7)	5 (10)	16 (16)	8 (16)	16 (16)	29 (10)	56 (9)
Moderate	11 (20)	34 (31)	16 (29)	29 (26)	9 (18)	20 (19)	8 (16)	16 (16)	97 (32)	203 (34)
Low	21 (39)	20 (18)	15 (27)	22 (20)	5 (10)	16 (16)	3 (6)	12 (12)	97 (32)	184 (31)
Lipid-lowering therapy use at baseline (RUTHERFORD-2, GAUSS-2) or screening (DESCARTES), n (%)^b										
Any	54 (100)	110 (100)	55 (100)	110 (100)	15 (29)	34 (33)	16 (31)	37 (36)	145 (48)	269 (45)
Statins	54 (100)	110 (100)	55 (100)	110 (100)	9 (18)	19 (18)	10 (20)	17 (17)	134 (44)	250 (42)
Bile acid sequestrants	4 (7)	8 (7)	4 (7)	10 (9)	3 (6)	3 (3)	2 (4)	6 (6)	0 (0)	0 (0)
Nicotinic acid	1 (2)	2 (2)	1 (2)	3 (3)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (0)
Ezetimibe	33 (61)	67 (61)	36 (66)	68 (62)	0 (0)	0 (0)	0 (0)	0 (0)	16 (5)	43 (7)
Concomitant lipid-lowering therapy use post-baseline (RUTHERFORD-2, GAUSS-2) or on-study (DESCARTES), (%)^c										
Any	54 (100)	110 (100)	55 (100)	110 (100)	15 (29)	37 (36)	16 (31)	38 (37)	19 (6)	49 (8)
Statins	54 (100)	110 (100)	55 (100)	110 (100)	9 (18)	19 (18)	10 (20)	18 (18)	2 (1)	12 (2)
Bile acid sequestrants	4 (7)	8 (7)	4 (7)	10 (9)	3 (6)	4 (4)	2 (4)	6 (6)	0 (0)	1 (0)
Nicotinic acid	1 (2)	1 (2)	2 (2)	3 (3)	1 (2)	1 (1)	1 (2)	0 (0)	1 (0)	1 (0)
Ezetimibe	33 (61)	68 (62)	36 (66)	68 (62)	0 (0)	3 (3)	0 (0)	0 (0)	1 (0)	2 (0)
Number of intolerable statins n (%)										
2	NR	NR	NR	NR	25 (49)	46 (45)	17 (33)	50 (49)	NR	NR
3	NR	NR	NR	NR	13 (25)	37 (36)	22 (43)	32 (31)	NR	NR

	RUTHERFORD-2				GAUSS-2				DESCARTES	
	PBO Q2W (N = 54)	EvoMab 140 mg Q2W (N = 110)	PBO QM (N = 55)	EvoMab 420 mg QM (N = 110)	PBO Q2W + EZE 10 mg OD (N = 51)	EvoMab 140 mg Q2W + placebo OD (N = 103)	PBO QM + EZE 10 mg OD (N = 51)	EvoMab 420 mg QM + placebo OD (N = 102)	PBO QM (N = 302)	EvoMab QM (N = 599)
≥ 4	NR	NR	NR	NR	13 (25)	20 (19)	12 (24)	20 (20)	NR	NR
References: RUTHERFORD-2 primary study publication¹⁰² and CSR¹⁰³ Table 9-2, 9-3, 9-4, 14-2.4.2, 14-2.5.1, 14-2.7.1, 14-4.21.4 and 14-8.8.2; GAUSS-2 primary study publication¹⁰⁴ and CSR¹⁰⁵ Tables 14-2.2.1, 14-2.4.2, 14-2.5.1, 14-2.6.2, 14-2.7.1, and 14-4.21.4, and 14-8.8.1; DESCARTES primary study publication¹⁰⁶ and CSR¹⁰⁷ Tables 9-2, 9-3, 9-4, 14-2.8.1, 14-2.8.2, and 14-8.8.1. ^aCalculated LDL-C. ^bPrior to randomisation to IP (RUTHERFORD-2 and GAUSS-2) or assignment to background lipid-lowering therapy (DESCARTES). ^cOther than randomised IP (or assigned background lipid-lowering therapy in DESCARTES). ApoA1, apolipoprotein A1, ApoB, apolipoprotein B; CHD, coronary heart disease; CSR, clinical study report; CV, cardiovascular; EvoMab, evolocumab; EZE, ezetimibe; FAS, full analysis set; HDL-C, high-density lipoprotein cholesterol; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; NCEP, National Cholesterol Education Program; non-HDL-C, non-high-density lipoprotein cholesterol; NR, not reported; OD, once daily; PBO, placebo; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; QM, monthly; SD, standard deviation										

4.6 *Quality assessment of the relevant randomised controlled trials*

Quality assessment was conducted using the criteria specified in the NICE User Guide for Company Submission of Evidence, adapted from the Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare.¹¹⁵

The risk of bias was assessed as low across all domains of each of the relevant RCTs. Participants randomised and allocation concealment was achieved using interactive voice/web response system, suggesting a low risk of both randomisation and allocation concealment bias. Patients and all trial personnel were blinded to treatment assignment. In addition, an independent data monitoring committee reviewed all data so as to further reduce the risk of bias. All randomised patients who received ≥ 1 dose of investigational product (IP) were included in the analysis in a modified intention-to-treat approach. Data were also reported for all outcomes identified as assessed in the trial methods, suggesting that the risk of selective reporting was low. There were no unexpected imbalances in drop-outs between groups across all four trials.

A summary of the risk of bias assessment is provided in Table 4-9.

Table 4-9 Quality assessment of the relevant RCTs

	20110117 (RUTHERFORD-2)	20110115 (LAPLACE-2)	20110116 (GAUSS-2)	20110109 (DESCARTES)
Was randomisation carried out appropriately?	Yes, patients were randomly assigned via a computer-generated randomisation schedule in 2:2:1:1 ratio	Yes, patients were randomly assigned via a computer-generated randomisation schedule (statin without ezetimibe ratio 2:2:1:1 and with ezetimibe ratio 2:2:1:1:1:1)	Yes, patients were randomly assigned via a computer-generated randomisation schedule in 2:2:1:1 ratio	Yes, patients were randomly assigned via a computer-generated randomisation schedule in 2:1 ratio.
Was the concealment of treatment allocation adequate?	Yes, allocation concealment was achieved using an IVRS			
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, no major differences existed between the randomised groups in baseline demographics or clinical characteristics.			
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, participants and investigators were blinded to treatment. An independent data monitoring committee reviewed all data to maintain the blinding.	Yes, participants and investigators were blinded to treatment (double-blind with matching volumes, double-dummy for additional ezetimibe randomisation for the atorvastatin group). An independent data monitoring committee reviewed all data to maintain the blinding.	Yes, participants and investigators were blinded to treatment. An independent data monitoring committee reviewed all data to maintain the blinding.	Yes, participants and investigators were blinded to treatment. An independent data monitoring committee reviewed all data to maintain the blinding.
Were there any unexpected imbalances in drop-outs between groups?	No, treatment groups were generally balanced with respect to discontinuations or withdrawals.			

	20110117 (RUTHERFORD-2)	20110115 (LAPLACE-2)	20110116 (GAUSS-2)	20110109 (DESCARTES)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, all efficacy and safety assessments listed in methods were reported in the results section of the CSR			
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the FAS included all patients who received ≥ 1 dose of IP (i.e. a modified ITT approach).			
CSR, clinical study report; FAS, full analysis set; IP, investigational product; ITT, intention-to-treat; IVRS, interactive voice/web response system; RCT, randomised controlled trial				

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Details of evidence presented

All pre-specified primary, secondary, and tertiary efficacy outcomes for all relevant RCTs (defined in Section 4.2) are provided in the main submission and submission appendices. Table 4-10 summarises details of those pre-specified efficacy outcomes presented in detail within the main submission. For the supplementary long-term extension studies, only mean percent change in LDL-C from parent study baseline is presented in the main submission to support evaluation of long-term efficacy, with additional outcomes available in the interim clinical study reports and relevant study publications. A more detailed rationale for the presentation of outcomes from the relevant RCTs in the main submission versus the submission appendices is provided in Appendix V.

Only LDL-C outcomes using the calculated approach to LDL-C assessment are provided in the main submission. This is in order to best reflect UK clinical practice (where LDL-C is routinely assessed by this method) and to align with the evolocumab's SmPC (which also cites calculated LDL-C values). Data for LDL-C outcomes using the primary LDL-C assessment method for each relevant RCT, i.e. reflexive in LAPLACE-2, RUTHERFORD-2, and GAUSS-2, and ultracentrifugation in DESCARTES are provided in Appendix V. See Section 4.2 for further details on the LDL-C assessment methods utilised in the relevant RCTs.

Table 4-10 Details of efficacy results presented from the relevant RCTs and LTE studies in the main submission

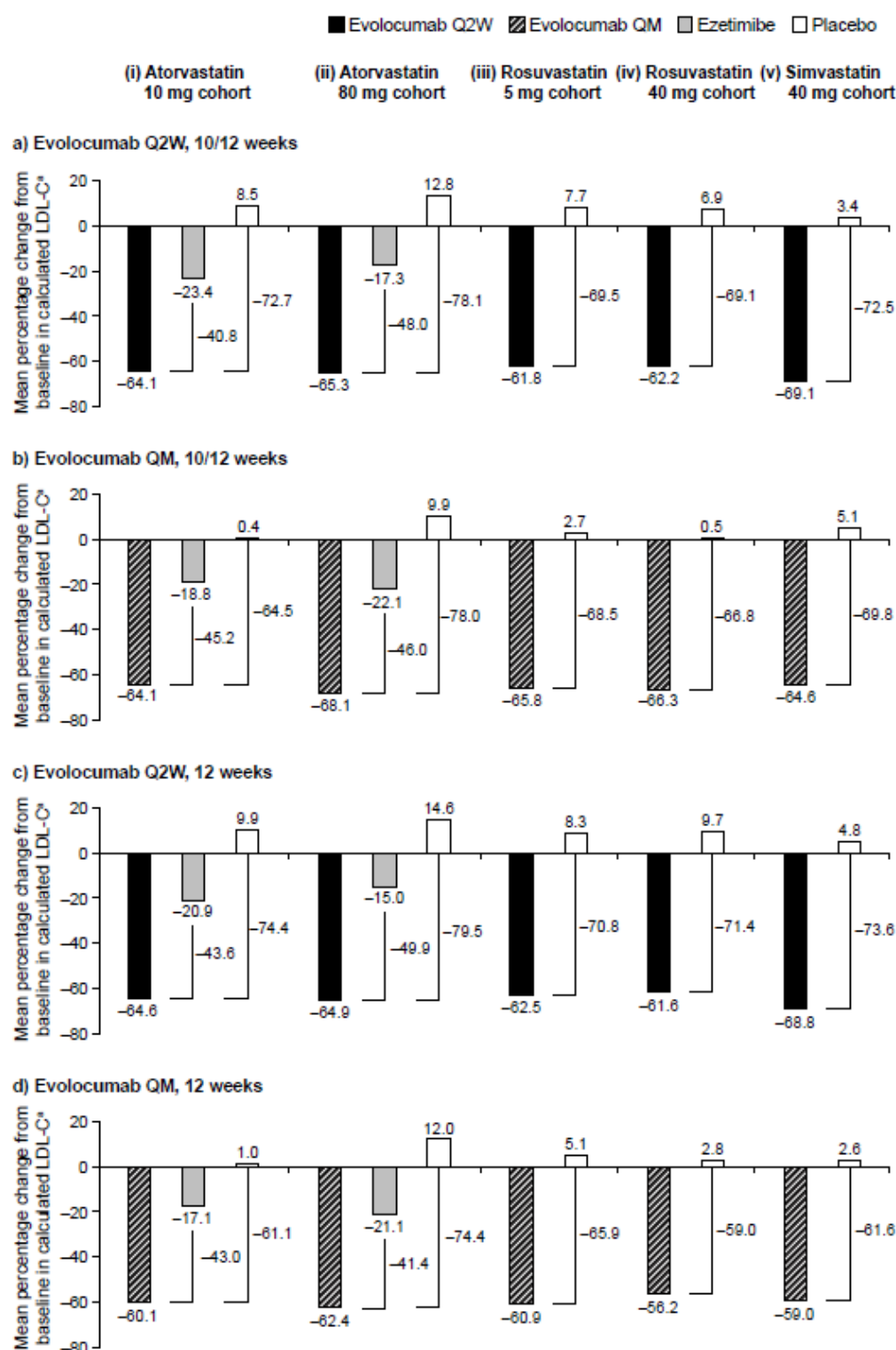
Study	Outcomes presented in main submission
Relevant RCTs	
20110115 (LAPLACE-2)	Co-primary endpoints at the mean of weeks 10/12 and at week 12: • LDL-C (calculated) – mean percent change from baseline and treatment differences • LDL-C (calculated) – mean percent change from baseline and treatment differences in a pooled analysis across all statin cohorts and in a pooled analysis across atorvastatin cohorts (LAPLACE-2 only)
20110117 (RUTHERFORD-2)	
20110116 (GAUSS-2)	
20110109 (DESCARTES)	Primary endpoint: • LDL-C (calculated) – mean percent change from baseline at week 52 and treatment differences
	Secondary endpoint: • LDL-C (calculated) – mean percent change from baseline at week 12 and treatment differences
Supplementary ongoing, randomised, controlled, open-label LTE studies	
20110110 (OSLER)	Secondary endpoints: • LDL-C (calculated) – mean percent change from parent study baseline to week 124 (OSLER) and week 24 (OSLER-2) and treatment differences at weeks 12 and 52 (OSLER) and weeks 12 and 24 (OSLER-2). Data cutoff 01 April 2014. • LDL-C (calculated) – mean percent change from parent study baseline to week 48 and treatment differences at week 12 (integrated analysis of OSLER and OSLER-2). Data cutoff 31 October 2014.
20120138 (OSLER-2)	
LDL-C, low-density lipoprotein cholesterol; LTE, long-term extension; RCT, randomised controlled trial	

Results of the relevant randomised controlled trials

LAPLACE-2 (evolocumab versus placebo and versus ezetimibe over 12 weeks in patients with primary hypercholesterolaemia and mixed dyslipidaemia receiving moderate- to high-intensity background statins)

LDL-C percent change from baseline (individual statin cohorts): Evolocumab 140 mg Q2W and 420 mg QM demonstrated statistically significant mean percent reductions in calculated LDL-C (from baseline at the mean of weeks 10/12) compared with placebo in each statin cohort, with treatment differences of -69.1% to -78.1% across statin cohorts in the Q2W group and -64.5% to -78.0% across statin cohorts in the QM group ($p < 0.001$ for all treatment differences) (Figure 4-7, Table 4-11, and Table 4-12). Compared with ezetimibe, treatment with evolocumab also resulted in statistically significant mean percent reductions in calculated LDL-C (from baseline at the mean of weeks 10/12) in each atorvastatin cohort, with treatment differences of -40.8% to -48.0% across atorvastatin cohorts in the Q2W group and -45.2% to -46.0% across atorvastatin cohorts in the QM group ($p < 0.001$ for all treatment differences) (Figure 4-7, Table 4-11, and Table 4-12). These results were consistent when the mean percent change in LDL-C was measured at week 12 (Figure 4-7, Table 4-11, and Table 4-12) and when LDL-C was measured using the reflexive approach to LDL-C assessment at both the mean of weeks 10/12 and at week 12 (Appendix V).

Figure 4-7 Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and and at week 12 in LAPLACE-2 (FAS)



References: LAPLACE-2 primary study publication appendix¹⁰⁰ and CSR¹⁰¹ Tables 10-3, 14-4.1.6, 14-4.1.7, 14-4.1.8, 14-4.1.9, and 14-4.1.10.

Note: Treatment differences were within each dose frequency group using placebo or ezetimibe in the same group as the reference. $p < 0.001$ for each treatment difference.

^aValues are least-squares means, which are from the repeated measures model that includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

CSR, clinical study report; FAS, full analysis set; IVRS, interactive voice/web response system; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly

Table 4-11 Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS)

	Atorvastatin 10 mg cohort					
	Placebo Q2W + ezetimibe 10 mg OD (N = 56)	Placebo Q2W + placebo OD (N = 56)	EvoMab 140 mg Q2W + placebo OD (N = 110)	Placebo QM + ezetimibe 10 mg OD (N = 55)	Placebo QM + placebo OD (N = 55)	EvoMab 420 mg QM + placebo OD (N = 110)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^a	-23.4 (-28.3, -18.5)	8.5 (3.9, 13.2)	-64.1 (-67.5, -60.8)	-18.8 (-24.0, -13.6)	0.4 (-4.8, 5.7)	-64.1 (-67.7, -60.4)
Week 12 mean percent change from baseline (95% CI) ^a	-20.9 (-26.4, -15.5)	9.9 (4.6, 15.1)	-64.6 (-68.3, -60.8)	-17.1 (-22.7, -11.4)	1.0 (-4.7, 6.7)	-60.1 (-64.1, -56.0)
	Atorvastatin 80 mg cohort					
	Placebo Q2W + ezetimibe 10 mg OD (N = 56)	Placebo Q2W + placebo OD (N = 55)	EvoMab 140 mg Q2W + placebo OD (N = 109)	Placebo QM + ezetimibe 10 mg OD (N = 54)	Placebo QM + placebo OD (N = 55)	EvoMab 420 mg QM + placebo OD (N = 110)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^a	-17.3 (-25.3, -9.3)	12.8 (4.5, 21.1)	-65.3 (-71.0, -59.5)	-22.1 (-29.0, -15.2)	9.9 (3.1, 16.7)	-68.1 (-72.9, -63.2)
Week 12 mean percent change from baseline (95% CI) ^a	-15.0 (-24.3, -5.8)	14.6 (5.1, 24.1)	-64.9 (-71.5, -58.4)	-21.1 (-28.7, -13.4)	12.0 (4.3, 19.6)	-62.4 (-67.9, -57.0)

	Rosuvastatin 5 mg cohort				Rosuvastatin 40 mg cohort				Simvastatin 40 mg cohort			
	Placebo Q2W (N = 58)	EvoMab 140 mg Q2W (N = 113)	Placebo QM (N = 57)	EvoMab 420 mg QM (N = 115)	Placebo Q2W (N = 56)	EvoMab 140 mg Q2W (N = 111)	Placebo QM (N = 55)	EvoMab 420 mg QM (N = 112)	Placebo Q2W (N = 56)	EvoMab 140 mg Q2W (N = 112)	Placebo QM (N = 55)	EvoMab 420 mg QM (N = 115)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^a	7.7 (2.8, 12.6)	-61.8 (-65.4, -58.2)	2.7 (-2.5, 7.8)	-65.8 (-69.5, -62.1)	6.9 (0.8, 13.1)	-62.2 (-66.6, -57.7)	0.5 (-6.8, 7.8)	-66.3 (-71.4, -61.3)	3.4 (-3.8, 10.5)	-69.1 (-75.3, -63.0)	5.1 (-5.1, 15.4)	-64.6 (-72.9, -56.4)
Week 12 mean percent change from baseline (95% CI) ^a	8.3 (2.7, 13.8)	-62.5 (-66.6, -58.5)	5.1 (-0.3, 10.4)	-60.9 (-64.7, -57.1)	9.7 (2.7, 16.7)	-61.6 (-66.7, -56.6)	2.8 (-5.9, 11.4)	-56.2 (-62.2, -50.2)	4.8 (-2.7, 12.3)	-68.8 (-75.2, -62.5)	2.6 (-8.0, 13.1)	-59.0 (-67.4, -50.6)
Reference: LAPLACE-2 CSR ¹⁰¹ Tables 14-4.1.6, 14-4.1.7, 14-4.1.8, 14-4.1.9, and 14-4.1.10.												
Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS and this analysis. Three patients did not receive IP as randomised (one in the evolocumab Q2W plus oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis.												
^a Values are least-squares means, which are from the repeated measures model that includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.												
CI, confidence interval; CSR, clinical study report; EvoMab, evolocumab; FAS, full analysis set; IP, investigational product; IVRS, Interactive Voice Response System; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; OD, once daily; QM, monthly												

Table 4-12 Treatment difference in mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and week 12 in LAPLACE-2 (FAS)

Mean of weeks 10/12		Evolocumab 140 mg Q2W vs. ezetimibe 10 mg OD or placebo Q2W					Evolocumab 420 mg QM vs. ezetimibe 10 mg OD or placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^{a,b}	-72.7 (-78.4, -66.9) p < 0.001 ^c	-78.1 (-88.1, -68.0) p < 0.001 ^c	-69.5 (-75.5, -63.4) p < 0.001 ^c	-69.1 (-76.6, -61.5) p < 0.001 ^c	-72.5 (-78.2, -66.8) p < 0.001 ^c	-64.5 (-70.9, -58.1) p < 0.001 ^c	-78.0 (-86.3, -69.6) p < 0.001 ^c	-68.5 (-74.8, -62.1) p < 0.001 ^c	-66.8 (-75.6, -58.0) p < 0.001 ^c	-69.8 (-78.5, -61.0) p < 0.001 ^c
	Treatment difference vs. ezetimibe (95% CI) ^{a,b}	-40.8 (-46.7, -34.9) p < 0.001 ^c	-48.0 (-57.8, -38.1) p < 0.001 ^c	-	-	-	-45.2 (-51.6, -38.9) p < 0.001 ^c	-46.0 (-54.4, -37.5) p < 0.001 ^c	-	-	-
Week 12		Evolocumab 140 mg Q2W vs. ezetimibe 10 mg OD or placebo Q2W					Evolocumab 420 mg QM vs. ezetimibe 10 mg OD or placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^{a,b}	-74.4 (-80.9, -68.0) p < 0.001 ^c	-79.5 (-91.0, -68.0) p < 0.001 ^c	-70.8 (-77.6, -64.0) p < 0.001 ^c	-71.4 (-80.0, -62.8) p < 0.001 ^c	-73.6 (-80.1, -67.2) p < 0.001 ^c	-61.1 (-68.0, -54.1) p < 0.001 ^c	-74.4 (-83.8, -65.0) p < 0.001 ^c	-65.9 (-72.5, -59.4) p < 0.001 ^c	59.0 (-69.5, -48.4) p < 0.001 ^c	-61.6 (-70.8, -52.4) p < 0.001 ^c
	Treatment difference vs. ezetimibe (95% CI) ^{a,b}	-43.6 (-50.2, -37.1) p < 0.001 ^c	-49.9 (-61.2, -38.7) p < 0.001 ^c	-	-	-	-43.0 (-49.9, -36.1) p < 0.001 ^c	-41.4 (-50.8, -31.9) p < 0.001 ^c	-	-	-

References: LAPLACE-2 primary study publication appendix¹⁰⁰ and CSR¹⁰¹ Tables 10-3, 14-4.1.6, 14-4.1.7, 14-4.1.8, 14-4.1.9, and 14-4.1.10.

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS and this analysis. Three patients did not receive IP as randomised (one in the evolocumab Q2W plus oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis.

^aValues are least squares means, which are from the repeated measures model that includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates. ^bTreatment differences were within each dose frequency group using oral placebo plus subcutaneous placebo or ezetimibe plus subcutaneous placebo as the reference. ^cNominal p value. No multiplicity adjustment was carried out for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy, although the least significant p value across the coprimary endpoints is < 0.001.

CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IP, investigational product; IVRS, Interactive Voice Response System; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; OD, once daily; QM, monthly

LDL-C percent change from baseline versus placebo (pooled statin cohorts):

Supportive analyses were conducted to pool treatment effects across all statins (evolocumab versus placebo, prespecified) and across the atorvastatin cohorts (evolocumab versus ezetimibe, ad-hoc).

For the comparison versus placebo, all patients in the FAS except those randomised to ezetimibe were included in the analyses. For the comparison versus ezetimibe, all patients in the FAS randomised to the atorvastatin cohorts were included in the analyses. Pooling of treatment effects was conducted using fixed and random effects meta-analysis models. Each statin cohort was treated as a separate study in the study level random effects model, and measures of heterogeneity in treatment effects across statin dose cohorts were provided.

Results from these supportive analyses are in accordance with the main study analyses. Evolocumab Q2W and QM were associated with statistically significant reductions compared with placebo and with ezetimibe in mean percent change in LDL-C from baseline at both the mean of weeks 10/12 and at week 12, irrespective of statin cohort (comparison versus placebo) or atorvastatin cohort (comparison versus ezetimibe), in both the fixed effects and random effects model (Table 4-13 and Table 4-14).

Table 4-13 Combined statin analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS)

		Placebo Q2W (N = 281)	Evolocumab 140 mg Q2W (N = 555)	Placebo QM (N = 277)	Evolocumab 420 mg QM (N = 562)
Mean of weeks 10/12	Mean percent change from baseline (95% CI) ^a	7.9 (5.4, 10.5)	-64.3 (-66.1, -62.5)	4.6 (1.7, 7.4)	-65.1 (-67.0, -63.1)
	Fixed effects treatment difference (95% CI) ^a	-	-72.3 (-75.4, -69.1) p < 0.001 ^d	-	-69.6 (-73.1, -66.1) p < 0.001 ^d
	Random effects treatment difference (95% CI) ^{b,c}	-	-71.8 (-74.7, -68.9) Q = 2.7; I ² = 0.0	-	-69.1 (-73.5, -64.8) Q = 6.7; I ² = 0.40
Week 12	Mean percent change from baseline (95% CI) ^a	9.5 (6.6, 12.4)	-64.3 (-66.4, -62.3)	5.6 (2.4, 8.7)	-59.1 (-61.3, -56.8)
	Fixed effects treatment difference (95% CI) ^{a,b}	-	-73.8 (-77.4, -70.3) p < 0.001 ^d	-	-64.6 (-68.5, -60.8) p < 0.001 ^d
	Random effects treatment difference (95% CI) ^{b,c}	-	-73.3 (-76.6, -70.0) Q = 2.0; I ² = 0.0	-	-64.4 (-69.2, -59.6) Q = 6.9; I ² = 0.40

Reference: LAPLACE-2 CSR¹⁰¹ Table 14-4.2.13.

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS. Three patients did not receive IP as randomised (one in the evolocumab Q2W plus oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS.

^aLeast-squares mean and fixed effects treatment difference are from the repeated measures model that includes the stratification factor, randomised statin dose cohort, randomised IP treatment group, visit, and randomised IP treatment group by visit. All patients in the FAS except those randomised to ezetimibe are included in the model. ^bTreatment differences were within each dose frequency group using oral placebo plus subcutaneous placebo as the reference. ^cTreatment difference estimated using DerSimonian-Laird random effect estimator. Q and I-squared statistics are provided as measures of heterogeneity. Treatment difference estimates for each statin cohort used in the random effect model are from the primary analysis model that includes all patients in the FAS in each statin cohort. ^dNominal p value. No multiplicity adjustment was carried out for this supportive analysis.

CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly

Table 4-14 Combined atorvastatin analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS)

		Placebo Q2W + EZE 10 mg OD (N = 112)	Evolocumab 140 mg Q2W (N = 219)	Placebo QM + EZE 10 mg OD (N = 109)	Evolocumab 420 mg QM (N = 220)
Mean of weeks 10/12	Mean percent change from baseline (95% CI) ^a	-20.2 (-24.6, -15.8)	-64.7 (-67.8, -61.6)	-20.4 (-24.5, 16.3)	-66.2 (-69.1, -63.3)
	Fixed effects treatment difference (95% CI) ^a	-	-44.5 (-49.9, -39.2) p < 0.001 ^d	-	-45.8 (-50.8, -40.8) p < 0.001 ^d
	Random effects treatment difference (95% CI) ^{b,c}	-	-43.3 (-50.0, -36.5) Q ₂ = 1.5; I ² = 0.4	-	-45.5 (-50.5, -40.5) Q ₂ = 0.0; I ² = 0.0
Week 12	Mean percent change from baseline (95% CI) ^a	-17.9 (-23.0, -12.8)	-64.8 (-68.3, -61.2)	-18.9 (-23.4, -14.5)	-61.4 (-64.6, -58.2)
	Fixed effects treatment difference (95% CI) ^{a,b}	-	-46.9 (-53.0, -40.7) p < 0.001 ^d	-	-42.5 (-47.9, -37.0) p < 0.001 ^d
	Random effects treatment difference (95% CI) ^{b,c}	-	-45.2 (-50.8, -39.6) Q ₂ = 0.9; I ² = 0.0	-	-42.4 (-48.0, -36.9) Q ₂ = 0.1; I ² = 0.0

Reference: LAPLACE-2 supplementary data table 14-4.41.413.¹¹⁶

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS. Three patients did not receive IP as randomised (one in the evolocumab Q2W plus oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS.

^aLeast-squares mean and fixed effects treatment difference are from the repeated measures model that includes the stratification factor, randomised statin dose cohort, randomised IP treatment group, visit, and randomised IP treatment group by visit. All patients in the FAS atorvastatin cohorts are included in the model.

^bTreatment differences were within each dose frequency group using ezetimibe plus subcutaneous placebo as the reference. ^cTreatment difference estimated using DerSimonian-Laird random effect estimator. Q and I-squared statistics are provided as measures of heterogeneity. Treatment difference estimates for each statin cohort used in the random effect model are from the primary analysis model that includes all patients in the FAS atorvastatin cohorts. ^dNominal p value. No multiplicity adjustment was carried out for this supportive analysis.

CI, confidence interval; CSR, clinical study report; EZE, ezetimibe; FAS, full analysis set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; OD, once daily; Q2W, every 2 weeks; QM, monthly.

Other LDL-C parameters: Consistent with the results above, evolocumab Q2W and QM also demonstrated significant improvements compared with placebo in each statin cohort and ezetimibe in each atorvastatin cohort across other LDL-C parameters:

- mean absolute (mmol/L) change from baseline in LDL-C assessed using both the reflexive and calculated approach to LDL-C assessment at both the mean of weeks 10/12 and week 12 (Appendix V)
- proportion of patients achieving LDL-C levels < 1.8 mmol/L assessed using both the reflexive and calculated approach to LDL-C assessment at both the mean of weeks 10/12 and week 12 (Appendix V).

Other lipid parameters: Evolocumab Q2W and QM also resulted in statistically significant improvements in other lipid parameters, including non-HDL-C, ApoB, and Lp(a), from baseline at the means of weeks 10/12 and at week 12 compared with placebo (Appendix V).

RUTHERFORD-2 (evolocumab versus placebo over 12 weeks in patients with HeFH receiving stable background lipid-lowering therapy (statin ± other lipid-lowering therapies))

LDL-C percent change from baseline: Evolocumab 140 mg Q2W and 420 mg QM demonstrated statistically significant mean percent reductions in calculated LDL-C (from baseline at the mean of weeks 10/12) compared with placebo with treatment differences of -61.3% in the Q2W group and -66.2% in the QM group ($p < 0.001$ for all treatment differences) (

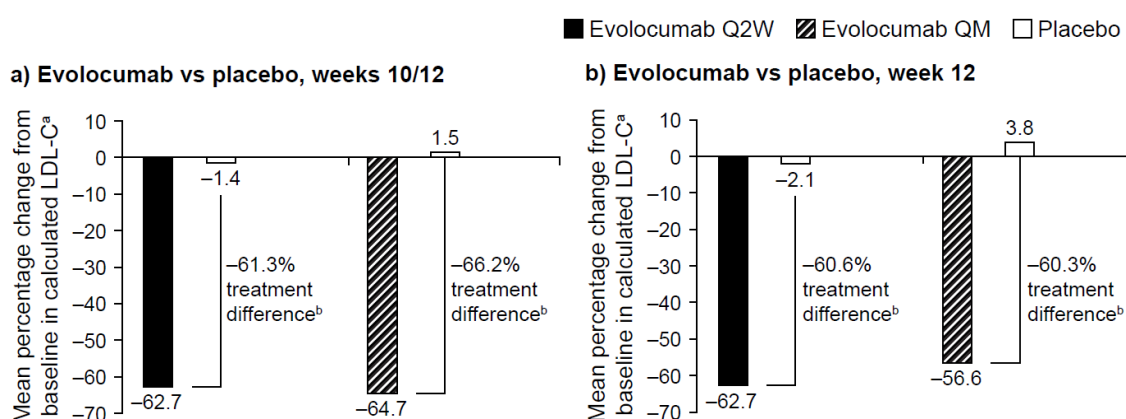
Figure 4-8 and

Table 4-15). These results were consistent when the mean percent change in LDL-C was measured at week 12 (

Figure 4-8 and

Table 4-15) and when LDL-C was measured using the reflexive approach to LDL-C assessment at both the mean of weeks 10/12 and at week 12 (Appendix V). A total of 62% of patients were receiving ezetimibe as part of the background lipid-lowering therapy strategy. Subgroup analyses presented in Section 4.8 show that the LDL-C-lowering effect of evolocumab is consistent irrespective of whether or not ezetimibe formed part of the background therapy.

Figure 4-8 Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in RUTHERFORD-2 (FAS)



Reference: RUTHERFORD-2 CSR¹⁰³ Tables 10-3 and 14-4.1.2.

^aValues are least-squares means, which are from the repeated measures model that includes treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates. ^bTreatment differences were within each dose frequency group using placebo in the same group as the reference. ^c $p < 0.001$ for all treatment differences.

CSR, clinical study report; FAS, full analysis set; IVRS, Interactive Voice Response System; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly

Table 4-15 Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in RUTHERFORD-2 (FAS)

	Evolocumab Q2W vs. placebo Q2W		Evolocumab QM vs. placebo QM	
	Placebo Q2W (N = 54)	Evolocumab 140 mg Q2W (N = 110)	Placebo QM (N = 55)	Evolocumab 420 mg QM (N = 110)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^a	-1.4 (-6.3, 3.6)	-62.7 (-66.2, -59.2)	1.5 (-3.2, 6.2)	-64.7 (-68.1, -61.4)
Mean of weeks 10/12 treatment difference (95% CI) ^{a,b}	-	-61.3 (-67.2, -55.4) $p < 0.001^c$	-	-66.2 (-71.9, -60.6) $p < 0.001^c$
Week 12 mean percent change from baseline (95% CI) ^a	-2.1 (-7.2, -3.0)	-62.7 (-66.3, -59.1)	3.8 (-2.5, 10.0)	-56.6 (-60.9, -52.3)
Week 12 treatment difference (95% CI) ^{a,b}	-	-60.6 (-66.7, -54.5) $p < 0.001^c$	-	-60.3 (-67.8, -52.9) $p < 0.001^c$
Reference: RUTHERFORD-2 CSR ¹⁰³ Tables 10-3 and 14-4.1.2.				
Note: The RUTHERFORD-2 efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS and this analysis. Two patients did not receive IP as randomised (one in the placebo Q2W group and one in the evolocumab Q2W group) and were excluded from the FAS and this analysis.				
^a Values are least-squares means, which are from the repeated measures model that includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates. ^b Treatment differences were within each dose frequency group using placebo in same group as the reference. ^c Nominal p value. No multiplicity adjustment was carried out for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy, although the least significant p value across the coprimary endpoints is < 0.001 .				
CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IP, investigational product; IVRS, Interactive Voice Response System; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly				

Other LDL-C parameters: Consistent with the results above, evolocumab Q2W and QM also demonstrated statistically significant improvements compared with placebo across other LDL-C parameters:

- mean absolute (mmol/L) change from baseline in LDL-C assessed using both the reflexive and calculated approach to LDL-C assessment at both the mean of weeks 10/12 and week 12 (Appendix V)

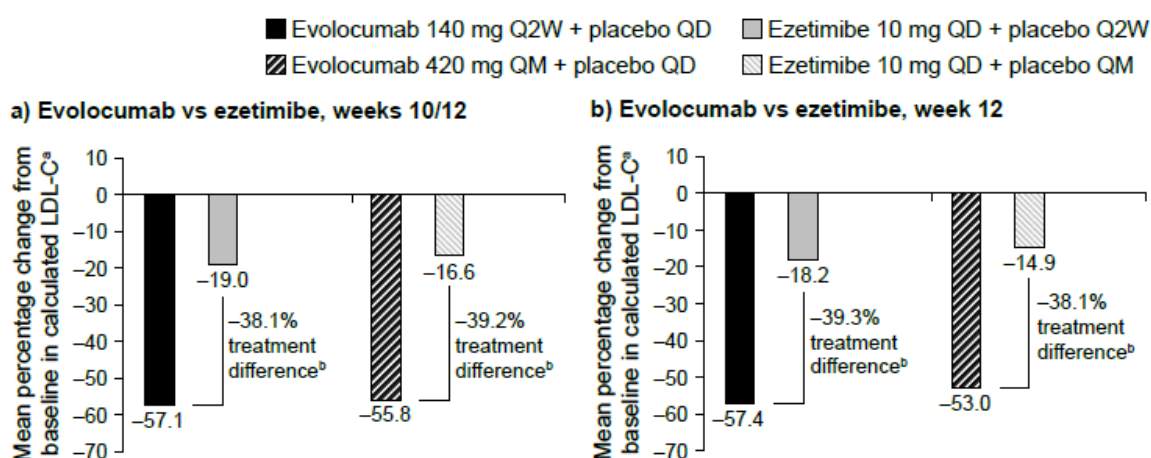
- proportion of patients achieving LDL-C levels < 1.8 mmol/L assessed using both the reflexive and calculated approach to LDL-C assessment at both the mean of weeks 10/12 and week 12 (Appendix V).

Other lipid parameters: Evolocumab Q2W and QM also resulted in statistically significant improvements in other lipid parameters, including non-HDL-C, ApoB, and Lp(a), from baseline at the mean of weeks 10/12 and at week 12 compared with placebo (Appendix V).

GAUSS-2 (evolocumab versus ezetimibe in statin-intolerant patients with primary hypercholesterolaemia and mixed dyslipidaemia over 12 weeks)

LDL-C percent change from baseline: Evolocumab 140 mg Q2W and 420 mg QM demonstrated statistically significant mean percent reductions in calculated LDL-C (from baseline at the mean of weeks 10/12) compared with ezetimibe, with treatment differences of -38.1% in the Q2W group and -39.2% in the QM group ($p < 0.001$ for both treatment differences) (Figure 4-9 and Table 4-16). These results were consistent when the mean percent change in LDL-C was measured at week 12 (Figure 4-9 and Table 4-16) and when LDL-C was measured using the reflexive approach to LDL-C assessment at both the mean of weeks 10/12 and at week 12 (Appendix V).

Figure 4-9 Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and week 12 in GAUSS-2 (FAS)



Reference: GAUSS-2 CSR¹⁰⁵ Tables 10-4 and 14-4.1.3.

^aValues are least-squares means, which is from the repeated measures model that includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates. ^bTreatment differences were within each dose frequency group using placebo plus ezetimibe in the same group as the reference. $p < 0.001$ for each treatment difference.

CSR, clinical study report; FAS, full analysis set; IVRS, Interactive Voice Response System; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; OD, once daily; QM, monthly

Table 4-16 Mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in GAUSS-2 (FAS)

	Evolocumab Q2W vs. ezetimibe		Evolocumab QM vs. ezetimibe	
	Placebo Q2W + ezetimibe 10 mg OD (N = 51)	Evolocumab 140 mg Q2W + placebo OD (N = 103)	Placebo QM + ezetimibe 10 mg OD (N = 51)	Evolocumab 420 mg QM + placebo OD (N = 102)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^a	-19.0 (-23.9, -14.1)	-57.1 (-60.8, -53.4)	-16.6 (-20.7, -12.5)	-55.8 (-58.9, -52.8)
Mean of weeks 10/12 treatment difference (95% CI) ^{a,b}	-	-38.1 (-43.6, -32.6) p < 0.001 ^c	-	-39.2 (-43.7, -34.8) p < 0.001 ^c
Week 12 mean percent change from baseline (95% CI) ^a	-18.2 (-23.2, -13.1)	-57.4 (-61.3, -53.6)	-14.9 (-19.2, -10.5)	-53.0 (-56.2, -49.8)
Week 12 treatment difference (95% CI) ^{a,b}	-	-39.3 (-45.0, -33.5) p < 0.001 ^c		-38.1 (-42.9, -33.4) p < 0.001 ^c
Reference: GAUSS-2 CSR ¹⁰⁵ Tables 10-4 and 14-4.1.3.				
Note: The GAUSS-2 efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS and this analysis. All patients received IP as randomised and were included in the FAS and this analysis.				
^a Values are least squares means, which is from the repeated measures model that includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates. ^b Treatment differences were within each dose frequency group using placebo plus ezetimibe in the same group as the reference. ^c Nominal p value. No multiplicity adjustment was carried out for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy, although the least significant p value across the coprimary endpoints is < 0.001.				
CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IP, investigational product; IVRS, Interactive Voice Response System; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; OD, once daily; QM, monthly				

Other LDL-C parameters: Consistent with the results above, evolocumab Q2W and QM also demonstrated significant improvements compared with ezetimibe across other LDL-C parameters:

- mean absolute (mmol/L) change from baseline in LDL-C assessed using both the reflexive and calculated approach to LDL-C assessment at both the mean of weeks 10/12 and week 12 (Appendix V)
- proportion of patients achieving LDL-C levels < 1.8 mmol/L assessed using both the reflexive and calculated approach to LDL-C assessment at both the mean of weeks 10/12 and week 12 (Appendix V).

Other lipid parameters: Evolocumab Q2W and QM also resulted in statistically significant improvements in other lipid parameters, including non-HDL-C, ApoB, and Lp(a), from baseline at the mean of weeks 10/12 and at week 12 compared with ezetimibe (Appendix V).

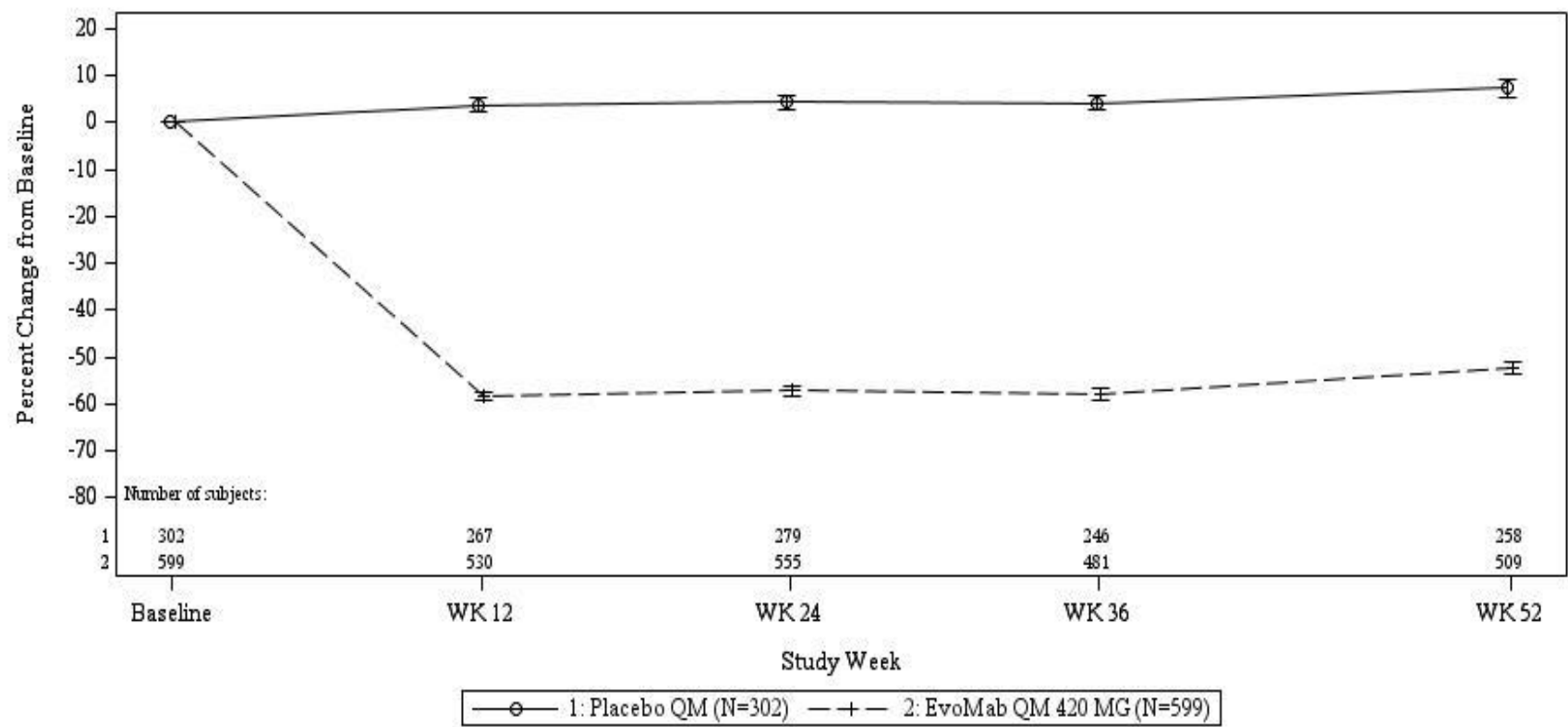
DESCARTES (evolocumab versus placebo over 52 weeks in patients with primary hypercholesterolaemia [heterozygous familial and non-familial] and mixed dyslipidaemia receiving background lipid-lowering therapy)

LDL-C percent change from baseline: Evolocumab QM maintained mean percent reductions in calculated LDL-C compared with placebo over the 52-week treatment period with treatment differences of -61.1% at week 12 and -59.3% at week 52 ($p < 0.001$ for both treatment differences) (Figure 4-10 and Table 4-17). These results were consistent with the effects observed with the same evolocumab dosing regimen in the relevant 12-week RCTs discussed earlier in this submission, and when LDL-C was measured using the ultracentrifugation approach to LDL-C assessment (Appendix V).

Table 4-17 Mean percent change in calculated LDL-C from baseline at week 12 and week 52 in DESCARTES (FAS)

	Placebo QM (N = 302)	Evolocumab QM (N = 599)
Week 12 mean percent change from baseline (95% CI) ^a	4.4 (1.7, 7.0)	-56.7 (-58.7, -57.8)
Week 12 treatment difference (95% CI) ^{a,b}	-	-61.1 (-64.3, -57.9) $p < 0.001^c$
Week 52 mean percent change from baseline (95% CI) ^a	8.7 (5.1, 12.4)	-50.6 (-53.2, -48.0)
Week 52 treatment difference (95% CI) ^{a,b}	-	-59.3 (-63.8, -54.9) $p < 0.001^c$
References: DESCARTES primary study publication appendix,¹⁰⁶ CSR¹⁰⁷ Table 14-4.1.3, and supplementary data table¹¹⁷ 14-4.1.1. Note: The DESCARTES efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS and this analysis. Four patients (three in the evolocumab group and one in the placebo group) did not receive IP as randomised and were excluded from the FAS and this analysis. ^aValues are least squares means, which is from the repeated measures model that includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates. ^bTreatment differences using placebo as the reference. ^cNominal p value. No multiplicity adjustment was carried out for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy. CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IP, investigational product; IVRS, Interactive Voice Response System; LDL-C, low-density lipoprotein cholesterol; QM, monthly		

Figure 4-10 Plot of mean percent change from baseline in calculated LDL-C by scheduled visit and IP in DESCARTES (FAS)



Reference: DESCARTES supplementary figure¹¹⁸ 14-4.41.401.

Note: Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.

EvoMab, evolocumab; FAS, full analysis set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; QM, monthly

Other LDL-C parameters: Consistent with the results above, evolocumab QM also demonstrated significant improvements across other LDL-C parameters:

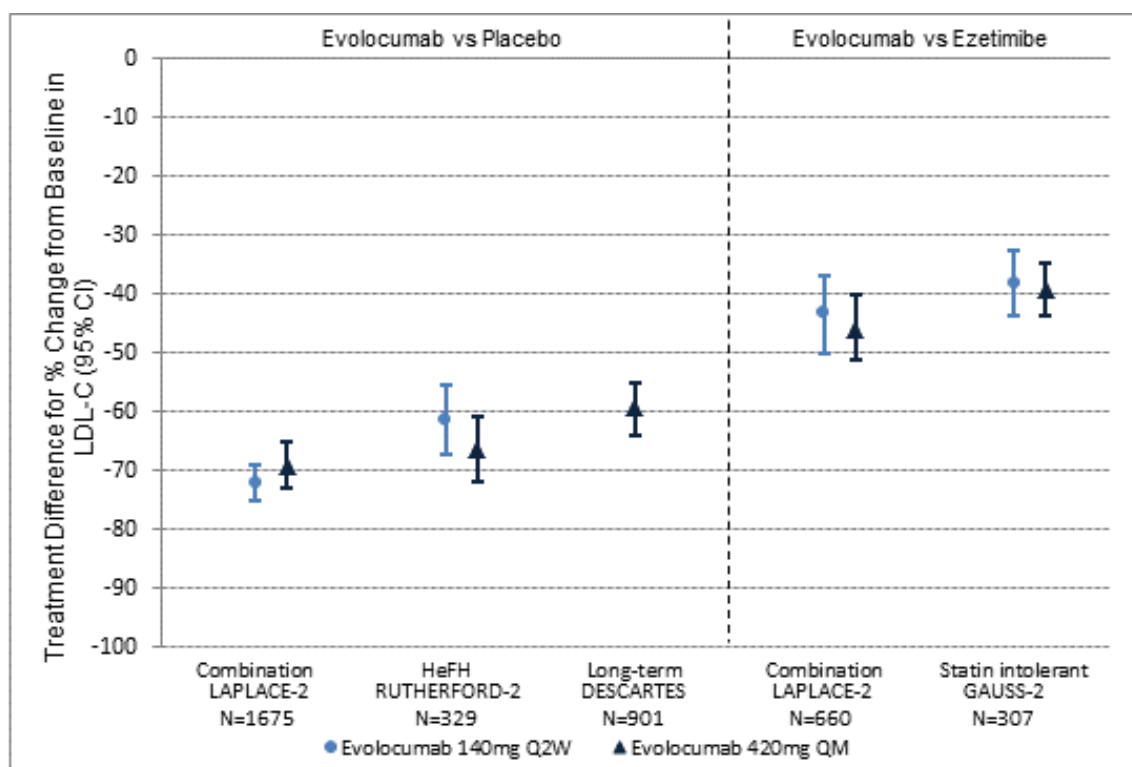
- absolute (mmol/L) change from baseline in LDL-C assessed using both the ultracentrifugation and calculated approach to LDL-C assessment at week 52 (Appendix V)
- proportion of patients achieving LDL-C levels < 1.8 mmol/L assessed using both the ultracentrifugation and calculated approach to LDL-C assessment at week 52 (Appendix V).

Other lipid parameters: Evolocumab QM also resulted in statistically significant improvements in other lipid parameters, including non-HDL-C, ApoB, and Lp(a), from baseline at week 52 compared with placebo (Appendix V).

Consistency of LDL-C-lowering treatment effect across the relevant RCTs

Efficacy results of the relevant RCTs in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia consistently demonstrated superiority of evolocumab in reducing LDL-C compared with placebo or ezetimibe, irrespective of study population and evolocumab dosing regimen (140 mg Q2W or 420 mg QM) (Figure 4-11).

Figure 4-11 Treatment differences (%; 95% CI) in percent change from baseline at the mean of weeks 10/12 (LAPLACE-2, RUTHERFORD-2, and GAUSS-2) and at week 52 (DESCARTES) in calculated LDL-C



CI, confidence interval; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; RCT, randomised controlled trial; Q2W, every 2 weeks; QM, monthly

Results of the supplementary randomised, controlled, open-label extension studies

OSLER (evolocumab plus SoC versus SoC in patients from qualifying phase 2 parent studies for up to 1 year; open-label evolocumab in year 2+)

LDL-C percent change from baseline: At the time of data cutoff (01 April 2014), an analysis of the treatment differences between treatment groups showed that evolocumab 420 mg QM plus SoC (N = 882) significantly reduced mean (standard error [SE]) calculated LDL-C (from parent study baseline) compared with SoC alone (N = 442), with a treatment difference of -54.6% (1.2%) at week 12 and -51.4% (1.5%) at week 52 ($p < 0.001$ for both treatment differences).¹¹⁹ Patients who received control in the parent study had unchanged LDL-C levels if they remained on control (SoC alone) during OSLER, but had LDL-C reductions from parent study baseline of approximately 60% at OSLER week 52 if they switched to evolocumab. Conversely, patients who received evolocumab in the parent study maintained consistent LDL-C reductions from parent study baseline at OSLER week 52 if they remained on evolocumab in OSLER, but LDL-C levels returned to approximate parent study baseline by OSLER week 12 if they switched to SoC alone. Detailed results are provided in Appendix V.

Patients who received evolocumab plus SoC during year 1 and continued to receive evolocumab plus SoC during year 2+ of OSLER had sustained mean percent reductions in calculated LDL-C to week 124. Patients who received SoC alone during year 1 of OSLER and switched to evolocumab plus SoC during year 2+ had a mean (SE) percent change (from parent study baseline) in LDL-C of -54.1% by the first visit after switching to evolocumab plus SoC (week 64), with these reductions sustained to week 124. Detailed results are provided in Appendix V.

OSLER-2 (evolocumab plus SoC versus SoC in patients from qualifying phase 3 parent studies for up to 1 year; open-label evolocumab in year 2+)

LDL-C percent change from baseline: At the time of data cutoff (01 April 2014), an analysis of the treatment differences between groups showed that evolocumab 140 mg Q2W or 420 mg QM plus SoC (N = 1951) significantly reduced mean calculated LDL-C (from parent study baseline) compared with SoC alone (N = 977), with a treatment difference (SE) of -64.5% (1.5%) at week 12 and -59.6% (1.7%) at week 24 ($p < 0.001$ for both treatment differences).¹²⁰ As data were only available for a few patients beyond week 24 (N = 7) at the time of data cutoff, these data are not shown, but are available in the OSLER-2 interim CSR. Patients who received control in the parent study had unchanged LDL-C levels if they remained on control (SoC alone) during OSLER-2, but had LDL-C reductions from parent study baseline of approximately 53.5% at OSLER-2 week 12 if they switched to evolocumab. Conversely, patients who received evolocumab in the parent study maintained consistent LDL-C reductions from parent study baseline at OSLER-2 week 24 if they remained on evolocumab in OSLER-2, but LDL-C levels returned to approximate parent study baseline by OSLER-2 week 12 if they switched to control (SoC alone). Detailed results are provided in Appendix V.

OSLER and OSLER-2 integrated analysis (evolocumab plus SoC versus SoC in patients from qualifying phase 2 and 3 parent studies over 48 weeks)

LDL-C percent change from baseline: At the time of data cutoff for an integrated analysis of data from OSLER and OSLER-2 (31 October 2014), results showed that by week 12 of the OSLER studies, reductions in calculated LDL-C (from parent study baseline) were 60.9% in patients receiving evolocumab plus SoC (N = 2,976) relative to SoC alone (N = 1,489, $p < 0.001$ for treatment difference).¹²¹ These reductions were maintained for 48 weeks.

4.8 Subgroup analysis

Pre-specified stratification factor and baseline covariate subgroup analyses

Overview of the subgroup analysis

Pre-specified subgroup analyses, controlling for stratification factors and other baseline covariates (including subgroups for screening and baseline LDL-C levels, subgroups for CVD risk, and subgroups for use of lipid-lowering therapies), were conducted for the relevant RCTs (defined in Section 4.2). The analyses were conducted for the coprimary/primary efficacy endpoints of each relevant RCT only (i.e. percent change from baseline in LDL-C at the mean of weeks 10/12 and at week 12 [LAPLACE-2, RUTHERFORD-2, GAUSS-2] or at week 52 [DESCARTES]). An overview of these subgroups and subgroup criteria is provided in Table 4-18. The statistical approach of the stratification factor and other baseline covariate subgroup analyses followed those of the primary efficacy analyses conducted for the overall trial populations (previously described in Section 4.4). Treatment effect differences among subgroups, which represent subgroup by treatment interactions, were estimated and tested based on statistics from the subgroup repeated measures models.

Table 4-18 Summary of pre-specified subgroup analyses by stratification factor and other baseline covariates in LAPLACE-2, RUTHERFORD-2, GAUSS-2, and DESCARTES

20110115 LAPLACE-2	20110117 RUTHERFORD-2	20110116 GAUSS-2	20110109 DESCARTES
• Subgroup by stratification factor ▪ Entry statin therapy (no statin use, non-intensive statin use, intensive statin use) ▪ Simvastatin-contraindicated therapy usage for first randomisation (any verapamil or diltiazem, amlodipine or amiodarone, or ranolazine alone, none) • Subgroup by baseline characteristics ▪ Age (< 65 years, ≥ 65 years) ▪ Sex (male, female) ▪ Race (black, white, other) ▪ Region (North America, Europe, other) ▪ Baseline LDL-C (< baseline median, ≥ baseline median) ▪ BMI (< 25 kg/m², 25 to ≤ 30 kg/m², > 30 kg/m²) ▪ Glucose tolerance status (diabetes mellitus type 2, metabolic syndrome, neither) ▪ Hypertension (yes, no) ▪ Current smoking status (yes, no)	• Subgroup by stratification factor ▪ Screening LDL-C (< 160 mg/dL, ≥ 160 mg/dL) ▪ Ezetimibe use at baseline (yes, no) • Subgroup by baseline characteristics ▪ Age (< 65 years, ≥ 65 years) ▪ Sex (male, female) ▪ Race (black, white, other) ▪ Region (North America, Europe, other) ▪ Baseline LDL-C (< baseline median, ≥ baseline median) ▪ BMI (< 25 kg/m², 25 to ≤ 30 kg/m², > 30 kg/m²) ▪ Glucose tolerance status (diabetes mellitus type 2, metabolic syndrome, neither) ▪ Hypertension (yes, no) ▪ Current smoking status (yes, no) ▪ Baseline CHD risk factors ≥ 2 (yes, no) ▪ Family history of premature CHD (yes, no)	• Subgroup by stratification factor ▪ Screening LDL-C (< 180 mg/dL, ≥ 180 mg/dL) ▪ Baseline statin use (yes, no) • Subgroup by baseline characteristics ▪ Age (< 65 years, ≥ 65 years) ▪ Sex (male, female) ▪ Race (black, white, other) ▪ Region (North America, Europe, other) ▪ Baseline LDL-C (< baseline median, ≥ baseline median) ▪ BMI (< 25 kg/m², 25 to ≤ 30 kg/m², > 30 kg/m²) ▪ Glucose tolerance status (diabetes mellitus type 2, metabolic syndrome, neither) ▪ Hypertension (yes, no) ▪ Current smoking status (yes, no) ▪ Baseline CHD risk factors ≥ 2 (yes, no) ▪ Family history of premature CHD (yes, no) ▪ Baseline PCSK9 level (< baseline	• Subgroup by stratification factor ▪ Background lipid-lowering therapy (diet alone, low-dose drug therapy [diet plus atorvastatin 10 mg], high-dose drug therapy [diet plus atorvastatin 80 mg], maximal drug therapy [diet plus atorvastatin 80 mg plus ezetimibe]) • Subgroup by baseline characteristics ▪ Age (< 65 years, ≥ 65 years) ▪ Sex (male, female) ▪ Race (black, white, Asian, other) ▪ Region (North America, Europe, other) ▪ Baseline LDL-C (< baseline median, ≥ baseline median) ▪ BMI (< 25 kg/m², 25 to ≤ 30 kg/m², > 30 kg/m²) ▪ Glucose tolerance status (diabetes mellitus type 2, metabolic syndrome, neither) ▪ Hypertension (yes, no) ▪ Current smoking status (yes, no) ▪ Baseline CHD risk factors ≥ 2 (yes, no)

20110115 LAPLACE-2	20110117 RUTHERFORD-2	20110116 GAUSS-2	20110109 DESCARTES
▪ Baseline CHD risk factors ≥ 2 (yes, no) ▪ Family history of premature CHD (yes, no) ▪ Baseline PCSK9 level ($<$ baseline median, $\geq$ baseline median) ▪ Baseline triglycerides ($<$ baseline median, $\geq$ baseline median; < 150 mg/dL, ≥ 150 mg/dL; < 200 mg/dL, ≥ 200 mg/dL) • NCEP high risk (yes, no)	▪ Baseline PCSK9 level ($<$ baseline median, $\geq$ baseline median) ▪ Baseline triglycerides ($<$ baseline median, $\geq$ baseline median; < 150 mg/dL, ≥ 150 mg/dL; < 200 mg/dL, ≥ 200 mg/dL) ▪ HeFH status (definite, possible) ▪ Lipid-lowering background therapy (intensive statin use, non-intensive statin use) ▪ NCEP high risk (yes, no)	- median, $\geq$ baseline median) ▪ Baseline triglycerides ($<$ baseline median, $\geq$ baseline median; < 150 mg/dL, ≥ 150 mg/dL; < 200 mg/dL, ≥ 200 mg/dL) ▪ Intolerance to statins (2, ≥ 3) ▪ Lipid-lowering therapy use (none, non-statin lipid-lowering therapy use, statin use) ▪ NCEP high risk (yes, no)	▪ Family history of premature CHD (yes, no) ▪ Baseline PCSK9 level ($<$ baseline median, $\geq$ baseline median) ▪ Baseline triglycerides ($<$ baseline median, $\geq$ baseline median; < 150 mg/dL, ≥ 150 mg/dL; < 200 mg/dL, ≥ 200 mg/dL) ▪ NCEP high risk (yes, no)
References: RUTHERFORD-2 CSR,¹⁰³ LAPLACE-2 CSR,¹⁰¹ GAUSS-2 CSR,¹⁰⁵ and DESCARTES CSR.¹⁰⁷ Note: The pre-specified stratification factor and other baseline covariate subgroup analyses were performed for the primary/coprimary endpoints using the primary LDL-C assessment method in these studies only. For RUTHERFORD-2, LAPLACE-2, and GAUSS-2, this was the reflexive approach where calculated LDL-C was employed unless the calculated LDL-C was < 1.0 mmol/L or triglycerides were > 4.5 mmol/L, in which case ultracentrifugation LDL-C was determined and utilised. For DESCARTES, this was ultracentrifugation. BMI, body mass index; CHD, coronary heart disease; CSR, clinical study report; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; PCSK9, proprotein convertase subtilisin/kexin type 9			

Results of the pre-specified subgroup analyses

Evolocumab 140 mg Q2W and 420 mg QM were consistently effective relative to placebo and to ezetimibe in lowering LDL-C (mean percent change from baseline at the mean of weeks 10/12 and at week 12 [RUTHERFORD-2, LAPLACE-2, GAUSS-2] or at week 52 [DESCARTES]) in all stratification factor and baseline covariate subgroups in each study, with no notable differences between subgroups.

Forest plots providing detailed results for each prespecified stratification factor and baseline covariate subgroup in each individual relevant RCT are provided in Appendix VI.

Of particular relevance to the NICE decision problem:

- Evolocumab Q2W and QM were consistently effective at lowering LDL-C relative to placebo (RUTHERFORD-2 and DESCARTES [QM only]) and to ezetimibe (GAUSS-2) irrespective of baseline and background lipid-lowering therapies.
 - In RUTHERFORD-2, evolocumab Q2W and QM were consistently effective at lowering LDL-C irrespective of whether or not the statin used as part of the background lipid-lowering therapy was intensive or non-intensive. This is of relevance to the decision problem as NICE recommends use of high-intensity statins as a first-line treatment option for patients with HeFH. Further, evolocumab Q2W and QM were consistently effective at lowering LDL-C, irrespective of whether ezetimibe was used as part of the background lipid-lowering therapy strategy. This is of relevance to the decision problem as the decision problem includes evolocumab in combination with statin and ezetimibe as a relevant intervention, and statin in combination with ezetimibe as a relevant comparator (comparison provided in the ezetimibe use 'yes' stratification factor subgroup).
 - In GAUSS-2, evolocumab Q2W and QM were consistently effective at lowering LDL-C relative to ezetimibe irrespective of whether or not statins were used at baseline. This is of relevance to the decision problem given that some patients considered intolerant to statins under NICE guidelines may continue to receive sub-optimal doses of statins in clinical practice in England and Wales. Further, evolocumab Q2W and QM were consistently effective at lowering LDL-C relative to ezetimibe irrespective of whether non-statin lipid-lowering therapy (including bile acid sequestrants or stanols), statins, or neither were used at baseline. This is of relevance to the decision problem given that some patients considered intolerant or contraindicated to statins under NICE guidelines may receive non-statin lipid-lowering therapies other than the randomised ezetimibe intervention in clinical practice in England and Wales.
 - In DESCARTES, evolocumab QM was consistently effective at lowering LDL-C relative to placebo irrespective of whether background lipid-lowering therapy was diet alone, diet plus atorvastatin 10 mg, diet plus atorvastatin 80 mg, or diet plus atorvastatin 80 mg plus ezetimibe. This is of relevance to the decision problem as (i) NICE recommends use of high-intensity statins as a first-line treatment option for primary and secondary prevention of CVD in patients who qualify for lipid-modification therapy under current NICE guidelines, as well as for the treatment of HeFH (reflected by the diet plus atorvastatin 80 mg stratification factor); and (ii) the decision problem includes evolocumab in combination with a statin and ezetimibe as a relevant intervention and statin plus ezetimibe as a relevant comparator

(comparison provided in the diet plus atorvastatin 80 mg plus ezetimibe stratification factor subgroup).

- Evolocumab Q2W and QM were consistently effective at lowering LDL-C relative to placebo (RUTHERFORD-2, LAPLACE-2, and DESCARTES [QM only]) and to ezetimibe (LAPLACE-2 and GAUSS-2) irrespective of whether baseline LDL-C was greater or less than the median. Evolocumab Q2W and QM were also consistently effective at lowering LDL-C relative to placebo (RUTHERFORD-2) and to ezetimibe (GAUSS-2) irrespective of whether screening LDL-C was greater or less than 160 mg/dL (RUTHERFORD-2) or 180 mg/dL (GAUSS-2). This is of relevance to the decision problem as (i) subgroups according to severity of hypercholesterolaemia are defined as relevant subgroups in the decision problem and (ii) minimum LDL-C thresholds for initiation of treatment with evolocumab in patients with primary hypercholesterolaemia (non-familial) and mixed dyslipidaemia are proposed, although it is noted that these thresholds are not fully aligned with the cut-offs used for these subgroup analyses.
- Evolocumab Q2W and QM were consistently effective at lowering LDL-C relative to placebo (LAPLACE-2, RUTHERFORD-2, and DESCARTES [QM only]) and to ezetimibe (LAPLACE-2 and GAUSS-2) irrespective of whether or not patients had two or more baseline CHD risk factors, were categorised as high-risk according to NCEP guidelines, or whether or not patients had specific CV risk factors (e.g. family history of premature CVD, diabetes mellitus type 2, hypertension, and smoking). This is of relevance to the decision problem as subgroups according to the risk of CVD are defined as relevant subgroups in the decision problem.
- Evolocumab Q2W and QM were consistently effective at lowering LDL-C relative to placebo (LAPLACE-2, RUTHERFORD-2, and DESCARTES [QM only]) and to ezetimibe (LAPLACE-2 and GAUSS-2) irrespective of study region. This is of relevance to the decision problem as the 'Europe' region subgroup might be considered more representative of patients in England and Wales than the 'North America' and 'other' region subgroups.

[illegible]

[REDACTED]

[illegible]

Results of the post-hoc subgroup analyses

Evolocumab 140 mg Q2W and 420 mg QM were consistently effective relative to placebo and to ezetimibe in lowering LDL-C in each post-hoc subgroup assessed for each relevant RCT, with treatment differences in mean percent change (from baseline at the mean of weeks 10/12 and at week 12 [RUTHERFORD-2, LAPLACE-2, GAUSS-2] or at week 52 [DESCARTES]) in calculated LDL-C similar to those observed in the overall trial populations.

Detailed results for each subgroup are provided in Appendix VI.

4.9 Meta-analysis

A meta-analysis was not conducted as it was not deemed necessary for the purposes of this appraisal.

4.10 Indirect and mixed treatment comparisons

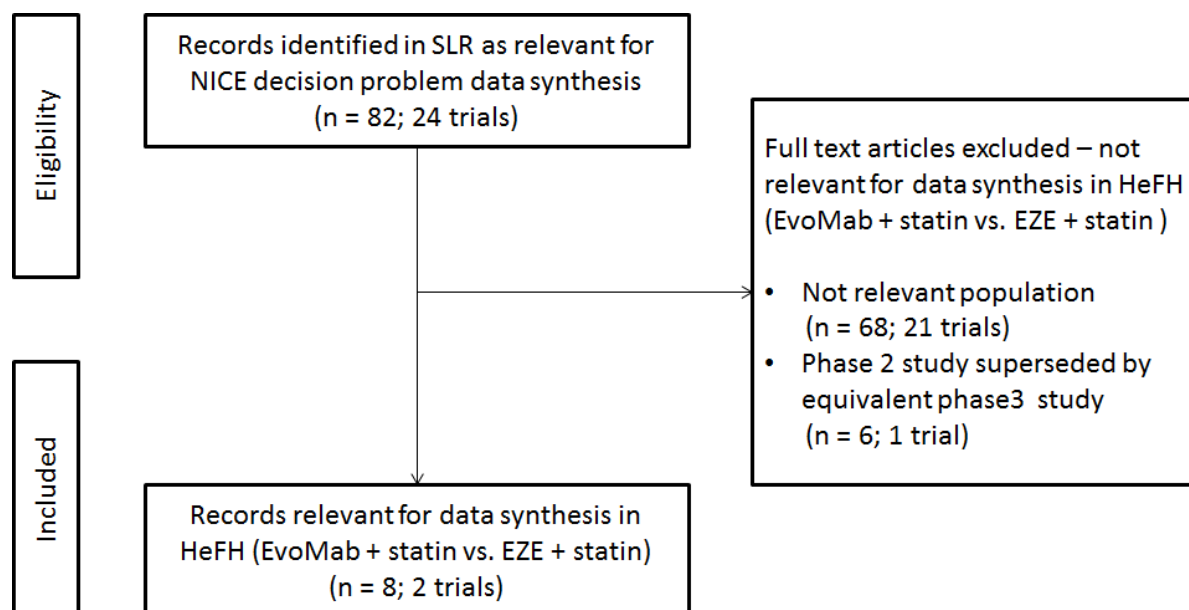
LAPLACE-2 and GAUSS-2, the phase 3 RCTs which comparing evolocumab (140 mg Q2W and 420 mg QM) with ezetimibe have been described in Section 4.2. There were no head-to-head RCTs evaluating evolocumab plus statin versus ezetimibe plus statin in patients with HeFH. Therefore, in order to address the decision problem set out in this submission, network meta-analysis techniques using direct and indirect evidence were evaluated to assess the feasibility of synthesising comparative efficacy for evolocumab plus statin versus ezetimibe plus statin in this population based on the studies identified as being potentially useful for data synthesis in the clinical efficacy SLR (Section 4.1 and Appendix III).

82 publications for 24 trials were identified in the SLR as being potentially useful for data synthesis (Section 4.1 and Appendix III). Of these studies, additional exclusion criteria were applied to identify studies that could potentially be useful to synthesise comparative efficacy data for evolocumab plus statin versus ezetimibe plus statin in patients with HeFH:

- exclusion of studies not specifically in patients with HeFH
- exclusion of studies that do not include either evolocumab plus statin or ezetimibe plus statin as a treatment arm
- exclusion of phase 2 studies if an equivalent phase 3 study in the same population had been conducted.

8 publications reporting data for 2 studies were identified as being potentially useful for synthesising comparative efficacy for evolocumab plus statin versus ezetimibe plus statin in patients with HeFH (Figure 4-12). All publications excluded were documented along with the reasons for exclusion (Appendix III).

Figure 4-12 PRISMA flow diagram for the clinical efficacy/safety SLR – identification of studies relevant for data synthesis in HeFH (evolocumab plus statin versus ezetimibe plus statin)



EvoMab, evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; SLR, systematic literature review

One of the two included studies was RUTHERFORD-2,¹⁰² and the other (ENHANCE),⁸³ assessed ezetimibe in combination with simvastatin versus simvastatin alone in patients with familial hypercholesterolaemia. The primary outcome of ENHANCE was to assess the change from baseline in ultrasonographic measurement of the mean carotid-artery intima-media thickness. The ENHANCE publication reported LDL-C levels at baseline and at end-of-study (2 years). Patients were washed out of prior lipid-lowering therapy before the randomisation and were then randomised to either simvastatin and placebo or simvastatin and ezetimibe. As such, the baseline LDL-C measurements were not comparable between ENHANCE and RUTHERFORD-2 given the patients in ENHANCE were untreated for a minimum of 6 weeks prior to baseline whereas the patients in RUTHERFORD-2 were being treated with stable dose(s) of a statin and lipid-regulating drugs for at least 4 weeks prior to screening and continued to be treated with these therapies on study. Because of the difference in the baseline LDL-C measurements, the percent change from baseline within each patient was not comparable between ENHANCE and RUTHERFORD-2 either, which meant the difference in percent change from baseline between the two studies could not be derived. Therefore, a network meta-analysis to synthesize comparative efficacy data was deemed neither appropriate nor feasible.

4.11 Non-randomised and non-controlled evidence

Only one non-randomised, non-controlled study (study 20110271; TAUSSIG) is considered to be relevant to this submission. A brief overview of this study is provided in Table 4-20.

Table 4-20 Overview of study 20110271 (TAUSSIG)

	Study 20110271 (TAUSSIG)
Objective	To assess the long-term safety and efficacy of evolocumab in patients with severe FH
Population	Patients with severe FH (HoFH or HeFH)
Intervention	Evolocumab 420 mg Q2W or 420 mg QM
Comparator	None
Primary study reference	Interim CSR, date of data cutoff 01 July 2014 ¹²³
Justification for inclusion	• Patients with HeFH are defined as a population of interest in the decision problem. Apart from study 20110117 (RUTHERFORD-2), this is the only other phase 3 study in the evolocumab clinical trial program that provides efficacy data for evolocumab specifically in patients with HeFH • Subgroups according to severity of hypercholesterolaemia are defined as relevant subgroups in the decision problem. This study provides clinical efficacy data for evolocumab in patients with severe HeFH • TAUSSIG also provides longer-term follow-up data in the HeFH population than RUTHERFORD-2
CSR, clinical study report; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; Q2W, every 2 weeks; QM, monthly	

Summary of methodology of the relevant non-randomised and non-controlled evidence

TAUSSIG is an ongoing long-term, open-label phase 2/3 study, which enrolls patients who completed study 20110233 (TESLA, a phase 2/3 study in patients with HoFH) as well as de novo patients with FH, including either HoFH or HeFH.¹²³

After being assessed for inclusion and exclusion criteria (Table 4-21), and after providing informed consent, patients received open-label evolocumab 420 mg. Patients not undergoing apheresis at enrolment or within the prior 8 weeks ('non-apheresis patients') initiated treatment with 420 mg QM and patients undergoing apheresis at enrolment ('apheresis patients') initiated treatment with evolocumab 420 mg Q2W.

Table 4-21 Key TAUSSIG eligibility criteria

Inclusion criteria	Major exclusion criteria
• Participated in a qualifying evolocumab parent protocol or has a diagnosis of FH • Males and females ≥ 12 to ≤ 80 years of age • Stable low-fat diet and lipid-lowering therapies for ≥ 4 weeks • LDL-C ≥ 3.4 mmol/L for patients without diagnosed CHD/CHD risk equivalent; ≥ 2.6 mmol/L for patients with diagnosed CHD or CHD risk equivalent; no LDL-C entry requirement for apheresis patients • Fasting triglycerides 4.5 mmol/L • Bodyweight of ≥ 40 kg at screening for patients < 18 years of age	• Heart failure (NYHA class III or IV or last known LVEF $< 30\%$) • MI, unstable angina, PCI, CABG, or stroke within 3 months of screening • Planned cardiac surgery or revascularisation • Uncontrolled cardiac arrhythmia • Uncontrolled hypertension
Reference: TAUSSIG interim CSR.¹²³ CABG, coronary artery bypass graft; CHD, coronary heart disease; CSR, clinical study report; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention	

Patients visited the site QM (non-apheresis patients) or Q2W (apheresis patients) until week 24, after which they received a 12-week supply of evolocumab if they decided to self-administer evolocumab. Beyond week 24, these patients visited the site every 12 weeks for central laboratory tests. Patients who decided to continue to receive evolocumab at the study centre continued to visit the site QM or Q2W. At week 12, patients with $< 5\%$ LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL could discontinue evolocumab. If serum unbound PCSK9 was ≥ 100 ng/mL with QM dosing, the patient could switch to evolocumab 420 mg Q2W treatment at week 12. Patients undergoing apheresis with $\geq 5\%$ LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL with Q2W treatment could switch to QM dosing at week 12. Patients will continue to receive open-label evolocumab for up to 5 years or until evolocumab becomes commercially available in the relevant patient population, whichever occurs first.¹²³

The prespecified primary endpoint in TAUSSIG was the incidence of treatment emergent adverse events during the extension period. Pre-specified secondary endpoints at each scheduled visit within each study period were:¹²³

- percent change in LDL-C from baseline
- percent change in non-HDL-C from baseline
- percent change in Lp(a) from baseline
- percent change in ApoB from baseline
- percent change in total cholesterol/HDL-C ratio from baseline
- percent change in ApoB/ApoA1 ratio from baseline
- response rate of patients with $\geq 15\%$ reduction in LDL-C.

Statistical analysis of the relevant non-randomised and non-controlled evidence

Statistical analyses in TAUSSIG were descriptive in nature. No statistical inference or missing-value imputation was planned.¹²³

The interim analysis included in the submission includes data collected to 01 July 2014. Analysis sets for this interim analysis included:

- interim analysis set: all patients enrolled in this study at the time of the data cutoff date who received ≥ 1 dose of evolocumab in TAUSSIG
- HoFH interim analysis set: all patients who received ≥ 1 dose of evolocumab in TAUSSIG and either met the clinical criteria of HoFH or who had supportive genetic information
- severe FH interim analysis set: all patients who received ≥ 1 dose of evolocumab in TAUSSIG and were not included in the HoFH interim analysis set.

As patients with HoFH are not relevant to the decision problem, only patients included in the severe FH interim analysis set (all of whom had severe HeFH, with a mean baseline calculated LDL-C of 4.9 mmol/L) will be discussed further in this submission.

Participant flow in the relevant non-randomised and non-controlled evidence

As of the 01 July 2014 data cutoff date, a total of 142 patients with severe HeFH were enrolled in TAUSSIG, including 16 apheresis patients and 126 non-apheresis patients, and were included in the severe FH interim analysis set. Approximately half of the patients (61%) were male, the majority were of white race (96%) and the majority were not of Hispanic or Latino ethnicity (96%). The mean (standard deviation) age of patients at baseline was 54 (12) years and mean (standard deviation) calculated LDL-C was 4.9 (1.6) mmol/L. Approximately 54% of patients had a prior diagnosis of coronary artery disease, 18% had a prior diagnosis of cerebrovascular disease or peripheral arterial disease, and approximately 11% had diabetes mellitus type 2.¹²³

Clinical efficacy results of the relevant non-randomised and non-controlled evidence

Details of evidence presented

Similar to clinical efficacy results for the relevant RCTs presented in Section 4.7, of the prespecified efficacy outcome, the only prespecified efficacy outcome presented in the main submission is percent change from baseline in calculated LDL-C. Results for other prespecified efficacy outcomes are available in the interim CSR.¹²³

As requirement of apheresis is included as an outcome of interest in the decision problem, results from an analysis of apheresis requirements prespecified in the statistical analysis plan (SAP) are also presented.¹²⁴

Clinical efficacy results

Treatment with evolocumab led to consistent mean percent reductions (from baseline to 36 weeks) in calculated LDL-C of approximately 50% in patients with severe HeFH (Table 4-22). Reductions at weeks 48 to 108 were generally consistent with those at the other visits, but the small number of patients who provided data at these visits limits interpretation of the results.¹²³

In the prespecified analysis of apheresis requirements, of the 16 patients with severe HeFH undergoing apheresis, 5 (31%) had stopped or reduced the frequency of apheresis at the time of data cut-off. This included 4 patients (25%) who stopped apheresis altogether, and 1 subject who was able to decrease apheresis frequency from two-weekly to monthly.¹²⁴

Table 4-22 Mean percent change from baseline in calculated LDL-C by scheduled visit to week 36 in TAUSSIG (severe FH interim analysis set)^{a,b}

		Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 36
Severe FH interim analysis set (N = 142)	n	133	132	117	56	18	17	9
	Mean % change from baseline (SE)	-54.1 (1.5)	-53.3 (1.6)	-54.3 (1.6)	-53.8 (1.9)	-46.5 (4.1)	-42.0 (7.4)	-50.5 (3.6)
Non-apheresis patients (N = 126)	n	119	119	112	54	18	17	9
	Mean % change from baseline (SE)	-52.7 (1.4)	-51.7 (1.6)	-54.0 (1.6)	-53.7 (1.9)	-46.5 (4.1)	-42.0 (7.4)	-50.5 (3.6)
Apheresis patients (N = 16)	n	14	13	5	2	0	0	0
	Mean % change from baseline (SE)	-66.3 (6.8)	-68.2 (5.2)	-60.3 (8.2)	-58.7 (20.1)	-	-	-

Reference: TAUSSIG interim CSR¹²³ Table 14-4.22.6.1.

Note: Summary is based on observed data. Baseline LDL-C for parent study rollover patients is defined at parent study baseline.

^a Data cutoff date 01 July 2014. ^b Only scheduled visits ≥ 4 weeks apart are shown and, due to low patient numbers, which limits interpretation of results, data beyond week 36 are not shown. Data for all scheduled visits to week 108 are available in Table 14-4.22.6.2 of the TAUSSIG interim CSR.

CSR, clinical study report; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; SE, standard error

4.12 Adverse reactions

Individual studies

A brief summary of safety and tolerability findings from the individual relevant RCTs (defined in Section 4.2), supplementary long-term, randomised, controlled, open-label extension studies (defined in Section 4.2), and one relevant non-randomised, non-controlled study (defined in Section 4.11) is provided in Table 4-23, with additional detailed safety data for the individual studies provided in Appendix VII.

A detailed overview of integrated safety and tolerability data from 6,026 patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia is provided later in Section 4.12.

Table 4-23 Summary of subject incidence of adverse events in the relevant RCTs, supplementary long-term, randomised, controlled, open-label extension studies, and non-randomised, non-controlled studies

Study	Exposure	Overall AEs n (%)	Serious AEs n (%)	AEs leading to IP discontinuation n (%)	Deaths n (%)
Relevant RCTs					
20110115 (LAPLACE-2)	Evolocumab vs. placebo^a • A total of 1675 patients received ≥ 1 dose of SC IP (1117 evolocumab, 558 placebo) with mean durations of exposure of 2.7 months for both the evolocumab and placebo groups Evolocumab vs. ezetimibe^b • A total of 881 patients received ≥ 1 dose of oral IP (439 evolocumab, 220 placebo, 221 ezetimibe) with mean durations of exposure of 2.8 months for the evolocumab group and 2.7 months for both the placebo and ezetimibe groups	<u>Evolocumab vs. placebo^a</u> • Evolocumab: 406 (36.3%) • Placebo: 219 (39.2%) <u>Evolocumab vs. ezetimibe^b</u> • Evolocumab: 162 (36.9%) • Placebo: 85 (38.5%) • Ezetimibe: 89 (40.3%)	<u>Evolocumab vs. placebo^a</u> • Evolocumab: 23 (2.1%) • Placebo: 13 (2.3%) <u>Evolocumab vs. ezetimibe^b</u> • Evolocumab: 10 (2.3%) • Placebo: 6 (2.7%) • Ezetimibe: 2 (0.9%)	<u>Evolocumab vs. placebo^a</u> • Evolocumab: 21 (1.9%) • Placebo: 12 (2.2%) <u>Evolocumab vs. ezetimibe^b</u> • Evolocumab: 10 (2.3%) • Placebo: 6 (2.7%) • Ezetimibe: 4 (1.8%)	<u>Evolocumab vs. placebo^a</u> • Evolocumab: 0 (0%) • Placebo: 1 (0.2%) <u>Evolocumab vs. ezetimibe^b</u> • Evolocumab: 0 (0%) • Placebo: 0 (0%) • Ezetimibe: 0 (0%)
20110117 (RUTHERFORD-2)	• A total of 329 patients received ≥ 1 dose of IP (220 evolocumab, 109 placebo) • The mean durations of exposure were 2.76 months for both evolocumab and placebo groups	• Evolocumab: 124 (56.4%) • Placebo: 53 (48.6%)	• Evolocumab: 7 (3.2%) • Placebo: 5 (4.6%)	• Evolocumab: 0 (0%) • Placebo: 0 (0%)	• Evolocumab: 0 (0%) • Placebo: 0 (0%)

Study	Exposure	Overall AEs n (%)	Serious AEs n (%)	AEs leading to IP discontinuation n (%)	Deaths n (%)
20110116 (GAUSS-2)	• A total of 307 patients received ≥ 1 dose of IP (205 evolocumab, 102 ezetimibe) • The mean durations of exposure were 2.7 months for both the evolocumab and ezetimibe groups	• Evolocumab: 135 (65.9%) • Ezetimibe: 74 (72.5%)	• Evolocumab: 6 (2.9%) • Ezetimibe: 4 (3.9%)	• Evolocumab: 17 (8.3%) • Ezetimibe: 13 (12.7%)	• Evolocumab: 0 (0%) • Ezetimibe: 0 (0%)
20110109 (DESCARTES)	• A total of 901 patients received ≥ 1 dose of IP (599 evolocumab, 302 placebo) • The mean durations of exposure were 11.1 months for the evolocumab group and 11.3 months for the placebo group	• Evolocumab: 448 (74.8%) • Placebo: 224 (74.2%)	• Evolocumab: 33 (5.5%) • Placebo: 13 (4.3%)	• Evolocumab: 13 (2.2%) • Placebo: 3 (1.0%)	• Evolocumab: 2 (0.3%) • Placebo: 0 (0%)
Supplementary randomised, controlled, open-label extension studies					
20110110 (OSLER) ^c	<u>Year 1</u> • A total of 882 patients were randomised to evolocumab plus SoC (881 patients received ≥ 1 dose of IP) and 442 patients were randomised to SoC • The mean duration of evolocumab exposure was 12.0 months <u>Year 2+</u> • A total of 937 patients received	<u>Year 1</u> • Evolocumab plus SoC: 722 (81.9%) • SoC: 324 (73.3%) <u>Year 2+</u> • Evolocumab plus SoC: 709 (75.7%)	<u>Year 1</u> • Evolocumab plus SoC: 67 (7.6%) • SoC: 30 (6.8%) <u>Year 2+</u> • Evolocumab plus SoC: 68 (7.3%)	<u>Year 1</u> • Evolocumab plus SoC: 27 (3.1%) • SoC: N/A <u>Year 2+</u> • Evolocumab plus SoC: 10 (1.1%)	<u>Year 1^d</u> • Evolocumab plus SoC: 1 (0.1%) • SoC: 2 (0.5%) <u>Year 2+^d</u> • Evolocumab plus SoC: 2 (0.2%)

Study	Exposure	Overall AEs n (%)	Serious AEs n (%)	AEs leading to IP discontinuation n (%)	Deaths n (%)
	≥ 1 dose of evolocumab plus SoC in year 2+ • The mean duration of evolocumab exposure was 12.9 months				
20120138 (OSLER-2) ^c	• A total of 1951 patients were randomised to evolocumab plus SoC (1949 patients received ≥ 1 dose of IP) and 977 patients were randomised to SoC • The mean duration evolocumab exposure was 6.6 months	• Evolocumab plus SoC: 988 (50.6%) • SoC: 456 (46.7%)	• Evolocumab plus SoC: 83 (4.3%) • SoC: 44 (4.5%)	• Evolocumab plus SoC: 31 (1.6%) • SoC: N/A	• Evolocumab plus SoC: 2 (0.1%) • SoC: 2 (0.2%)
Non randomised, non-controlled studies					
20110271 ^{e,f} (TAUSSIG)	• A total of 142 patients were exposed to evolocumab • The mean duration of evolocumab exposure was 4.3 months	• 80 (56.3%)	• 3 (2.1%)	• 1 (0.7%)	• 0 (0%)
References: LAPLACE-2 CSR ¹⁰¹ Tables 12-1, 12-5, 14-6.1.1 and 14-6.1.7; RUTHERFORD-2 CSR ¹⁰³ Tables 12-1 and 14-6.1.1; GAUSS-2 CSR ¹⁰⁵ Tables 12-1 and 14-6.1.1; DESCARTES CSR ¹⁰⁷ Tables 12-1 and 14-6.1.1; OSLER CSR ¹¹⁹ Tables 12-1, 12-2, 12-12, and 12-13; OSLER-2 CSR ¹²⁰ Table 12-1; FDA 120-day update ¹²⁵ Table 6. ^a Description of events in this group is based on all FAS patients (patients randomised to IP who received ≥ 1 dose of IP [SC or oral] in any statin cohort) except those who received ezetimibe. ^b Description of events in this group is based on all FAS patients in the atorvastatin 10 and 80 mg cohorts only. Events that occurred in the evolocumab and placebo patients in this group (i.e. those who did not receive ezetimibe) were also captured. ^c Ongoing study. Data cutoff data 01 April 2014. ^d Recorded as adjudicated clinical events as opposed to fatal adverse events. ^e Ongoing study. Data cutoff date 01 July 2014. ^f Severe FH interim analysis set only. AE, adverse event; CSR, clinical study report; FAS, full analysis set; FDA, Food and Drug Administration; HeFH, heterozygous familial hypercholesterolaemia; IP, investigational product; N/A, not applicable; RCT, randomised controlled trial; SC, subcutaneous; SoC, standard of care					

Integrated safety data

Overview of integrated safety analyses

Integrated analyses of safety data were conducted for the purposes of regulatory assessment, including data from 16 phase 2 and phase 3 studies: ^{126,125}

- 12 studies that were ~12 weeks in duration and four studies that were long-term studies (one 52-week completed study and three ongoing extension studies)
- two of the 16 studies were conducted in patients with HoFH, and data from these studies are not integrated or presented in this submission as patients with HoFH are excluded from the decision problem.

Three integrated analysis sets are used to describe the data from the primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia studies:

- the integrated parent analysis set comprises integrated data from the parent studies (the 12-week studies in addition to the 52-week study)
- the integrated extension SoC-controlled period analysis set comprises integrated data from year 1 (the controlled period) of the long-term extension studies
- the integrated extension all-IP period analysis set comprises integrated data from year 2+ (the all-IP period) of the long-term extension studies.

Details of these analysis sets, and studies contributing to each, are provided in Table 4-24.

Table 4-24 Safety analysis sets in the integrated primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia studies

Analysis set	Source	General description	Source of data	Additional information
Integrated parent analysis set	Summary of clinical safety ¹²⁶ Toth et al, 2015 ¹²⁷	Phase 2 and phase 3 parent studies (including all data up to the end of the parent study)	• Patients in primary hypercholesterolaemia and mixed dyslipidaemia studies ▪ 20101154 (MENDEL)^a ▪ 20101155 (LAPLACE)^a ▪ 20090158 (RUTHERFORD)^a ▪ 20090159 (GAUSS)^a ▪ 20110114 (MENDEL-2)^a ▪ 20110115 (LAPLACE-2) ▪ 20110116 (GAUSS-2) ▪ 20110117 (RUTHERFORD-2) • Patients in device home-use studies (20120348 [THOMAS-1] and 20120356 [THOMAS-2])^a • Japanese patients with primary hyperlipidaemia and mixed dyslipidaemia in Study 20110231 (YUKAWA)^a • Patients in the double-blind, placebo-controlled, long-term parent study (20110109 [DESCARTES])	• Data cutoff 01 April 2014
Integrated extension SoC-controlled period analysis set	FDA day 120 update ¹²⁵ Toth et al, 2015 ¹²⁷	Year 1 of the extension studies (controlled period)	• Patients randomised in year 1 of the long-term, controlled, OLE studies 20110110 (OSLER)^a and 20120138 (OSLER-2)^a	• Both studies are ongoing • Includes cumulative data to a 01 July 2014 data cutoff date
Integrated extension all-IP period analysis set		Year 2+ of the extension studies (OLE period)	• Patients who were on-study at the start of the all-IP period in studies 20110110 (OSLER)^a and 20120138 (OSLER-2)^a and received ≥ 1 dose in that period	• Both studies are ongoing • Includes cumulative data to a 01 July 2014 data cutoff date
^a Study not defined as relevant RCT; see Section 4.2. FDA, Food and Drug Administration; IP, investigational product; OLE, open-label extension; RCT, randomised controlled trial				

Overview of adverse events in the integrated safety analyses

Exposure to evolocumab in the clinical program was extensive and provides for a robust and comprehensive assessment of the overall safety of evolocumab. A total of 6,026 patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia have been administered evolocumab (alone or in combination with a variety of statins and other lipid-lowering therapies), placebo, or any control (including SoC) in phase 2 and 3 studies, representing 7,235 patient-years of exposure, including 5,246 patient years exposure to evolocumab. Of the 5,115 patients who received any dose of evolocumab, 709 have received more than 2 years of treatment.

In the integrated parent studies, the incidence of adverse events was balanced between treatment groups (any evolocumab 51.1%, [REDACTED], any control 49.6%) (Table 4-25). Most adverse events were mild to moderate in severity (grade 1 and grade 2), and serious adverse events and adverse events leading to discontinuation of IP were infrequently reported and generally similar across treatment groups. Serious adverse events were reported in 2.8% of patients in the any evolocumab group and 2.1% of patients receiving any control (Appendix VII). [REDACTED]

[REDACTED]

[REDACTED]

The incidence of adverse events in the long-term extension studies, which is higher than that in the integrated parent studies, cannot be directly compared with the parent studies due to the long exposure periods in the extension studies and different controls utilised. In the year 1 SoC-controlled period of the extension studies, the patient incidence of adverse events was 65% in the evolocumab plus SoC group and 61% in the SoC group. A potential bias toward reporting more adverse events in the evolocumab group than the control group may be due to the greater number of protocol-specified visits for the evolocumab group than the control group and the open-label study design. In year 1, adverse events leading to discontinuation of IP in the evolocumab plus SoC group was 2.3%. Serious adverse events were balanced between the evolocumab plus SoC group (6.6%) and the SoC alone group (6.7%) (Appendix VII). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Across all safety analysis sets, there were no patterns in the types of adverse events that were grade 3 or grade 4, or for serious adverse events across the treatment groups.

Table 4-25 Overview of adverse events in the integrated primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia studies

	Integrated parent analysis set ^a						OSLER/OSLER-2 Year 1 (IECAS) ^b		OSLER/ OSLER-2 Year 2+ (IEAAS) ^b
	Control			EvoMab			SoC (N = 1489) n (%)	EvoMab + SoC (N = 2976) n (%)	EvoMab n (%)
	Any placebo n (%)	Ezetimibe n (%)	Any control (N = 2080) n (%)	EvoMab 140 mg Q2W or 420 mg QM n (%)	EvoMab 420 mg QM + ezetimibe n (%)	Any EvoMab (N = 3946) n (%)			
All adverse events			1031 (49.6)			2016 (51.1)	910 (61.1)	1946 (65.4)	
Grade ≥ 2									
Grade ≥ 3									
Grade ≥ 4									
Serious adverse events			43 (2.1)			110 (2.8)	100 (6.7)	197 (6.6)	
Leading to IP discontinuation			48 (2.3)			75 (1.9)	N/A	68 (2.3)	
Serious									
Non-serious									
Fatal adverse events									
References: IPAS: Summary of Clinical Safety¹²⁶ Tables 14-6.1.1 and 14-6.1.2; IECAS and IEAAS: FDA 120-day update¹²⁵ Tables 14-6.1.3 and 14-6.1.4, and Toth et al, 2015.¹²⁷ ^aIncludes data from the following studies: LAPLACE-TIMI 57, RUTHERFORD, GAUSS, MENDEL, LAPLACE-2, RUTHERFORD-2, GAUSS-2, MENDEL-2, DESCARTES, YUKAWA, THOMAS, and THOMAS-2. ^bData cutoff date 01 July 2014. CV, cardiovascular; EvoMab, evolocumab; FDA, Food and Drug Administration; IECAS, integrated extension SoC-controlled period analysis set; IEAAS, integrated extension all-investigational product period analysis set; IP, investigational product; IPAS, integrated parent analysis set; Q2W, every 2 weeks; QM, monthly; SoC, standard of care									

Common adverse events in the integrated safety analyses

The common adverse events in the integrated parent studies and those in the extension studies were similar to those seen in the individual studies in the evolocumab trial program. There were no differences in the safety profile of evolocumab at varying doses and dosing intervals, including the 140 mg Q2W and 420 mg QM doses. The most common adverse events reported during the integrated parent studies for evolocumab were nasopharyngitis, upper respiratory tract infection, headache, and back pain (Table 4-26). In the extension studies (year 1 SoC-controlled and year 2+ open-label periods), similar common adverse events were reported (Appendix VII).

Table 4-26 Overview of common adverse events ($\geq 2\%$ in the EvoMab 140 mg Q2W/420 mg QM group) in the integrated primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia parent studies (IPAS)

Preferred term	Control			EvoMab		
	Any placebo ██████ n (%)	EZE ██████ n (%)	Any control (N = 2080) n (%)	EvoMab 140 mg Q2W/420 mg QM ██████ n (%)	EvoMab 420 mg QM + EZ ██████ n (%)	Any EvoMab (N = 3946) n (%)
Nasopharyngitis	██████	██████	99 (4.8)	██████	██████	231 (5.9)
Upper respiratory tract infection	██████	██████	56 (2.7)	██████	██████	127 (3.2)
Back pain	██████	██████	57 (2.7)	██████	██████	117 (3.0)
Headache	██████	██████	66 (3.2)	██████	██████	120 (3.0)
Influenza	██████	██████	41 (2.0)	██████	██████	83 (2.1)
Myalgia	██████	██████	55 (2.6)	██████	██████	98 (2.5)
Arthralgia	██████	██████	45 (2.2)	██████	██████	91 (2.3)
Nausea	██████	██████	37 (1.8)	██████	██████	81 (2.1)
Pain in extremity	██████	██████	39 (1.9)	██████	██████	73 (1.8)
Diarrhoea	██████	██████	50 (2.4)	██████	██████	79 (2.0)
Reference: Summary of Clinical Safety ¹²⁶ Tables 14-6.2.1 and 14-6.2.2.						
EvoMab, evolocumab; EZE, ezetimibe; IPAS, integrated parent analysis set; Q2W, every 2 weeks; QM, monthly; SoC, standard of care						

Adjudicated cardiovascular events and noncoronary revascularisations in the integrated safety analyses

The number of positively adjudicated CV events (including revascularisation procedures), was small and similar between evolocumab and controls during the parent studies. In the extension studies, preliminary empirical evidence from safety analyses suggests that long-term use of evolocumab to lower LDL-C may be associated with reduced risk of CV events (including revascularisation procedures). In the extension studies, the proportion of patients in the evolocumab plus SoC group who experienced an adjudicated CV clinical event

[REDACTED]

[REDACTED] (Table 4-27). Ad-hoc analyses of more recent integrated data from the extension studies (21 January 2015 data cutoff date) showed a larger difference, with rates of CV events at 1 year being reduced from 2.18% in the SoC group to 0.95% in the evolocumab plus SoC group (HR in the evolocumab group, 0.47; 95% CI 0.28, 0.78; p = 0.003).¹²¹

To date, the observed event reduction is similar to, if not even better than, the event reduction predicted from the CTTC relationship between LDL and CV outcomes. As discussed earlier in Section 4, reductions of approximately 50% to 60% in LDL-C concentrations were observed and maintained with long-term administration of evolocumab plus SoC compared with SoC alone during the year-long controlled treatment periods of the extension studies. It is estimated that the average absolute reduction in LDL-C with evolocumab plus SoC was 1.85 mmol/L in OSLER/OSLER-2 during weeks 12 to 48.¹²¹ If the relationship, as described by the CTTC between reduction in LDL-C and relative risk of major CV events for the statins, were to apply to evolocumab (risk ratio per 1 mmol/L reduction in LDL-C = 0.78), the estimated risk of major CV events in the evolocumab arm is anticipated to be 0.63 ($0.78^{1.85}$) x the risk in the SoC arm.

Although it is acknowledged that these data are preliminary and the trials are not powered to detect a difference in major CV events, the point estimates provided are in the direction and of the magnitude that would be expected, and are consistent with similar ad-hoc analyses with another PCSK9 inhibitor (alirocumab).¹¹⁴ These results are also consistent with a meta-analysis of safety data from randomised clinical trials of PCSK9 inhibitors.¹²⁸ This meta-analysis showed that, compared with no PCSK9 inhibitor, use of PCSK9 inhibitors resulted in a statistically significant reduction in all-cause mortality (OR = 0.45; 95% CI 0.23, 0.86; p = 0.015), a reduction in CV mortality (OR = 0.50; 95% CI 0.23, 1.10; p = 0.084), and a significant reduction in the rate of MI (OR = 0.49; 95% CI 0.26, 0.93; p = 0.030).

No patterns or changes in electrocardiogram parameters were observed.

Table 4-27 Overview of positively adjudicated cardiovascular events and non-coronary revascularisations in the integrated primary hypercholesterolaemia and mixed dyslipidaemia studies

	Integrated parent studies (IPAS) ^a		OSLER/OSLER-2 Year 1 (IECAS) ^b		OSLER/ OSLER-2 Year 2 + (IEASS) ^b
	Any control ██████ n (%)	Any EvoMab ██████ n (%)	SoC ██████ n (%)	EvoMab + SoC ██████ n (%)	EvoMab ██████ n (%)
██████████	██████	██████	██████	██████	██████
Death	2 (0.1)	4 (0.1)	4 (0.3)	3 (0.1)	3 (0.2)
CV	2 (0.1)	4 (0.1)	1 (0.1)	3 (0.1)	2 (0.1)
Non-CV	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	1 (0.1)
Undetermined	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
██████████	██████	██████	██████	██████	██████
██████████	██████	██████	██████	██████	██████
██████████	██████	██████	██████	██████	██████
██████████	██████	██████	██████	██████	██████
██████████	██████	██████	██████	██████	██████
██████████	██████	██████	██████	██████	██████
██████████	██████	██████	██████	██████	██████
██████████	██████	██████	██████	██████	██████
██████████	██████	██████	██████	██████	██████

	Integrated parent studies (IPAS) ^a		OSLER/OSLER-2 Year 1 (IECAS) ^b		OSLER/ OSLER-2 Year 2 + (IEASS) ^b
	Any control ██████ n (%)	Any EvoMab ██████ n (%)	SoC ██████ n (%)	EvoMab + SoC ██████ n (%)	EvoMab ██████ n (%)

References: IPAS: Summary of Clinical Safety¹²⁶ Table 43; ICEAS and IEASS: FDA 120-day update¹²⁵ Table 25.

Note: A more detailed breakdown of adjudicated CV events and noncoronary revascularisations is available in the Summary of Clinical Safety (IPAS) and FDA 120-day update (ICEAS and IEASS).

^aIncludes data from the following studies: LAPLACE-TIMI 57, RUTHERFORD, GAUSS, MENDEL, LAPLACE-2, RUTHERFORD-2, GAUSS-2, MENDEL-2, DESCARTES, YUKAWA-1, THOMAS-1, THOMAS-2. ^bData cutoff data 01 July 2014.

CV, cardiovascular; EvoMab, evolocumab; FDA, Food and Drug Administration; IECAS, Integrated Extension SoC-Controlled Period Analysis Set; IEAAS, Integrated Extension All-Investigational Product Period Analysis Set; IPAS, Integrated Parent Analysis Set; MI, myocardial infarction; Q2W, every 2 weeks; QM, monthly; SoC, standard of care; TIA, transient ischaemic attack; UA, unstable angina

Adverse events of interest in the integrated safety analyses

No safety issues were noted for adverse events associated with other lipid-lowering therapies (i.e. diabetes, liver, and muscle events), events associated with other injectable protein therapies (i.e. hypersensitivity events, injection site reactions), or events that could theoretically be associated with PCSK9 inhibition/LDLR upregulation (i.e. hepatitis C events).

Muscle and creatine kinase: Using the standard MedRA query (SMQ) narrow search strategy for potential muscle-related adverse events, [REDACTED] were reported in any evolocumab-treated patients during the parent studies and year 1 SoC-controlled period of the extension studies; [REDACTED] was reported during year 2+ of the extension studies.

The incidence of creatine kinase (CK) > 5 x upper limit of normal (ULN) or > 10 x ULN in the integrated parent and the integrated extension analyses was similar and was also comparable across treatment groups within the analysis periods. In the integrated parent studies, 0.7% of patients in both the any evolocumab group and the any control group had CK > 5 x ULN at any postbaseline visit. For CK > 10 x ULN, the incidence was also the same between the groups: 0.2% of patients in both the any evolocumab group and the any control group. In the year 1 SoC-controlled period of the extension studies, 0.6% of patients in the evolocumab plus SoC group, and 1.2% of patients in the SoC alone group had CK > 5 x ULN at any postbaseline visit. For CK > 10 x ULN, the incidence was also similar between the groups: 0.2% of patients in the evolocumab plus SoC group and 0.6% of patients in the SoC alone group. In the year 2+ open-label period of the extension studies, [REDACTED] of patients had CK > 5 x ULN and [REDACTED] patients had CK > 10 x ULN at any postbaseline visit.

Liver enzymes: The incidence of liver function test abnormalities was similar in the parent and extension studies, and was also comparable across treatment groups within the three safety analysis sets. In the integrated parent studies, the incidence of aspartate aminotransferase or alanine aminotransferase > 5 x ULN at any postbaseline visit was 0.2% and 0.3% in the any evolocumab and any control groups, respectively. The incidence of aspartate aminotransferase or alanine aminotransferase > 5 x ULN remained low in the extension studies.

Diabetes: Using the SMQ narrow search strategy for potential diabetes events, the incidence of diabetes events was low in the integrated parent studies (any evolocumab 0.9%; any control 0.8%), the year 1 SoC-controlled period of the extension studies (evolocumab plus SoC 2.2%; SoC alone 2.1%), and the year 2+ open-label period of the extension studies [REDACTED]. Changes in haemoglobin A_{1c} and fasting blood glucose in the integrated parent and the long-term extension studies were similar and were also comparable across treatment groups within the analysis periods. There were no differences in adverse events, haemoglobin A_{1c} levels, fasting blood glucose levels, or proteinuria in patients with type 2 diabetes mellitus, metabolic syndrome, or neither type 2 diabetes mellitus nor metabolic syndrome at baseline.

Hepatitis C: Using the SMQ narrow search strategy with multiple preferred terms possibly associated with potential hepatitis C events, no events of hepatitis C infection were noted in the parent studies, and the incidence of potential hepatitis C was low in the year 1 SoC-controlled

period of the extension studies [REDACTED] and the year 2+ open-label period of the extension studies [REDACTED]. Hepatitis C infection was infrequent across all periods, with a total of [REDACTED] patients in the clinical development program who were hepatitis C virus RNA positive.

Neurocognitive events: Overall, no important findings were noted from a review of the Nervous System or Psychiatric Disorders system organ class in the three integrated safety analysis sets. Upon medical review of the neurocognitive events, no overall pattern related to time to onset, resolution, or outcome was identified. The majority of events occurred in patients who had risk factors (medical history and/or concomitant medications) for potential neurocognitive events. Neurocognitive events were not increased with evolocumab compared with control during the integrated parent studies. In the year 1 SoC-controlled period of the extension studies, the rate of neurocognitive events was low (< 1%) and consisted primarily of amnesia and memory impairment. In ad-hoc analyses of more recent integrated data from the extension studies (31 October 2014 data cutoff date), more neurocognitive events were observed with evolocumab plus SoC compared with SoC alone (0.9% vs: 0.3%).¹²¹ The potential effect of variable visit schedules between arms is unknown. In the open-label extension studies, primarily with OSLER, scheduled clinic visits occurred more frequently for patients receiving evolocumab plus SoC than for patients receiving SoC alone in order for patients to receive protocol-specified in-clinic evolocumab administrations. Notably, the incidence of neurocognitive events did not appear to be related to on-treatment LDL-C. A sub-study of the ongoing FOURIER outcomes study (EBBINGHAUS) will provide a robust assessment of cognitive function (Section 4.14).

Hypersensitivity and injection site reactions: Using the SMQ narrow search strategy with multiple preferred terms possibly associated with hypersensitivity, the incidence of hypersensitivity was low in the integrated parent studies ([REDACTED]), the year 1 SoC-controlled period of the extension studies ([REDACTED]), and the year 2+ open-label period ([REDACTED]). Most events were mild to moderate in severity. Rash and urticaria were determined to be adverse drug reactions with evolocumab use. The incidence of injection site reactions with evolocumab was also low and similar between treatment groups in the integrated parent studies ([REDACTED]), the year 1 SoC-controlled period of the extension studies (evolocumab plus SoC 4.1%; SoC alone did not receive injections), and the year 2+ open-label period of the extension studies ([REDACTED]). Most events were mild to moderate in severity. Injection site reactions were determined to be adverse drug reactions with evolocumab use. The most common injection site reaction adverse events were erythema, pain, and bruising.

Immunogenicity: Anti-evolocumab antibodies were infrequent; the cumulative incidence of binding antibodies after ≥ 1 dose of evolocumab was 0.3% (13 out of 4,915 patients) in the integrated phase 2 and phase 3 studies (as of 01 July 2014). No neutralising anti-evolocumab antibodies have been detected in any patient. Based on a review of adverse events for the patients with binding antibodies, there were no adverse events (i.e. hypersensitivity) determined

to be due to the presence of a binding antibody. No serious adverse events were temporally associated with a positive antibody result.

Adverse events in patients with low LDL-C: Evolocumab represents a novel treatment that significantly reduces LDL-C levels with total reductions of magnitudes not previously demonstrated with statins and/or ezetimibe. Because cholesterol is critical to and involved in many aspects of membrane function and is a precursor for several classes of steroid hormones, adverse events potentially associated with low levels of LDL-C were explored. In the integrated parent studies, the type and incidence of adverse events observed in patients with LDL-C concentrations < 0.6 mmol/L and < 1.0 mmol/L were generally similar to those observed in patients with LDL-C concentrations $\geq$ 1.0 mmol/L. Adverse events were reported in 826 (51%) patients in the any evolocumab group who achieved LDL-C < 0.6 mmol/L and 1308 (51%) patients in the any evolocumab group who achieved LDL-C < 1.0 mmol/L compared with 696 (52%) patients in the any evolocumab group with $\geq$ 1.0 mmol/L and 1018 (50%) patients in the any control group with LDL-C $\geq$ 1.0 mmol/L. However, few patients in the any control group achieved LDL-C < 0.6 mmol/L; therefore, meaningful comparisons with the control group could not be made. No safety signal was identified for neurocognitive adverse events with evolocumab regardless of LDL-C level. Analyses of vitamin E and steroid analytes were performed by LDL-C subgroup, and the analyses were consistent across subgroups in the extension studies. Overall, no pattern in adverse events was noted with further reduction of LDL-C when evolocumab was administered long term.

Safety and tolerability conclusions

Analyses of the safety and tolerability data from the evolocumab studies show that evolocumab has a favourable safety and tolerability profile in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. In an integrated safety analysis (of 6,026 patients, representing 7,235 patient-years of exposure), as well as across populations and therapeutic settings in individual studies, adverse events were overall balanced between treatment groups. Most adverse events were mild to moderate in severity, with serious adverse events and adverse events leading to treatment discontinuation infrequently reported. The most common adverse events reported during the integrated parent studies for evolocumab were nasopharyngitis, upper respiratory tract infection, headache, and back pain. Exploratory safety data from the long-term extension studies suggest that evolocumab is associated with a reduction in CV events of approximately 50%, which is consistent with that predicted (per CTTC) given the magnitude of its LDL-C lowering. No safety issues were detected for events of interest associated with other lipid-lowering therapies (i.e. diabetes events, liver events, muscle events), those associated with other injectable protein therapies (i.e. hypersensitivity events, injection site reactions), those that could theoretically be associated with PCSK9 inhibition/LDL-C receptor upregulation (i.e. hepatitis C events). Anti-evolocumab antibodies were infrequent, non-neutralising, and not associated with clinically relevant adverse events.

4.13 Interpretation of clinical effectiveness and safety evidence

Summary of the principal findings from the clinical evidence base

Benefits

A side-by-side analysis of efficacy across the relevant studies included within this submission support the following key efficacy conclusions.

- Evolocumab consistently reduced LDL-C by up to approximately 72% compared with placebo and up to approximately 46% compared with ezetimibe, in addition to any background lipid-lowering therapy patients were receiving (e.g. statins), with reductions sustained with long-term therapy.
- Evolocumab 140 mg Q2W and 420 mg QM dosing regimens are clinically equivalent, with no clinically meaningful differences in efficacy or safety observed between the two doses.
- Reductions in LDL-C are consistent across patient populations and patient subgroups (including subgroups according to presence or risk of CVD and severity of hypercholesterolaemia).
- Reductions in LDL-C are consistent irrespective of presence and type of background lipid-lowering therapy.

In summary, results from evolocumab clinical studies provide substantial evidence that inhibition of the PCSK9 pathway with evolocumab translates into consistent and intensive reductions in serum LDL-C concentrations.

Risks

The results of the analyses conducted in the primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia integrated safety analysis set for evolocumab support the following key safety conclusions.

- Adverse events were overall balanced between groups in all three periods of the integrated safety data set, as well as across populations and therapeutic settings.
- Most adverse events were mild to moderate in severity, and serious adverse events and adverse events leading to discontinuation of IP were infrequently reported and generally similar across treatment groups.
- No safety issues were detected for adverse events of interest associated with other lipid-lowering therapies (i.e. diabetes events, liver events, muscle events) and those that could theoretically be associated with PCSK9 inhibition/LDL-C receptor upregulation (i.e. hepatitis C events).
- Presence of anti-evolocumab antibodies was infrequent, non-neutralising, and not associated with clinically relevant adverse events.
- The type and incidence of adverse events observed in patients with LDL-C concentrations < 0.6 mmol/L and < 1.0 mmol/L were similar to those observed in patients with LDL-C concentrations $\geq$ 1.0 mmol/L.

Benefit:risk conclusions

The robust and long-term effects of evolocumab on LDL-C and other lipids, combined with its favourable safety and tolerability profile, demonstrate that evolocumab represents a major clinical advancement and revolutionary step-change in the management of primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. Evolocumab will, for the first time, enable clinicians to provide high-risk patients who would otherwise remain vulnerable to CV events (because of inadequate LDL-C reduction with existing therapies) with consistent and intensive LDL-C reductions to reduce their risk of major CV events.

Strengths and limitations of the clinical evidence base

Internal validity

The clinical evidence base for evolocumab included in this submission includes data from relevant large, international phase 3 RCTs, the highest quality evidence for presenting and evaluating clinical efficacy. All of the relevant RCTs included in this submission were determined to be high quality (low risk of bias) following completion of an SLR, as described in Section 4.6.

The relevant RCTs and subgroup analyses consistently demonstrate superiority of evolocumab in reducing LDL-C compared with placebo and ezetimibe, irrespective of:

- patient population and patient characteristics (including presence or risk of CVD and severity of hypercholesterolaemia)
- evolocumab dosing regimen (Q2W or QM)
- presence and type of background lipid-lowering therapy.

This consistent LDL-C-lowering effect was sustained for more than 2 years, demonstrating durability of effect.

Analyses of safety and tolerability have been conducted based on a total of 6,026 patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia who have been administered evolocumab (alone or in combination with a variety of statins), placebo, or any control (including SoC) in phase 2 and 3 studies, representing 7,235 patient-years of exposure. This safety dataset provides a robust estimate of the safety and tolerability of evolocumab, and shows that evolocumab is generally well tolerated with a favourable safety profile.

External validity

All of the relevant RCTs included in this submission included patient populations that are consistent with the overall patient population defined in the decision problem i.e. patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-lowering therapies would be considered in line with current NICE guidance.

Patients with primary hypercholesterolaemia and mixed dyslipidaemia (NICE CG71, CG181 and TA132)

Evidence supporting the efficacy of evolocumab in this patient population comes from the 12-week relevant RCT LAPLACE-2, the 52-week relevant RCT DESCARTES, and the ongoing supplementary long-term extension studies OSLER and OSLER-2.

LAPLACE-2

Population: LAPLACE-2 enrolled patients with primary hypercholesterolaemia and mixed dyslipidaemia receiving moderate- to high-intensity background statin therapy. The clinical characteristics of patients enrolled in LAPLACE-2 were consistent with those of patients in real-world clinical practice in the UK (Appendix VIII). Pre-specified and post-hoc subgroup analyses provided in Section 4.8 provide clinical efficacy data for patient subgroups defined in the decision problem, including presence or risk of CVD and severity of hypercholesterolaemia.

Intervention: LAPLACE-2 included an assessment of evolocumab used in accordance with its MA (i.e. 140 mg Q2W or 420 mg QM) (Appendix I).

Comparator: The comparators in LAPLACE-2 were placebo and ezetimibe, the latter of which was administered in accordance with its UK SmPC (i.e. 10 mg OD). The background moderate- to high-intensity statin therapies used in LAPLACE-2 were generally consistent with those recommended in NICE guidance and used in UK clinical practice (Appendix VIII). In the context of the background statin therapy, comparisons can be made between (i) evolocumab plus statin versus ezetimibe plus statin (relevant intervention and comparator in the decision problem) and (ii) evolocumab plus statin versus statin alone (relevant intervention, but not comparator).

DESCARTES

Population: DESCARTES enrolled patients with primary hypercholesterolaemia and mixed dyslipidaemia receiving background lipid-lowering therapy. The clinical characteristics of patients enrolled in DESCARTES were consistent with those of patients in real-world clinical practice in the UK (Appendix VIII). Pre-specified and post-hoc subgroup analyses provided in Section 4.8 provide clinical efficacy data for patient subgroups defined in the decision problem, including presence or risk of CVD and severity of hypercholesterolaemia.

Intervention: DESCARTES included an assessment of evolocumab used in accordance with its MA (i.e. 420 mg QM) (Appendix I).

Comparator: This was a placebo-controlled study in patients receiving background lipid-lowering therapies. The background lipid-lowering therapies used in DESCARTES were generally consistent with those recommended in NICE guidance and used in UK clinical practice (Appendix VIII). Using the pre-specified background therapy stratification factor subgroups, comparisons can be made between (i) evolocumab plus statin plus ezetimibe plus diet versus statin plus ezetimibe plus diet (relevant intervention and relevant comparator); (ii) evolocumab plus statin plus diet versus statin plus diet (relevant intervention but not comparator); and (iii) evolocumab plus diet versus diet alone (not relevant intervention or comparator).

OSLER/OSLER-2

Population: OSLER and OSLER-2 included a heterogeneous population which completed a range of parent phase 2 and phase 3 studies, respectively. Although this diversity might be viewed as a strength in terms of the generalisability of the findings, some of the included parent studies enrolled patients (i) at low CV risk who did not receive statin therapy at baseline; or (ii) were from a Japanese patient population, which may not represent the population that would ultimately receive evolocumab in clinical practice in England and Wales.

Intervention: OSLER and OSLER-2 included an evolocumab plus SoC intervention arm during the 1-year randomised, controlled period. OSLER and OSLER-2 included an assessment of evolocumab used in accordance with its MA (420 mg QM in OSLER and 140 mg Q2W or 420 mg QM in OSLER-2) (Appendix I).

Comparator: The comparator in OSLER and OSLER-2 was SoC. The definition of SoC was based on local guidelines, but the majority of patients were using statins and ezetimibe at the start of each of these studies.

Patients with HeFH (NICE CG71 and TA132)

Patients with HeFH are defined as a relevant subgroup in the decision problem. Evidence supporting the efficacy of evolocumab in this patient population comes from the 12-week relevant RCT RUTHERFORD-2 and the ongoing non-randomised, non-controlled TAUSSIG study.

RUTHERFORD-2

Population: RUTHERFORD-2 enrolled patients with HeFH unable to achieve adequate LDL-C control despite stable lipid-lowering therapy (statin $\pm$ other lipid-lowering therapy). The inclusion criteria for this study specified that patients needed to have a clinical diagnosis of HeFH according to Simon Broome criteria, which is consistent with the recommended diagnostic method specified in NICE CG71. The clinical characteristics of patients enrolled in RUTHERFORD-2 were consistent those of patients with HeFH in real-world clinical practice in the UK (Appendix VIII). Pre-specified and post-hoc subgroup analyses provided in Section 4.8 provide clinical efficacy data for patient subgroups defined in the decision problem, including presence or risk of CVD and severity of hypercholesterolaemia.

Intervention: RUTHERFORD-2 included an assessment of evolocumab used in accordance with its MA (i.e. 140 mg Q2W or 420 mg QM) (Appendix I).

Comparator: This was a placebo-controlled study patients receiving stable background lipid-lowering therapy (statins $\pm$ other lipid-lowering therapies). The stable background lipid-lowering therapies received by patients in RUTHERFORD-2 were generally consistent with those recommended in NICE guidance and used in UK clinical practice (Appendix VIII). Using the pre-specified ezetimibe use (yes/no) stratification factor subgroups, it is possible to make a comparison between: (i) evolocumab plus statin plus ezetimibe versus statin plus ezetimibe (relevant intervention and comparator); and (ii) evolocumab plus statin versus statin (relevant intervention, but not relevant comparator). However, due to the design of the trial, it is not

possible to make a comparison between evolocumab plus statin versus ezetimibe plus statin (a relevant intervention and comparator in the decision problem). Many patients with HeFH unable to control LDL-C with statins alone may already be receiving additional lipid-lowering therapies such as ezetimibe (62% of patients in RUTHERFORD-2 were receiving ezetimibe at baseline), and it would not have been ethical to discontinue ezetimibe use for washout prior to randomisation to IP in RUTHERFORD-2 in these high-risk patients. Further, given the uncertainty of the treatment effect of evolocumab, it would not have been ethical to enrol patients with HeFH who had not already been offered optimal treatment with currently available therapies e.g. ezetimibe. Following a review of studies identified in the SLR as being potentially useful to synthesize comparative efficacy data for evolocumab plus statin versus ezetimibe plus statin, a network meta-analysis was deemed neither appropriate nor feasible (Section 4.10). Further, no comparison of evolocumab monotherapy versus ezetimibe monotherapy (a relevant intervention and comparator in statin intolerant or contraindicated patients) in the HeFH population in RUTHERFORD-2 is possible given that all patients were required to be on stable doses of statins, and subgroups of patients according to history of intolerance to statins were not investigated. Given the consistency of treatment effect of evolocumab across multiple studies in different populations, it is reasonable to assume that the relative efficacy of evolocumab plus statin versus ezetimibe plus statin (based on LAPLACE-2) and relative efficacy of evolocumab monotherapy versus ezetimibe monotherapy in statin intolerant or contraindicated patients (based on GAUSS-2) are generalisable to the HeFH population. This is supported by the economic evaluation of ezetimibe that was utilised in NICE TA132, in which an assumption was made that the treatment effect of ezetimibe in non-HeFH patients was generalisable to patients with HeFH, in the absence of HeFH-specific efficacy data.⁶²

TAUSSIG

Population: TAUSSIG included patients with severe HeFH (mean baseline LDL-C 4.9 mmol/L), which is relevant to patients in England and Wales who also have severe forms of this disease (Figure 3-1).

Intervention: Patients in TAUSSIG received evolocumab 420 mg QM (non-apheresis patients) or 420 mg Q2W (apheresis patients). The QM dose is in accordance with evolocumab's MA for patients with HeFH but the Q2W dose is not (Appendix I). Generalisability across the two doses of evolocumab is limited as patients could discontinue, or switch between the two doses, pending achievement of defined LDL-C levels.

Comparator: Not applicable.

Patients for whom statins are not tolerated or are not clinically appropriate (NICE CG181 and TA132)

Patients with statin intolerance are defined as a relevant subgroup in the decision problem. Evidence supporting the efficacy of evolocumab in this patient population comes from the 12-week relevant RCT GAUSS-2.

Population: The clinical characteristics of patients enrolled in GAUSS-2 were consistent with those of patients in real-world clinical practice in the UK (Appendix VIII). GAUSS-2 enrolled patients with previous intolerance to two or more statins, defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects. The use of muscle symptoms as a key identifier of statin intolerance is consistent with the definition of statin intolerance provided in NICE CG71 and TA132. CG181 specifies that statin intolerance should be defined clinically as the inability to tolerate 3 different statins,⁹² which is more than the minimum number of statins patients were required to be intolerant to in GAUSS-2, though > 50% patients enrolled in GAUSS-2 were intolerant to ≥ 3 statins (Section 4.5). The definition of statin intolerance used in GAUSS-2 is also consistent with clinical practice in the UK, where respondents to a clinician survey reported that 74% and 66% of patients with potential statin intolerance and established statin intolerance (following e.g. statin rechallenge, statin regimen modification, and CK/transaminase testing), respectively, presented with muscle symptoms.¹²⁹ Further, 75% of respondents indicated that they would try two or more statins before considering a patient statin intolerant. Pre-specified and post-hoc subgroup analyses provided in Section 4.8 provide clinical efficacy data for patient subgroups defined in the decision problem, including presence or risk of CVD and severity of hypercholesterolaemia. Although GAUSS-2 did not include any patients contraindicated to statins, it is reasonable to assume that the treatment effect of evolocumab in GAUSS-2 is representative of this patient population in the absence of specific evidence in statin-contraindicated patients.

Intervention: GAUSS-2 included an assessment of evolocumab used in accordance with its MA (i.e. 140 mg Q2W or 420 mg QM) (Appendix I).

Comparator: The comparator in GAUSS-2 was ezetimibe, which was administered in accordance with its MA (i.e. 10 mg OD); this comparator is consistent with the relevant comparator in the decision problem for this population (i.e. ezetimibe monotherapy). A minority (18%) of the patients enrolled in GAUSS-2 remained on low-dose statin at baseline. This is reflective of clinical practice in the UK where statin-intolerant patients may continue to be prescribed statins (Appendix VIII).

Outcomes

The current evidence base does not include an assessment of the incidence of CV events as an efficacy outcome (although a CV outcomes study, FOURIER, is ongoing [Section 4.14]), the evidence supporting LDL-C as a therapeutic target and validated surrogate for CV outcomes is multi-faceted, as discussed in Section 3. Epidemiological and interventional studies demonstrate a proportional and continuous relationship between LDL-C and CV outcomes irrespective of treatment mechanism, whilst genetic variants that are associated with variations in LDL-C demonstrate the expected impact on CVD risk. This is recognised in NICE guidance (TA132).⁶² Further, exploratory safety data from the long-term extension studies suggest that evolocumab is associated with a reduction in CV events of approximately 50%, which is consistent with that predicted (per CTTC) given the magnitude of its LDL-C lowering.

Interpretation of clinical efficacy and safety evidence conclusions

The clinical evidence base included in this submission includes robust, high-quality evidence (with low risk of bias) on the consistent, intensive, and long-term efficacy of evolocumab with respect to lowering LDL-C across various patient populations and therapeutic settings, as well as its favourable safety and tolerability profile. The evidence base adequately addresses the decision problem, provides data in relevant patient populations and versus relevant comparators, and is generalisable to patients who will ultimately receive evolocumab in clinical practice in England and Wales.

4.14 Ongoing studies

Amgen is currently conducting studies intended to evaluate the long-term safety and efficacy of evolocumab in LDL-C lowering, the effect of evolocumab in reducing CV morbidity/mortality (FOURIER) and coronary atherosclerosis using intravascular ultrasound (GLAGOV), the effect of evolocumab in special populations (e.g. patients with statin intolerance [GAUSS-3] and paediatric patients with FH [HAUSER]), and the effect of evolocumab on neurocognitive function (EBBINGHAUS). Table 4-28 summarises all ongoing studies of evolocumab.

Within 12 months of this submission (i.e. through July 2016), we anticipate that the following will be published:

- a 52-week analysis of the effects of evolocumab on vitamin E and steroid hormone levels based on the DESCARTES study
- an analysis of the efficacy and safety of evolocumab in statin-treated, Japanese patients at high CV risk based on the YUKAWA-2 study
- 52-week results from the ongoing TAUSSIG study
- results from the FLOREY study, which assessed the impact of evolocumab in combination with atorvastatin on lipoprotein kinetics
- an analysis of the relationship between long-term reduction in LDL-C and Lp(a).

Table 4-28 Ongoing studies of evolocumab (as of 01 July 2015)

Study	Description	Interventions	No. of patients	Population (countries included)	Primary outcome measure	Estimated completion dates
Outcomes studies						
20120153 (GLAGOV)	Phase 3, RCT	•Placebo QM •Evolocumab 420 mg QM	970	AR, BE, BR, CA, CH, CL, CZ, DE, DK, ES, FR, GR, HU, IL, IS, I.E.IT, KR, MY, MX, NL, NO, PH, PL, RU, SE, SG, TW, UK, US, ZA	Nominal change in PAV from baseline to week 78 post-randomisation, as determined by IVUS	Completion date: July 2016 Primary completion date ^a : July 2016
20110118 (FOURIER)	Phase 3, RCT	•Placebo Q2W •Evolocumab 140 mg Q2W •Placebo QM •Evolocumab 420 mg QM	27,564	AR, AT, AU, BE, BG, BR, CA, CH, CL, CN, CO, CZ, DE, DK, EE, ES, FI, FR, GR, HK, HU, I.E.IL, IN, IS, IT, JP, KR, LT, LV, MY, MX, NL, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SK, TR, TW, Ukraine, UK, US, ZA	Time to CV death, MI, stroke, hospitalisation for UA, or coronary revascularisation, whichever occurs first	Completion date: February 2018 Primary completion date ^a : October 2017
Long-term extension studies						
20110110 (OSLER)	Phase 2, open-label extension	•SoC^b •Evolocumab 420 mg QM + SoC^b	1,324	AU, BE, CA, CZ, DE, DK, ES, FI, HK, HU, JP, NL, NO, SE, SG, UK, US, ZA	Patient incidence of treatment emergent AEs (timeframe: approximately 1 year)	Completion date: July 2016 Primary completion date ^a : July 2016

Study	Description	Interventions	No. of patients	Population (countries included)	Primary outcome measure	Estimated completion dates
20140128 (GLAGOV OLE)	Phase 3, open-label extension	•Evolocumab	642 (estimated)	AU, BE, CA, CZ, ES, HU, IT, NL, NO, PO, RU, US	Patient incidence of AEs	Completion date: July 2018 Primary completion date ^a : July 2018
20120138 (OSLER-2)	Phase 3, open-label extension	•SoC ^b •Evolocumab 140 mg Q2W or 420 mg QM + SoC ^b	4,428 (estimated)	AT, AU, BE, CA, CH, CZ, DE, DK, ES, FR, HK, HU, IT, JP, KR, NL, NO, NZ, PL, RU, SE, TW, UK, US, ZA	Patient incidence of AEs (timeframe: 156 weeks)	Completion date: May 2018 Primary completion date ^a : May 2018
20110271 (TAUSSIG)	Phase 2/3, open-label	•Evolocumab 420 mg Q2W •Evolocumab 420 mg QM	300	AU, BE, BR, CA, CZ, ES, FR, GR, HK, IL, IT, JP, LB, NL, NZ, UK, US, ZA	Patient incidence of treatment emergent AEs over 5 years	Completion date: March 2020 Primary completion date ^a : March 2020
LDL-C lowering in special populations (paediatric FH, statin intolerance)						
20120123 (HAUSER)	Phase 3, RCT	•Placebo (QM) •Evolocumab QM	150 (estimated)	NR	Percent change from baseline in LDL-C at week 24	Completion date: August 2017 Primary completion date ^a : April 2017
20120332 (GAUSS-3)	Phase 3, RCT	<u>Part A – Cross-over statin rechallenge</u> •Placebo OD •Atorvastatin 20 mg OD <u>Part B – Comparison of evolocumab and</u>	519	AU, CA, CZ, DE, DK, FR, IT, NL, NO, NZ, UK, US, ZA	Mean percent change from baseline in LDL-C at weeks 22 and 24 and mean percent change from baseline in LDL-C at week 24 in part B	Completion date: November 2017 Primary completion date ^a : October 2015

Study	Description	Interventions	No. of patients	Population (countries included)	Primary outcome measure	Estimated completion dates
		<u>ezetimibe</u> • Placebo QM + ezetimibe OD • Evolocumab 420 mg QM + Placebo OD <u>Part C – open-label extension</u> • Evolocumab 420 mg QM or 140 mg Q2W				
Cognitive function studies						
20130385 (EBBINGHAUS) ^c	Phase 3, RCT	• Evolocumab Q2W or QM + effective statin dose • Placebo Q2W or QM + effective statin dose	4,000 (estimated)	AU, BE, CA, CZ, DE, DK, EE, ES, FI, FR, GR, HK, HU, IT, JP, LT, LV, MY, NL, NZ, NO, PL, PT, RU, SK, SE, TR, US, ZA	Mean change from baseline over time in spatial working memory index of executive function	Completion date: February 2018 Primary completion date ^a : October 2017
^a Final data collection date for primary outcome measure. ^b SoC therapy as per local practices. This could include prescribed therapies and/or dietary/exercise regimens. ^c EBBINGHAUS evaluates the effect of evolocumab on cognitive function in a subset of patients enrolled in FOURIER. AE, adverse event; AR, Argentina; AT, Austria; AU, Australia; BE, Belgium; BG, Bulgaria; BR, Brazil; CA, Canada; CH, Switzerland; CL, Chile; CN, China; CO, Colombia; CV, cardiovascular; CZ, Czech Republic; DE, Germany; DK, Denmark; EBBINGHAUS, (Evaluating PCSK9 Binding AntiBody Influence oN CoGnitive HeAlth in High CardiovascUlar Risk Patients); EE, Estonia; ES, Spain; FI, Finland; FR, France; GR, Greece; HK, Hong Kong; HU, Hungary; I.E.Ireland; IL, Israel; IN, India; IS, Iceland; IT, Italy; IVUS, intravascular ultrasound; JP, Japan; KR, Republic of Korea; LB, Lebanon; LDL-C, low-density lipoprotein cholesterol; LT, Lithuania; LV, Latvia; MI, myocardial infarction; MY, Malaysia; MX, Mexico; NL, Netherlands; NO, Norway; NZ, New Zealand; NR, not reported; OLE, open-label extension; PAV, percent atheroma volume; PH, Republic of the Philippines; PL, Poland; PT, Portugal; Q2W, every 2 weeks; OD, once daily; QM, monthly; RCT, randomised controlled trial; RO, Romania; RU, Russian Federation; SE, Sweden; SG, Singapore; SK, Slovakia (Slovak Republic); SoC, standard of care; TR, Turkey; TW, Taiwan; UA, unstable angina; UK, United Kingdom; US, United States; ZA, South Africa						

5 Cost effectiveness

- A *de novo* cost-effectiveness Markov model analysis was developed for the economic evaluation and undertaken in accordance with the NICE reference case. A lifetime analysis was performed (cycle length of one year; half-cycle correction used). Costs and outcomes were discounted at 3.5% per annum.
- Drug costs were taken from the NHS Drug Tariff. The acute and long-term care costs of CV events were based on a retrospective longitudinal observation cohort study using CPRD and HES data.
- Health state utilities were based on NICE CG181 for acute and long-term CVD states.
- Baseline characteristics from the relevant phase 3 evolocumab RCTs were used for the populations under assessment to inform baseline CV risk using Framingham Heart Study and Reach registry risk equations.
- Baseline CV rates were calibrated based on estimations for patients with and without existing CVD and HeFH using CPRD and FH registry data.
- LDL-C reductions from the relevant phase 3 evolocumab RCTs were used for evolocumab and ezetimibe to model the translation between LDL-C and CV events for the treatment strategies, based on the CTTC meta-analysis for LDL-C reduction and major CV events.
- Populations: The following populations have been considered in the context of NICE guidance for whom lipid-lowering therapies would be considered; patients with and without existing CVD at high residual risk due to additional risk factors, and patients with HeFH.
- Evolocumab and ezetimibe (comparator) were considered in accordance with their MAs.
- Parameter uncertainty was assessed in a series of scenario analyses, deterministic sensitivity analyses and probabilistic sensitivity analysis.
- Threshold analyses indicate the evolocumab represents a cost-effective treatment option compared with ezetimibe in patients without existing CVD and at high residual risk due to additional risk factors (based on QRISK2 score) according to the severity of hypercholesterolaemia.
- Base case deterministic results show that when age and gender are taken into consideration, the incremental cost per QALY gained is less than £30,000 in patients with existing CVD and at high residual risk due to the presence of one or more additional risk factors (e.g. diabetes mellitus or CKD) according to the severity of hypercholesterolaemia.
- The incremental cost per QALY gained is approximately £[REDACTED] to £[REDACTED] for evolocumab versus ezetimibe in patients with HeFH when assessed across the four treatment scenarios.
- The cost-effectiveness results were robust to a number of scenario analyses, univariate sensitivity analyses and probabilistic sensitivity analysis conducted to assess uncertainty.

5.1 Published cost-effectiveness studies

Identification of studies

A SLR was conducted to systematically identify, critically review, and summarise studies evaluating the cost-effectiveness of evolocumab, statins, and ezetimibe for LDL-C reduction in adults with hypercholesterolaemia. The review of model structures was used to inform the cost-effectiveness model used for this appraisal. The SLR was conducted in accordance with general guidelines for conducting systematic reviews published by the Centre for Reviews and Dissemination (CRD).¹³⁰

Information sources

The search included peer-reviewed journal articles, HTA documents, and data from relevant conference proceedings (i.e. published studies only) identified through the systematic search process described below.

Databases

The literature review was conducted on 31 December 2014, and the following electronic databases were searched:

- MEDLINE
- Embase
- Econlit
- National Health Service Economic Evaluations Database (NHS EED).

MEDLINE, Embase, and Econlit were accessed via the Ovid gateway, and NHS EED was accessed via the CRD website. The search was limited to articles with abstracts written in the English language and published between 2000 and 2014.

Searches before 2000 were not performed because no relevant economic evaluations were expected to be published before that date. Furthermore, estimates of resource use and unit costs published more than 15 years ago would be outdated; the resource use quoted in older articles would not be reflective of current clinical practice and unit costs may not represent current prices.

The search strategy used was formulated using terms focussing on (i) LDL-C, (ii) lipid-lowering therapy, and (iii) economic evaluations. Appendix F of the NICE lipid modification CG (CG181)¹³¹ was used to inform the search terms for the lipid-lowering therapy, health conditions, and excluded publication types. Medical Subject Headings and keyword searches were used and edited in line with the appropriate search syntax for the different databases used. All search strategies are provided in Appendix IX.

Conference proceedings

In the conference proceedings search, conference abstracts published in 2013 and 2014 from the following congresses were reviewed:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- American College of Cardiology (ACC)
- American Heart Association (AHA)
- European Society of Cardiology (ESC)
- European Atherosclerosis Society (EAS).

The 2-year timeframe for the conference abstract search was selected as full publications were anticipated following this period. The conference proceeding search used the same strategy as the Embase search strategy. All conferences were indexed in Embase except ESC 2014, EAS 2014, and EAS 2013. The websites of the conferences not indexed by Embase were searched manually for relevant abstracts. Conference abstracts presented at ESC 2014 were indexed via www.congress365.escardio.org, and abstracts presented at EAS 2014 were indexed via www.atherosclerosis-journal.com. There was no website available for the EAS 2013 conference abstracts. All search strategies are provided in Appendix IX.

HTA documents

In addition, HTA documents assessing economic evaluations of lipid-lowering drug therapies were identified through a manual search of the HTA websites of the UK (including NICE, All Wales Medical Strategy Group, and the SMC), Spain, Sweden, France, Australia, Canada, Netherlands, Belgium, Austria, Ireland, Portugal, Poland, Hungary, Slovenia, Mexico, and Brazil. Economic evaluations of lipid-lowering therapies reported in HTA submissions between 2000 and 2014 were selected. Searches before 2000 were not performed because no relevant economic evaluations were expected to be published beyond the time horizon of the past 15 years. All search strategies are provided in Appendix IX.

Other sources

Reference sections of review articles identified in search results were hand searched for original relevant articles fitting the identified search criteria of economic studies, describing a health condition in cardiovascular diseases, evaluating lipid-lowering therapies, and published in the English language between 2000 and 2014.

Study selection

Publications were included if they met the eligibility criteria as outlined in Table 5-1.

Table 5-1 Eligibility criteria used in the economic evaluations SLR

Component	Inclusion	Exclusion	Rationale/comments
Population	Adults with LDL hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies would be considered	- Children (< 18 years of age) - Non-humans	Studies assessing the cost-effectiveness of statins and ezetimibe only in children were excluded in accordance with the scope of NICE CG181 ⁷⁷
Intervention/ comparators	- Evolocumab - Statins - Ezetimibe	- Surgical procedures - Lifestyle modification - Dietary modification	The interventions included in this review reflect the NICE scope for evolocumab
Outcomes	- Cardiovascular event reduction - Treatment costs - QALYs or other quality of life measures - Cost-effectiveness and/or cost-utility results for the interventions of interest (i.e. ICER)		
Study design	- Full economic evaluations - Abstracts included - Conference proceedings - HTA documents	- Models that do not involve economic evaluations - Studies that only assess cost, utilisation, or efficacy - Studies that do not present cost-effectiveness measures - Non-human studies	
Language restrictions	English language		Studies reported in a language other than English are not expected to provide additional information for this NICE submission
Country restrictions (HTAs only)	HTA documents from the UK, Spain, Sweden, France, Australia, Canada, Netherlands, Belgium, Austria,		

	Ireland, Portugal, Poland, Hungary, Slovenia, Mexico, and Brazil		
Date restrictions	• Database search and HTAs: 2000-2014 • Conference proceedings: 2013-2014		Database search and HTAs: no relevant economic evaluations were expected to be published before 2000 Conference proceedings: full publications were anticipated following the 2-year time period
CG, clinical guideline; HTA, Health Technology Assessment; ICER, incremental cost-effectiveness ratio; LDL, low-density lipoprotein; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; SLR, systematic literature review			

Validity assessment

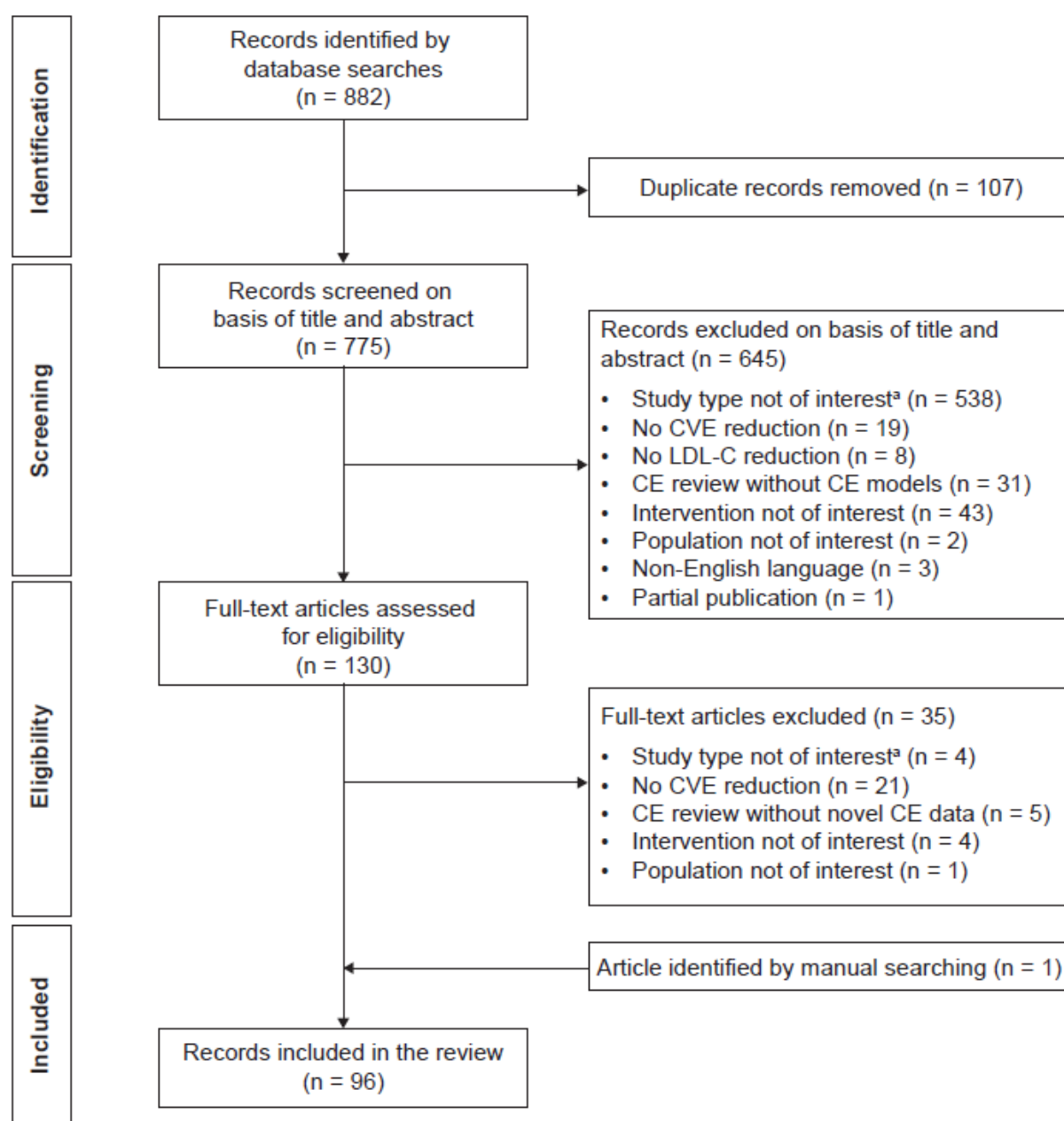
After the literature had been obtained from the databases, the conference proceedings, and HTA searches, a three-stage process was used to identify relevant articles for extraction. In the first stage, titles and abstracts from the peer-reviewed literature and HTA documents were reviewed for eligibility against inclusion/exclusion criteria. The articles and documents meeting the criteria were selected for full-text review (stage 2). The first two stages of the literature review were carried out by two researchers independently. If a study did not meet the eligibility criteria, the reason for exclusion was noted in a data extraction form. Articles considered eligible after full-text review were selected for data extraction, which constituted the third stage of the review process.

Description of identified studies

The database literature search (in MEDLINE, Embase, Econlit, and NHS EED) identified 882 citation results. Of these, 107 articles were duplicates and subsequently removed from the review for a total of 775 unique articles that could proceed to phase 1 selection. A list of the duplicate studies can be found in Appendix IX. Of the unique articles, 645 were excluded after a review of titles/abstracts (stage 1). During stage 1 of the review process, one additional hand-searched article was identified, for a total of 131 articles retrieved for full-text review (stage 2). After full-text review, during which a further 35 studies were excluded, a total of 96 studies from the database search were included for data extraction. A full list of the 35 excluded studies from stage 2, can be found in Appendix IX.

The PRISMA flow chart of the inclusion and exclusion of the studies from the database search is presented in Figure 5-1.

Figure 5-1 PRISMA flow diagram for the economic evaluations SLR



^aStudy types not of interest include: screening, risk modelling, switching programme, guidelines, non-cardiovascular disease, clinical trial, and utilisation studies.

CE, cost-effectiveness; CVE, cardiovascular event ; LDL-C, low-density lipoprotein cholesterol; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review

In addition to the above-mentioned articles, a search of conference proceedings through Embase yielded 33 abstracts, of which only one assessed the cost-effectiveness of at least one treatment of interest. A manual search of conferences not indexed in Embase yielded 184 abstracts. However, none of these studies assessed the cost-effectiveness of the treatments of interest.

A manual search of HTA websites identified 11 HTA review documents that contained cost-effectiveness models relevant to the decision problem.

For the final data extraction, 108 studies were included (96 identified through database searches, 11 HTA documents, and one conference proceeding). A full list of studies reporting relevant economic evaluations and the main items included during data extraction are presented in Appendix IX. This table is composed of publications from the database search (n = 96; highlighted green), HTA documents (n = 11; highlighted orange), and conference proceedings (n = 1; highlighted blue).

The data extraction was focussed on the population consisting of adults with hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-lowering therapies would be considered. This population is eligible for treatment with evolocumab and of interest for the cost-effectiveness model, as described in more detail in section 5.2. Most of the papers presented results based on models with a UK focus (n = 28). A further two studies were from Argentina, seven from Australia, two from Belgium, 11 from Canada, two from Finland, two from Greece, three from Ireland, two from Japan, two from Korea, five from Netherlands, two from Spain, four from Sweden, 19 from the USA, and 10 were conducted in multiple countries. Additionally, single studies were identified that focussed on Austria, Brazil, China, Czech Republic, France, Hungary, Italy, Philippines, Portugal, Tanzania.

Of the 108 extracted studies, most used a Markov model (n = 66) and 53 (approximately 50%) studies modelled a lifetime time horizon (25 years or more). None of the identified publications presented an economic evaluation of evolocumab.

Economic evaluation summary data extraction tables.

Table 5-2 highlights the data extracted from studies with a UK focus that present a Markov model with a lifetime time horizon. A full overview table, providing details from all studies that underwent data extraction is provided in Appendix IX.

Table 5-2 Economic evaluation summary data extraction table of UK studies presenting a Markov model with a lifetime time horizon

First author, year	Model type/ modelled population	Time horizon and cycle length	Health states	Patient demographics (average age, comorbidities)	Intervention and comparators (treatment and treatment duration)	QALYs (intervention, comparator)	Costs (year, currency) (individual intervention, comparator costs)	ICER (per QALY gained)
Ara, 2009 ¹³²	Markov model with various adherence scenarios Prevention: secondary	Time horizon: Lifetime Cycle length: 1 year	UA, MI, revascularisation, stroke, hospitalisation for UA, MI with ACS history, MI + stroke, new stroke + ACS, hospitalisation for UA + stroke + ACS, non-CVD mortality, CVD mortality	60 years; men with ACS	Intervention: - Comparators: ATO 80 mg; ROS 40 mg; SIM 40 mg; SIM 80 mg; placebo; treatment duration not reported	SIM 40 mg: 7.38-7.55 SIM 80 mg: 7.39-7.66 ATO 80 mg: 7.51-7.78 ROS 40 mg: 7.54-7.86	In 2009 £; SIM 40 mg: £14,511-15,232 SIM 80 mg: £15,053-15,830 ATO 80 mg: £17,971-18,572 ROS 40 mg: £17,851-18,464	SIM 40 mg: £5,226-59,200 SIM 80 mg: £18,663-28,540 ATO 80 mg: Dominated ROS 40 mg: £13,683-16,344
Ara, 2012 ¹³³	Markov model with various adherence scenarios Prevention: secondary	Time horizon: Lifetime Cycle length: 1 year	UA, MI, revascularisation, stroke, hospitalisation for UA, MI with ACS history, MI + stroke, new stroke + ACS, hospitalisation for UA + stroke + ACS, non-CVD mortality, CVD mortality	60 years; men with ACS	Intervention: - Comparators: SIM 40 mg; ATO 80 mg; ROS 40 mg; treatment duration not reported	Cohort of 1000 men SIM 40 mg: 7545-7383 ATO 80 mg: 7507-7778 ROS 40 mg: 7540-7862	In 2007 £; Cohort of 1000 men SIM 40 mg: £14,522,000-15,232,000 ATO 80 mg: £17,971,000-18,572,000 ROS 40 mg: £17,851,000-18,464,000	ATO 80 mg vs. SIM 40 mg: £17,217-21,938 ROS 40 mg vs. SIM 40 mg: £12,277-16,592
Ara (Am J Cardiovasc Drugs), 2008 ¹³⁴	Markov model Prevention: secondary	Time horizon: Lifetime Cycle length: 1 year	New SA, new UA, new non-fatal MI, new non-fatal stroke, post-SA, post-UA, post-MI, post-TIA, post-stroke, fatal CHD, fatal stroke, fatal other	55 years; primary hyperlipidaemia, history of CVD, baseline LDL of 4.0 mmol/L who do not tolerate statins or in whom they are contraindicated	Intervention: EZE monotherapy; treatment duration not reported Comparators: No treatment	Cohort of 1,000 men EZE: 8,400 No treatment: 8,189	In 2006 £; Cohort of 1,000 men EZE: £14,458,088 No treatment: £9,597,278	EZE vs. no treatment: £23,026
Ara (Clin Ther),	Markov model	Time horizon:	New SA, new UA, new non-fatal MI, new non-	55 years; primary hyperlipidaemia,	Intervention: EZE + statin; treatment	Cohort of 1,000 men	In 2006 £; Cohort of 1,000 men	EZE + statin vs. statin: £27,475

First author, year	Model type/ modelled population	Time horizon and cycle length	Health states	Patient demographics (average age, comorbidities)	Intervention and comparators (treatment and treatment duration)	QALYs (intervention, comparator)	Costs (year, currency) (individual intervention, comparator costs)	ICER (per QALY gained)
2008 ¹³⁵	Prevention: secondary	Lifetime Cycle length: 1 year	fatal stroke, post-SA, post-UA, post-MI, post-TIA, post-stroke, fatal CHD, fatal stroke, fatal other	history of CVD, baseline LDL of 3.0 mmol/L whose cholesterol levels are not appropriately controlled with a statin alone	duration not reported Comparators: Statin monotherapy; treatment duration not reported	EZE + statin: 8,386 Statin monotherapy: 8,252	EZE + statin: £16,560,000 Statin monotherapy: £12,867,000	
Ara (Health Technol Assess), 2008 ¹³⁶	Markov model with various treatment scenarios Prevention: primary and secondary	Time horizon: Lifetime Cycle length: 1 year	MI, SA, UA, CHD death, TIA, stroke, CVD death, other death, event free	45-75 years (average age not reported); individuals who tolerate statin treatment, individuals in whom statin treatment is contraindicated, and those in whom statins are not tolerated	Intervention: - Comparators: 1) EZE 10 mg + statin vs. titrated statin; 2) EZE vs. no treatment; 3) EZE 10 mg + SIM 20-40 mg vs. ATO 20-40 mg; 4) EZE 10 mg + statin vs. statin; 5) EZE 10 mg + ROS 40 mg vs. ROS 40 mg; 6a) EZE 10 mg + PRA 10 mg vs. SIM 10 mg; 6b) EZE 10 mg + statin vs. same dose of more potent statin; treatment duration not reported	1) Not reported 2) 63.7-246.9 3) Not reported 4) Not reported 5) Not reported 6a) Not reported 6b) Not reported	In 2006 £; 1) Not reported 2) Primary: £2,707,000-6,088,000; Secondary: £2,609,000-6,286,000 3) Not reported 4) Not reported 5) Not reported 6a) Not reported 6b) Not reported	1) Primary: £24,400-61,600; Secondary: £24,200-42,000 2) Primary: £24,100-42,500; Secondary: £26,200-34,000 3) Primary: £1500-4100; Secondary: £3700-6500 4) Primary: £18,700-47,300; Secondary: £20,700-37,800 5) Primary: £19,000-47,500; Secondary: £21,000-38,200 6a) Primary: £32,000-81,000; Secondary: £31,000-53,800

First author, year	Model type/ modelled population	Time horizon and cycle length	Health states	Patient demographics (average age, comorbidities)	Intervention and comparators (treatment and treatment duration)	QALYs (intervention, comparator)	Costs (year, currency) (individual intervention, comparator costs)	ICER (per QALY gained)
								6b) Primary: <£5,000; Secondary: <£5,000
AWMSG 1311, 2011 ¹³⁷	Markov model Prevention: primary	Time horizon: Lifetime Cycle length: 1 year	CVD free, UA, non-fatal MI, TIA, non-fatal stroke, CVD death, death from other cause	High risk patients intolerant to simvastatin	Intervention: PRA 40 mg Comparators: ROS 20 mg	Not reported	In 2011 £; No individual cost reported	In £/QALY: ROS vs. PRA £129-7,805
Heart Protection Study Group, 2006 ¹³⁸	Markov model Prevention: primary and secondary	Time horizon: Lifetime Cycle length: 1 year	Healthy, death from vascular cause, non-fatal major vascular event, non-fatal other vascular event, death from non-vascular cause	Men and women (aged 40-80) in the Heart Protection Study with coronary disease, other occlusive arterial disease, or diabetes	Intervention: SIM 40 mg; treatment duration not reported Comparators: Placebo; treatment duration not reported	Generic SIM 40 mg: 0.09-1.19 (Heart Protection Study population)	In £ (year not reported); Lifetime cost Generic SIM 40 mg: £460 to £1,180	Lifetime use of generic SIM vs. placebo: -£1,310 to 110
Mihaylova, 2006 ¹³⁸	Markov model Prevention: secondary	Time horizon: Lifetime Cycle length: annual	Well, non-fatal major vascular event, non-fatal other vascular event only, death from non-vascular cause, death from vascular cause	40-80 years (average age not reported); in the Heart Protection Study with CHD, other arterial disease, or diabetes	Intervention: SIM 40 mg; 5 years Comparators: Placebo; 5 years	Not applicable	In 2001 £; Lifetime cost of treatment with SIM for Heart Protection Study population Age 40-49 years: £880-1,180 Age 50-59 years: £760-1,030 Age 60-69 years: £590-840 Age ≥ 70 years:	In £/LYG: Age 40-49: -£440 to -£990 Age 50-59: -£370 to -£720 Age 60-69: -£140 to -£400 Age 70+: £80 to -£140

First author, year	Model type/ modelled population	Time horizon and cycle length	Health states	Patient demographics (average age, comorbidities)	Intervention and comparators (treatment and treatment duration)	QALYs (intervention, comparator)	Costs (year, currency) (individual intervention, comparator costs)	ICER (per QALY gained)
							£460-670	
Nherera, 2010 ¹³⁹	Markov model Prevention: primary	Time horizon: Lifetime Cycle length: 1 year	Well, MI, stroke, PAD, CHF, revascularisation, UA, death	20-70 years (average age 50 years); FH patients, treatment time not reported	Intervention: Low-intensity statins over lifetime Comparators: High-intensity statins over lifetime	Over lifetime: low intensity: 12.02 high intensity: 12.44	In 2008-2009 £; Low-intensity: £9,448 High-intensity: £14,095	Low intensity vs. high intensity: £11,103
NICE CG 181, 2014 ⁷⁷	Markov model Prevention: primary (ICERs not available for secondary prevention)	Time horizon: Lifetime Cycle length: 1 year	CV death, SA, UA, MI, TIA, CHF, PAD, non-CV death	60 years; adults without CVD, with diabetes and without CVD, or with CVD in England and Wales	Intervention: No treatment Comparators: Low-intensity statins (FLU 20-40 mg, PRA 10-40 mg, SIM 10 mg); Medium-intensity statins (FLU 80 mg, SIM 20-40 mg, ATO 10 mg, ROS 5 mg); High-intensity statins (SIM 80 mg, ATO 20-80 mg, ROS 10-40 mg)	No treatment: 6.862 Low-intensity statins: 7.230 Medium-intensity statins: 7.307 High-intensity statins: 7.480	In 2014 £; No treatment: £9,404 Low-intensity statins: £11,116 Medium-intensity statins: £11,057 High-intensity statins: £11,307	Low intensity vs. no treatment £4,605 Medium intensity vs. low intensity: Dominates Medium intensity vs. no treatment £3,559 High vs. medium intensity: £1,397 High vs. no treatment: £2,959
NICE TA 132, Issue date: 2007 Review date: 2010 ⁶²	Markov model Prevention: primary and secondary	Time horizon: 20 years and lifetime Cycle length: not reported	Not reported	Adults; CVD, with ≥ 20% 10-year risk of developing CVD	Intervention: EZE; 20 years and lifetime Comparators: Statins; 20 years and lifetime	Not reported	In 2006 £; Obtained from published literature and expert opinion	In £/QALY: Scenario 1 ICER £24,000-43,000 Scenario 2 ICER £24,000-42,000 Scenario 3

First author, year	Model type/ modelled population	Time horizon and cycle length	Health states	Patient demographics (average age, comorbidities)	Intervention and comparators (treatment and treatment duration)	QALYs (intervention, comparator)	Costs (year, currency) (individual intervention, comparator costs)	ICER (per QALY gained)
								ICER £1,500-4,600 Scenarios 4 and 5 ICER £19,000-33,000
Reckless, 2010 ¹⁴⁰	Markov decision-analytic model Prevention: secondary	Time horizon: Lifetime Cycle length: 1 year	Well, MI, angina, CHD death, non-CHD death	INFORCE study patients	Intervention: EZE/SIM 10/40 mg; over 12 weeks Comparators: Double statin dose; over 12 weeks	EZE/SIM 10/40 mg: 6.42-7.41 Double statin dose: 6.67-7.10	In 2008 £; EZE/SIM 10/40 mg: £3,372-7,610 Double statin dose: £3,430-5,380	Low potency EZE/SIM 10/40 mg vs. double statin dose: £13,552 Medium potency EZE/SIM 10/40 mg vs. double statin dose: £11,930 High potency EZE/SIM 10/40 mg vs. double statin dose: £10,148
SMC 725/11, 2011 ¹⁴¹	Markov model Prevention: primary	Time horizon: Lifetime Cycle length: not reported	Unstable angina, MI, TIA, CVD death, non-CVD death, non-fatal stroke	Patients at high risk of CVD event (> 20% 1-year CVD risk) and in whom SIM is not tolerated or contraindicated	Intervention: ROS 20 mg Comparators: PRA 40 mg	Not reported	In £; No individual cost reported	In £/QALY; Men £1,303-7,491 Women £1,342-7,256 Overall estimate £5,527
Ward, 2007 ¹⁴²	Markov model	Time horizon: Lifetime	Event free, MI, SA, UA, CHD death, TIA, stroke, CVD death, death from	Average age not reported; increased risk of death or	Intervention: Statin; treatment duration not	Not reported	(in 2004 £); No individual cost reported	Primary prevention Men: £20,000-

First author, year	Model type/ modelled population	Time horizon and cycle length	Health states	Patient demographics (average age, comorbidities)	Intervention and comparators (treatment and treatment duration)	QALYs (intervention, comparator)	Costs (year, currency) (individual intervention, comparator costs)	ICER (per QALY gained)
	Prevention: primary	Cycle length: 1 year	other causes, post-MI, post-SA, post-UA, post-TIA, post-stroke	other CV events from CHD	reported Comparators: No treatment; treatment duration not reported			27,000 Women: £21,000-57,000 Secondary prevention £10,000-17,000 (little difference between men and women)
ACS, acute coronary syndrome; ATO, atorvastatin; CHD, coronary heart disease; CV, cardiovascular; EZE, ezetimibe; FLU, fluvastatin; ICER, incremental cost-effectiveness ratio; LDL, low-density lipoprotein; LYG, life-years gained; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; PAD, peripheral arterial disease; PRA, pravastatin; QALY, quality-adjusted life year; ROS, rosuvastatin; SA, sensitivity analysis; SIM, simvastatin; TA, technology assessment; TIA, transient ischaemic attack								

One of the publications presented in Table 5-2 is NICE CG181. The economic evaluation was based on a Markov model with a lifetime time horizon and 1-year cycle length from a UK NHS perspective. The model was used to investigate the effect of low-, medium-, and high-intensity statin therapy on the occurrence of CV events in adults without CVD, with diabetes and without CVD, and with existing CVD in England and Wales. The model inputs used are extracted from the SLR.

Quality assessment

Quality assessments for the extracted studies were conducted using the Drummond and Jefferson instrument (1996).¹⁴³ The Drummond and Jefferson instrument comprises 36 items that assess the comprehensiveness of cost-effectiveness studies. An example quality assessment form and the completed quality assessment forms are presented in Appendix IX. Of the 108 studies extracted, 19 (17.6%) were deemed to be of low quality (scored < 75%), 63 (58.3%) to be of average quality (scored 75-89%), and 26 (24.1%) to be of high quality (scored ≥ 90%). Studies were not selected or excluded from the review based on quality assessment.

5.2 De novo analysis

Patient population

The overall patient populations included in the economic evaluation reflect both the anticipated indication for evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia and the patient populations evaluated in the relevant phase 3 studies.

In the context of existing NICE CG and TA guidance for the management of hypercholesterolaemia with lipid-lowering therapies, the economic evaluation considered evolocumab in combination with a statin and/or other lipid-lowering therapies in the following specific patient populations according to severity of hypercholesterolaemia (as outlined in the decision problem):

- presence or risk of CVD
- patients with HeFH
- patients with statin intolerance or for whom a statin is contraindicated.

For the assessment of patients with presence or risk of CVD, the patient population from LAPLACE-2 was used on the basis of baseline characteristics for CVD history in patients with primary hypercholesterolaemia and mixed dyslipidaemia. For patients without existing CVD, analyses were conducted on the basis of baseline LDL-C (severity of hypercholesterolaemia) to establish the 10-year CVD risks (measured using a risk assessment tool such as QRISK2) at which treatment with evolocumab in accordance with its MA would be deemed a cost-effective use of NHS resources.

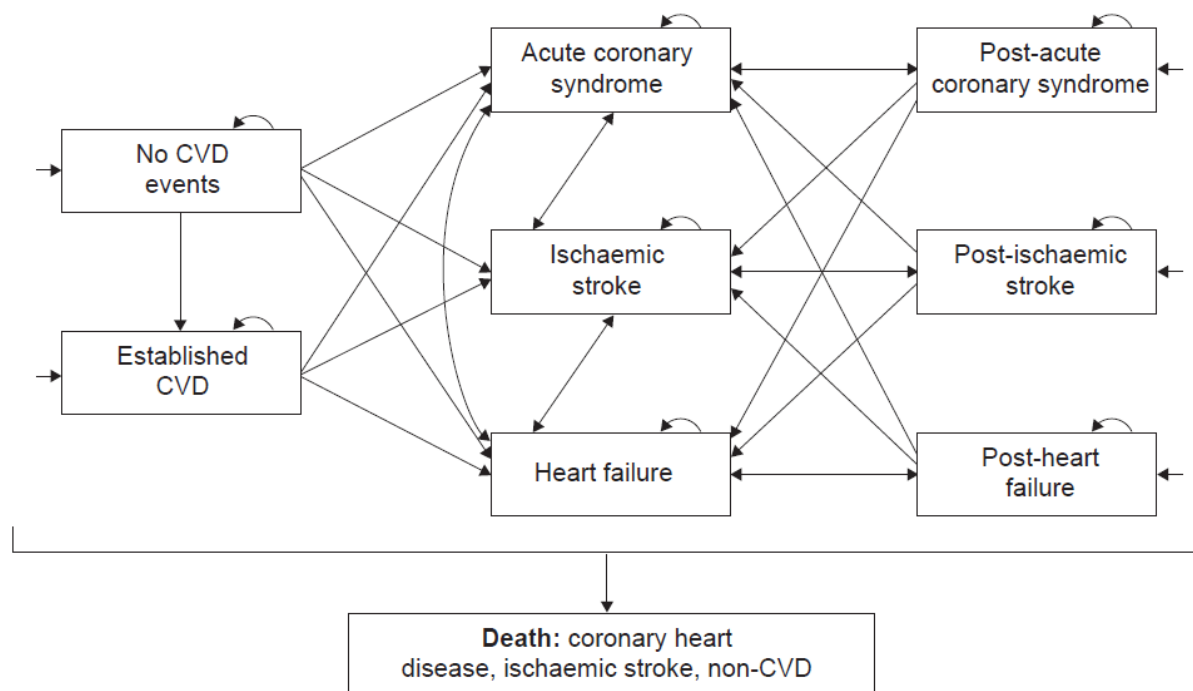
For the assessment of patients with HeFH, the patient population from RUTHERFORD-2 has been used since it specifically enrolled patients with HeFH (Simon Broome criteria) who did not achieve adequate LDL-C control (i.e. LDL-C ≥ 2.6 mmol/L).

GAUSS-2 enrolled patients with primary hypercholesterolaemia and mixed dyslipidaemia unable to tolerate any statins or a statin dose high enough to control their LDL-C levels. However, for the purposes of the economic evaluation, the patient populations from LAPLACE-2 and RUTHERFORD-2 were used since statin intolerance or contraindication is considered a subgroup of the primary hypercholesterolaemia and mixed dyslipidaemia, and HeFH populations. Furthermore, there is no RCT assessing evolocumab in a HeFH population with statin intolerance. LAPLACE-2 and RUTHERFORD-2 were used instead of GAUSS-2, since patients that are intolerant or contraindicated to statins are anticipated to have a greater severity of hypercholesterolaemia as they cannot achieve adequate LDL-C control with lipid-lowering therapies (e.g. low dose statin or alternative lipid-lowering therapy). Baseline LDL-C levels were 2.7 mmol/L to 2.9 mmol/L, 3.9 mmol/L to 4.2 mmol/L, and 5.0 mmol/L to 5.1 mmol/L in LAPLACE-2, RUTHERFORD-2 and GAUSS-2, respectively. Therefore, the LAPLACE-2 and RUTHERFORD-2 patient populations were used with additional cost-effectiveness analyses based on severity of hypercholesterolaemia (baseline LDL-C) to represent populations that are intolerant or contraindicated to statins.

Model structure

A *de novo* cost-effectiveness Markov model was developed for the economic evaluation of evolocumab in accordance with its MA. The model was developed to capture the lifetime progression of CVD among adults with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. A Markov modelling approach was chosen because it adequately captures the scope of the disease and clinical practice of CVD. Furthermore, this approach is commonly applied in other published economic evaluation studies evaluating the cost-effectiveness of drugs for LDL-C reduction in hypercholesterolaemia.^{62,77,134,140,142,144-148} Figure 5-2 illustrates the core model structure with possible transitions indicated by arrows between the model health states.

Figure 5-2 Economic model structure



CVD, cardiovascular disease

Health states

The following key health states are included in the model:

- no CVD
- established CVD
- ACS (including MI or unstable angina)
- IS
- HF
- post-ACS
- post-IS
- post-HF
- CVD death (including CHD and stroke death)
- non-CVD death.

In each health state, a single severity of disease is assumed. Therefore, the model aims to represent the risk, cost, and utility of future events of a typical ‘average’ patient who has experienced a particular CV event. We acknowledge that there is a broad spectrum of severity for each CV event, which can lead to a range of costs, utilities and risk of future events. This is partly addressed by including both acute and chronic states in the model.

No CVD

Patients without existing CVD enter the model in the ‘No CVD’ health state (presented on the left side of Figure 5-2). Patients remain in the ‘No CVD’ health state until they experience a CV event and transition to one of the relevant CVD health states (‘established CVD’, ‘ACS’, ‘IS’ or ‘HF’). Moreover, patients can only transition from ‘No CVD’ to CVD health states, but not the other way around. The rationale being that once a patient has experienced a CV

event (e.g. IS) and has moved to a post-CVD health state (e.g. 'post-IS'), this patient cannot return to a less severe health state ('No CVD') as if the CV event with greater severity had never occurred. This health state is relevant when modelling patients without CVD or for a mixed population including patients with and without existing CVD (e.g. HeFH).

Established CVD (ECVD):

The 'established cardiovascular disease' ('ECVD') health state (presented on the left side of Figure 5-2) is used to model patients that have a history of any of the following CV events:

- stable angina
- TIA
- carotid stenosis
- revascularisation without history of MI (PCI or CABG)
- abdominal aortic aneurism
- peripheral vascular disease.

The 'ECVD' health state was developed to consolidate these specific CV events for simplification of the model since they typically represent a lower baseline CV risk, management cost and higher utility than more severe CV events such as ACS, IS or HF. Following the same principle as 'No CVD', patients that experience ACS, IS or HF cannot transition back to the 'ECVD' health state since this represents a less severe health state.

ACS, IS and HF: As described above, patients with a history of ACS, IS, or HF are excluded from the 'ECVD' health state. For these CVD conditions, two health states are used in the model: an acute event health state (e.g. 'ACS'), and a post-event health state (e.g. 'post-ACS'). Patients remain within the acute health state for a single cycle unless they experience the same acute event again whilst in the acute health state. In the cycle following either 'ACS', 'IS', or 'HF', patients automatically transition to the relevant post-event health state or to another acute health state if a further CV event occurs. Post-event health states are chronic health states in which patients remain until they experience a new acute non-fatal CV event or a fatal (CV or non-CV) event.

At the point of entering the model, patients with a CVD history of one of the explicitly modelled CV events ('ACS', 'IS', and 'HF') start in the corresponding long-term health state ('post-ACS', 'post-IS', or 'post-HF'). The model has flexibility to also allow patients to start in any of the acute health states for scenario analyses.

The rationale for disaggregating CV health states into acute and chronic health states is based on three main elements:

- Risk: CVD risk is higher in the short term following an event than in the long term.²⁶
- Costs: Acute CVD costs are greater than the long-term management costs.^{133-135,140,142,149}
- Utility: Utility is lower in the short term following a CVD event than in the long term.¹⁵⁰⁻¹⁵²

This approach of disaggregating CV health states is consistent with other published economic evaluations in CVD.^{133-135,140,142,149,153}

Combined CVD states: In addition to the health states summarised above, the model contains 13 combined CVD states which can include acute and post-CVD health state (not shown in Figure 5-2 for simplicity).

Combined post-CVD health states can contain up to three single health states, as outlined below:

- combined IS and ACS state:
 - 'IS and post-ACS' – experiencing an IS event while having experienced an ACS more than 1 year previously
 - 'ACS and post-IS' – experiencing an ACS event while having experienced an IS more than 1 year previously
 - 'post-IS and post-ACS' – having experienced an IS and an ACS event more than 1 year previously
- combined HF and ACS state:
 - 'HF and post-ACS'; 'ACS and post-HF'; 'post-HF and post-ACS'
- combined HF and IS state:
 - 'HF and post-IS'; 'IS and post-HF'; 'post-HF and post-IS'
- combined HF, IS, and ACS state:
 - 'HF, post-IS and post-ACS'; 'ACS, post-HF and post-IS'; 'IS, post-HF and post-ACS'; 'post-HF, post-IS, and post-ACS'.

The purpose of these additional combined health states is to allow the cohort to experience recurring CV events over the time horizon allowing appropriate costs and benefits (utilities) for the experienced CV events to be applied in the model. In this way, combined health states prevent losing track of the crucial CV event history of patients and partially attenuate the memory-less attribute of Markov models. These combined health states are a direct means of associating CVD history for risk, costs and utilities. Previous economic evaluations have indirectly considered subsequent CV events, for example, reduced benefits based on further utility decrements associated with a 2nd or 3rd CV event.¹¹⁸

In modelling the transition probabilities, costs, and utilities of the combined health states, the following principles are used.

- Risk: The transition probability from a combined health state to a new event is defined by the highest probability of the individual health state transitions to that new event. For instance, for a patient with a history of ACS and IS (i.e. 'post-ACS and post-IS'), the probability of a new ACS event would be the maximum probability from either 'post-ACS' to 'ACS' or 'post-IS' to 'ACS'.
- Costs: The cost for a combined health state is defined by the highest of the costs of the individual contributing health states (note that the cost used for combined health states is not the sum of the individual health states as summing individual inpatient episodes in this way may overestimate or double count the total CV event cost).
- Utility: The utility of a combined health state is defined by the lowest utility of the individual contributing health states, as the health state with the worst experienced utility will define the overall experienced quality of life (a combined health state is not expected to be cumulatively more or less severe than the individual included health states).

As an example description of utility calculation for a combined health state, the utility of a post-acute HF event (0.683) is lower than the utility of a post-acute ACS event (0.880). Hence, a patient having had a HF event, and later experiencing an ACS event, would encounter an improved health state utility following the ACS event as compared with staying in the HF health state if only the last experienced event would determine the long-term utility. By creating combined health states and selecting the combined health state utility to be

defined by the lowest of the individual contributing health state utilities, the model accounts for disease severity due to event recurrence. In this case, the utility of the combined health state (post-HF and post-ACS) is set to the lower post-HF utility (0.683 versus 0.880 for post-ACS), ensuring the worst health state utility is maintained. Note that this approach allows the acute impact of an event to affect the short-term utility (assuming that the acute event always has a lower utility than any long-term utilities) while another event may not necessarily have an impact on the long-term utility.

Revascularisation procedures: In addition to the health states described above, the model considers revascularisation procedures. Revascularisation is not included as a stand-alone health state. Only the costs of revascularisation procedures are included based on a proportion of patients requiring revascularisation procedures in the 'ACS' and 'post-ACS' health states.

CVD death and non-CVD death: Patients can die without experiencing a CV event (non-CVD death) or die as a result of an acute CV event ('CVD death'). A CVD death can be specifically defined as either 'CHD death' or 'stroke death'.

Mortality from non-CVD causes is taken from England and Wales life tables published by the Office for National Statistics based on 2010-2012 mortality data. Mortality rates were used to establish population mortality for men and women for ages 40 to 100 years.^{154,155} The Office for National Statistics-based mortality data were used to calculate the proportion of deaths for each 5-year age group that were CV or non-CV related. These proportions were applied to the mortality rate to estimate the risk of death due to non-CV causes for age and both men and women. This approach for life expectancy and mortality is consistent with NICE CG181.⁷⁷

The death states absorb the health states; once in one of these states, patients remain there until the end of the model and do not accrue costs or benefits.

Further model characteristics

As observed in other published economic evaluation studies identified in the SLR,^{62,77,133,140,142,144,146,148,156-159} a lifetime horizon (to a maximum age of 100 years) was used. This time horizon was chosen to reflect the disease pathway and account for the fact that CVD risk and outcomes are relevant for the duration of a patient's life. CV events can re-occur during a patient's life and, during each acute and long-term CV event, different levels of costs and utilities are applied. The model was programmed with a 1-year cycle length which is consistent with other published economic evaluation studies in CVD.^{77,133-135,137,145,146,160-162}

Owing to the long time horizon and the use of distinct, mutually exclusive, and re-occurring health states, a Markov model is the most suitable and efficient option for an economic evaluation of evolocumab in patients at high risk of CVD. A Markov model enables the combination of data from different sources and extrapolation of outcomes beyond the observed period(s) provided in these sources with the aim of assessing the costs and benefits associated with evolocumab treatment. More details on the costs and utilities applied in the model can be found in Sections 5.4 and 5.5.

Table 5-3 outlines the key model characteristics for the Markov model structure used. The model perspective is that of the National Health Service and Personal Social Services, all costs and effects are discounted by 3.5% annually, and half-cycle correction has been applied.

Table 5-3 Features of the *de novo* analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (to a maximum age of 100 years)	Patients diagnosed with LDL-C hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia will be treated for the rest of their lives. Moreover, the lifetime horizon accounts for the fact that CVD risk and outcomes are relevant for the duration of a patient's life
Were health effects measured in QALYs; if not, what was used?	Health effects are measured in QALYs. Life years have also been assessed	NICE reference case 2013 ¹⁶³
Discount of 3.5% for utilities and costs	3.5% applied for both costs and health effects	NICE reference case 2013 ¹⁶³
Cycle length	1-year cycle length	Usual practice in published economic evaluations of LDL-C hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia (e.g. NICE CG181). ⁷⁷ Provides best balance of efficiency and accuracy in terms of capturing clinical pathway
Half-cycle correction	Half-cycle correction has been applied	NICE reference case 2013 ¹⁶³
Perspective (NHS/PSS)	NHS and PSS	NICE reference case 2013 ¹⁶³
CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALY, quality-adjusted life year		

Intervention technology and comparators

Evolocumab (Section 2) and ezetimibe (Table 5-4) have been implemented in the model in accordance with their MAs for the management of hypercholesterolaemia and consistent with the decision problem with regards intervention and comparators. Statins which represent background lipid-lowering therapy for evolocumab and ezetimibe have also been incorporated in accordance with their MAs. The indication for atorvastatin, the statin recommended in NICE CG181 for primary and secondary prevention, is summarised in Table 5-4.

Table 5-4 Marketing authorisation of ezetimibe and atorvastatin

Medicine	Indication
Ezetimibe	<u>Primary Hypercholesterolaemia</u> Ezetimibe, co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone. Ezetimibe monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.
Atorvastatin (statin)	<u>Hypercholesterolaemia</u> Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, low-density lipoprotein-cholesterol, apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate. <u>Prevention of cardiovascular disease</u> Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors
HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA	

Therefore, the cost-effectiveness of evolocumab was assessed in the following scenarios for the populations defined within the decision problem. These four scenarios in the treatment pathway are presented in Figure 5-3.

Scenario 1: in combination with statin

- Addition of evolocumab to current high-intensity statin versus addition of ezetimibe to current high-intensity statin.

Scenario 2: monotherapy

- Evolocumab alone versus ezetimibe alone in patients who are either statin-intolerant or contraindicated to statins.

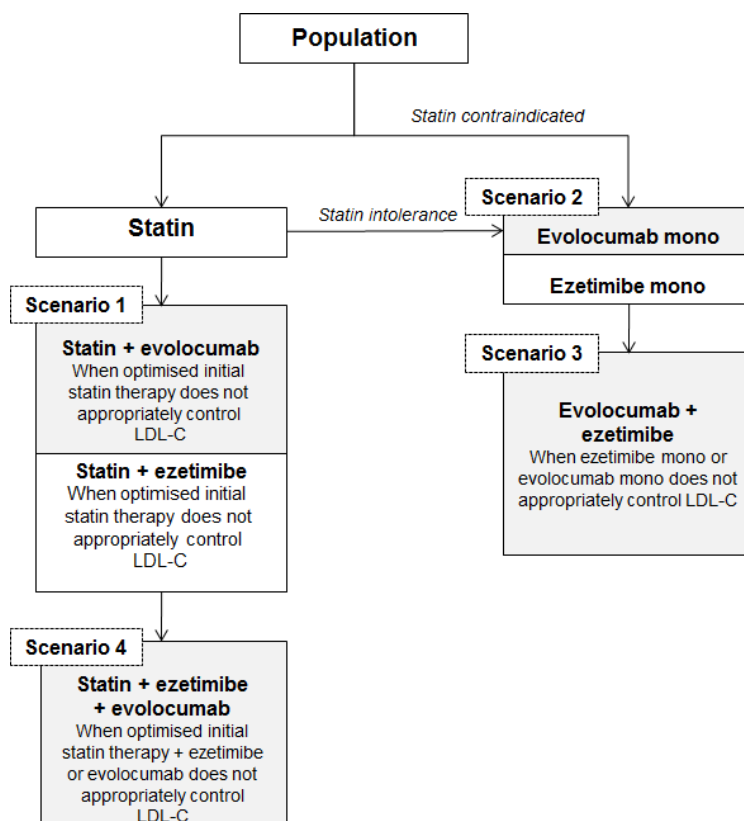
Scenario 3: in combination with ezetimibe

- Addition of evolocumab to ezetimibe versus ezetimibe alone in patients who are either statin-intolerant or contraindicated to statins.

Scenario 4: in combination with statin and ezetimibe

- Addition of evolocumab to current high-intensity statin and ezetimibe versus current high-intensity statin and ezetimibe.

Figure 5-3 Treatment pathway and modelled treatment scenarios



LDL-C, low-density lipoprotein cholesterol; mono, monotherapy

Scenarios 1 and 2 represent the introduction of evolocumab as another option in the pathway alongside ezetimibe, whilst scenarios 3 and 4 represent the introduction of evolocumab as combination therapy with ezetimibe with or without background lipid-lowering therapy. The statin intolerant or contraindicated subgroup was addressed with scenarios 2 and 3 (evolocumab monotherapy or in combination with ezetimibe).

5.3 Clinical parameters and variables

Estimation of population CV event rates

The transition probabilities were calculated based on the following step-wise sequence described in the overview below and in Figure 5-4. Detailed information relating to each of these steps (e.g. CV risk equations) is described in this section.

Step 1: Estimation of population CV event rates

- Patient-level data used to predict individual patient CV event rates from risk equations (10 years for D'Agostino 2008¹⁵⁷ and 20 months for Wilson 2012²⁶).
- Cohort CV event rates estimated by averaging patient level CV event rates.
- Annualised cohort CV event rates estimated ensuring the sum of the annual rates (10 years for D'Agostino 2008¹⁵⁷ and 20 months for Wilson 2012²⁶) is equivalent to the rates predicted from the risk equations.¹⁶⁴

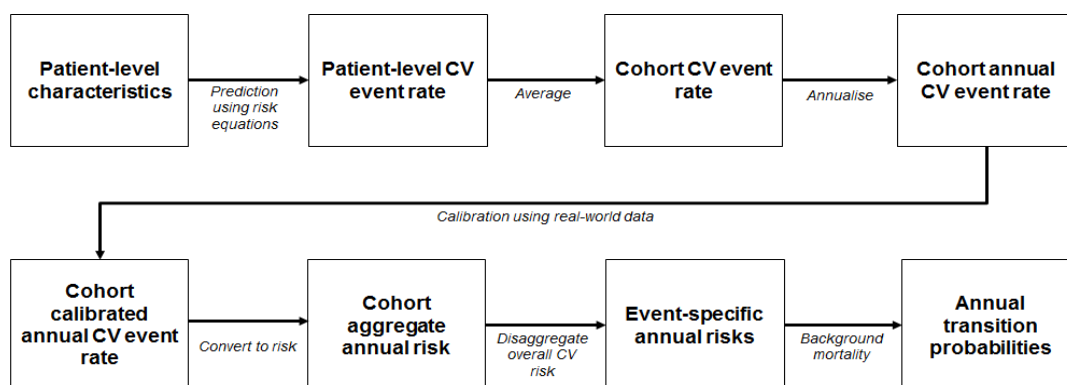
Step 2: Calibration of cohort CV event rates

- Annualised cohort CV event rates calibrated using real-world data.
- Conversion of annualised rates to aggregated annual CVD risk assuming an exponential survival function.

Step 3: Estimation of event-specific annual risks and transition probabilities

- Disaggregation of annual risk to CV event-specific annual risk using data from the CPRD.
- Computation of annual transition probabilities by age and gender including non-CV background mortality.

Figure 5-4 Step-wise sequence of estimating event-specific transition probabilities from patient-level characteristics



CV, cardiovascular

Population characteristics

Presence or risk of CVD: Baseline patient-level characteristics were retrieved from LAPLACE-2. Patients were stratified on the basis of CVD history in accordance with the decision problem for patients with presence or risk of CVD. For the purposes of the patient-level risk estimation, patients with a LDL-C > 2.5 mmol/L were included to represent a high risk CV population. This was equivalent to 1074 (56.6%) of the 1896 patients enrolled in LAPLACE-2 for which data was complete in order to predict risk from the equations. A summary of the population characteristics are presented in Table 5-5.

HeFH: Baseline patient-level characteristics were used from RUTHERFORD-2. Further details on RUTHERFORD-2 are presented in Section 4. A summary of the population characteristics are presented in Table 5-5.

Table 5-5 Baseline population characteristics

Characteristic	Hypercholesterolaemia (non-familial) and mixed dyslipidaemia		Heterozygous familial hypercholesterolaemia		
	No history of CVD	History of CVD	All	No history of CVD	History of CVD
Number	744	330	329	203	126
Age (mean, years)	58	62	51	49	55
Female	50.0%	33.6%	42.3%	48.8%	32.0%
Smoking	16.4%	12.7%	15.8%	17.2%	13.5%
Diabetes mellitus	10.0%	18.5%	7.3%	4.9%	11.1%
Hypertensive therapy	45.8%	77.3%	32.5%	22.2%	49.2%
Acetylsalicylic acid	14.4%	67.6%	38.6%	23.2%	63.5%
SBP (mg Hg) (mean)	128.8	129.3	125.7	124.8	127.3
BMI < 20 kg/m ²	0.9%	2.1%	1.8%	1.5%	2.4%
LDL-C (mmol/L) (mean)	3.37	3.59	4.02	4.00	4.06
Total-C (mmol/L) (mean)	5.51	5.69	5.99	5.98	5.99
HDL-C (mmol/L) (mean)	1.44	1.33	1.32	1.37	1.25
Triglycerides (mmol/L) (mean)	1.53	1.70	1.41	1.36	1.50
Existing CVD	No	Yes	38.3%	No	Yes
ECVD	-	46.4%	61.1%	-	61.1%
ACS	-	0.0%	0.0	-	0.0
Post-ACS	-	27.9%	25.4%	-	25.4%
IS	-	0.0%	0.0%	-	0.0%
Post-IS	-	4.8%	2.4%	-	2.4%
HF	-	0.0%	0.0%	-	0.0%
Post-HF	-	8.5%	0.8%	-	0.8%
Post-ACS and post-IS	-	0.9%	4.0%	-	4.0%
Post-ACS and post-HF	-	10.9%	4.8%	-	4.8%
Post-IS and post-HF	-	0.6%	0.0%	-	0.0%
Post-ACS, post-IS and post-HF	-	0.0%	1.6%	-	1.6%
Number of vascular beds ^a	-	1.21	1.21	-	1.21
Atrial fibrillation ^b	11.7%	11.7%	11.7%	11.7%	11.7%
^{a,b} Vascular beds (number) and atrial fibrillation (%) included based on the REACH registry baseline characteristics for recurrent CV events. ²⁵ ACS, acute coronary syndrome; BMI, body mass index; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HDL-C, high-density lipoprotein-cholesterol; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; Total-C, total cholesterol					

Risk equations to estimate baseline CVD risk

A targeted literature review was conducted to identify relevant risk equations for the purposes of estimating baseline CVD risks for primary and recurrent CV events. The risk equation by D'Agostino¹⁵⁷ (2008) based on the Framingham Heart Study was selected for estimating primary CVD events. This was selected due to a broad definition of CVD events and death. CVD was defined as a composite of CHD (coronary death, MI, coronary insufficiency, and angina), cerebrovascular events) including IS, haemorrhagic stroke, and TIA), peripheral arterial disease (intermittent claudication) and HF. NICE CG181 recommends that QRISK2 risk assessment tool is used to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years.⁷⁷ In contrast with the D'Agostino (2008) risk equation, QRISK2 assesses risk of a narrower definition of CVD events (CHD i.e. angina or MI, stroke, or TIA). The D'Agostino (2008) risk equation was selected instead of QRISK2 given the preference for fewer variables to estimate baseline CVD risk (14 variables for QRISK2 and seven for Framingham). Furthermore, the predicted CVD event rates would be calibrated regardless of selected risk equation based on real-world CV event rates for patients without existing CVD.

For recurrent CVD, the recent REACH registry²⁶ risk prediction model was selected since it was the only recurrent CVD model that predicted aggregated CVD risks of recurrent non-fatal and fatal CV events. Other risk prediction models based on the Framingham Heart Study included either recurring CHD events alone, stroke events alone or HF events alone. For the presence or risk of CVD and HeFH populations, the baseline CVD risk is based on the CVD risk associated with background lipid-lower therapy treatment. Table 5-6 and Table 5-7 present the risk factors and included CV events in the primary and recurrent event risk predictions included in the model from Framingham and REACH Registry. As for primary CV events, the predicted CVD rates for recurrent CV events would be calibrated based on real-world CV event rates for patients with existing CVD.

Table 5-6 Risk predictions – primary and recurrent CV events, included risk factors, and CV events

Risk model	Framingham D'Agostino, 2008	REACH registry, Wilson et al, 2012
Statistical survival modelling approach	Cox proportional hazards	Cox proportional hazards
CVD risk prediction	Primary CV events, fatal and non-fatal	Secondary CV events, fatal and non-fatal
Included risk factors	•Age (years) •Gender (male/female) •Hypertension (treated, y/n) •SBP (mmHg) •Smoking (y/n) •Diabetes mellitus (y/n) •Total cholesterol •HDL-C	•Age (years) •Gender (male/female) •Smoking (y/n) •Diabetes mellitus (y/n) •BMI < 20 kg/m² •Number of vascular beds (1, 2, 3) •Cardiovascular event in previous year (y/n) •Congestive heart failure (y/n) •Atrial fibrillation (y/n) •Statins (y/n) •Acetylsalicylic acid (y/n) •Eastern Europe or Middle East (y/n) •Japan or Australia (y/n)
Included CV events	All CVD primary CV events, including CHD, cerebrovascular disease and PAD, and HF ^a	All recurrent CV events (MI, stroke and CV hospitalisation) and CVD-related death (fatal stroke, fatal MI or other CV death)

^aCHD, coronary death; myocardial infarction; coronary insufficiency; angina; cerebrovascular, cerebrovascular death; ischaemic stroke; haemorrhagic stroke; transient ischaemic attack; peripheral artery disease; intermittent claudication; heart failure.

BMI, body mass index; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease; REACH, REduction of Atherothrombosis for Continued Health; SBP, systolic blood pressure; y/n, yes/no

Table 5-7 Risk predictions – overview of risk prediction parameters

Study	Framingham (D'Agostino 2008 ¹⁶⁵)		REACH Registry (Wilson 2012 ²⁶)	
Events predicted	CVD		CVD	
Primary or recurrent events	Primary		Recurrent	
Type of CV event (non-fatal or fatal)	Both		Fatal	Non-fatal
Gender	Male	Female	Both	
β *mean(x)	23.9802	26.1931	4.03317	2.68845
Baseline risk	0.88936	0.95012	0.97749	0.93681
Male	-	-	0.24519	0.10246
Age	3.06117	2.32888	0.04966	0.03089
Systolic blood pressure if not hypertensive therapy	1.93303	2.76157	-	-
Systolic blood pressure if hypertensive therapy	1.99881	2.82263	-	-
Total cholesterol	1.1237	1.20904	-	-
HDL-C	-0.93263	-0.70833	-	-
Diabetes mellitus	0.57367	0.69154	0.46141	0.37824
Event in previous year	-	-	0.26681	0.38168
Heart failure in previous year	-	-	0.89976	0.51873
Atrial fibrillation	-	-	0.42705	0.26652
Vascular beds	-	-	0.24928	0.30277
BMI < 20 kg/m ²	-	-	0.55132	0.31428
Smoking	0.65451	0.52873	0.30925	0.24121
Statins	-	-	-0.22296	-0.28332
Acetylsalicylic acid	-	-	-0.17968	-0.10151
Eastern Europe or Middle East	-	-	0.25934	0.27574
Japan or Australia	-	-	-0.65524	-0.31604
BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; REACH, REduction of Atherothrombosis for Continued Health				

Risk predictions for supplementary risk factors

In addition to the CV risk factors identified in REACH, the following risk factors were also identified based on ESC/EAS guidelines for the management of dyslipidaemias and clinical opinion (see Table 3-5):

- patients with moderate to severe CKD (eGFR < 60 mL/min/1.73 m²)
- two or more documented acute ischaemic CV events or revascularisation procedures
- Elevated plasma Lp(a) ≥ 77 mg/dL (≥ 90% centile).

In the absence of estimates for the risk of fatal or non-fatal CV events associated with these factors, it has been assumed that they are equivalent to diabetes mellitus. For example, expert clinical opinion indicated that patients with progressive CVD had a risk of recurrent events equivalent to or greater than the risk of CV events associated with presence of diabetes mellitus. This assumption was deemed clinically plausible for patients with moderate to severe CKD and elevated Lp(a).

Baseline CV rate calibration according to UK observational data

Previous economic models evaluating the impact of treatments in secondary prevention have utilised real-world data for CV risk estimates.¹⁶⁶ The transition probabilities used in NICE CG181 between primary and secondary CV health states after the first event has taken place have been based on estimates identified in systematic reviews by Ward, et al.¹⁶⁷ supplemented by sources identified for the National Collaborating Centre for Primary Care (NCCPC) model (2008)¹⁶⁸. The primary sources used in NICE CG181 are the Nottingham Heart Attack Register,¹⁶⁹ the South London Stroke Register,¹⁷⁰ Juul-Möller et al. (1992),¹⁷¹ Caro et al. (2005),¹⁷² the SOLVD study,¹⁷³ and the CURE study.¹⁷⁴ A critical appraisal of these source publications was conducted (Appendix X) and identified that these studies were generally of good to high methodological quality. However, some significant limitations were identified in most of these sources. Specifically, the primary sources were based on analyses conducted during the period 1980-1990s. As such, a primary aim was to derive relevant appropriate data to support baseline CV rate estimation that would be applicable in the current clinical setting and high risk populations with respect to the decision problem. Therefore a study was undertaken in the CPRD to estimate CV rates.

The primary objectives of the CPRD study were:

- To estimate CV event rates in cohorts of patients with different CV risk profiles receiving high-intensity statin therapy in UK clinical practice.
- To estimate a cohort-specific calibration factor to facilitate conversion between the observed CV event rates and those predicted using Framingham and REACH risk equations.

A summary of the methodology used to estimate the real-world CV risk estimates is provided below. Full study details for the estimation and calibration of CV event rates are available in Appendix XI.

A retrospective observational cohort study was conducted to estimate CV event rates in multiple cohorts using integrated primary and secondary care data. Data were obtained from

the CPRD (primary care), HES (secondary care), and the Office of National Statistics (cause of death). The study population consisted of patients who were alive and observable in both CPRD and HES data as of 1 January 2005. At least 2 years of data prior to the index date, during which patients must have received at least one high intensity statin prescription, was required for each patient to be included in the study.

Five cohorts definitions were included; without existing CVD (i.e. primary prevention) (diabetes) and four cohorts of patients with existing CVD (ECVD, ACS, IS and HF) for analysis, and an index date for each individual was defined. ECVD cohort excluded patients with ACS, IS or HF in accordance with the model structure (as of 1 January 2005). For the primary prevention cohorts the index date was 1 January 2005. For the existing CVD cohorts, the index date was set as the date of the CV event that qualified that patient as a secondary prevention patient. Patients were followed from their index date until a subsequent event, death, or end of follow-up. Follow-up was continued until 31 December 2011. CV events were defined as hospitalisations with a primary diagnosis code for MI, IS, HF, or unstable angina (UA). All hospitalisations were identified using ICD-10-CM codes. Crude CV event rates were calculated by dividing event counts by person-years of follow-up. Patients were stratified by age group, diabetes (except diabetes cohort), and follow-up period (secondary prevention cohorts only). Figure 5-5 provides an example for the ACS cohort crude composite CV event rate indicating the higher CV event rate observed during the first year (acute period) compared with the subsequent long term period.

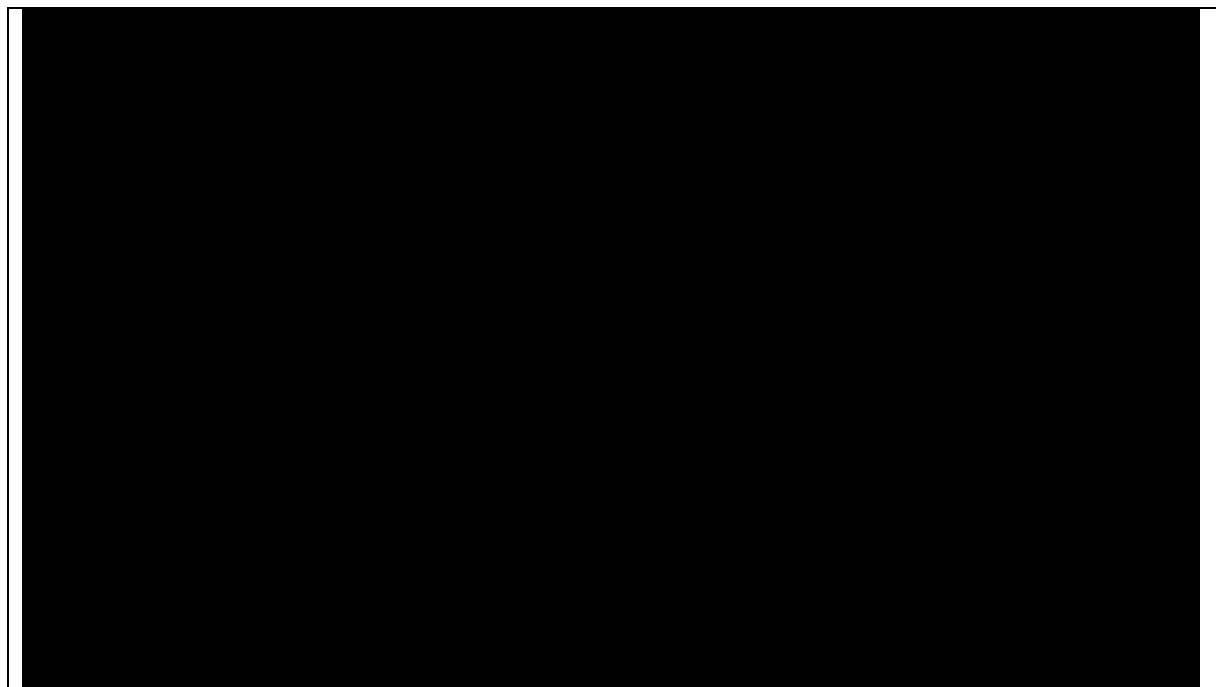
Figure 5-5 ACS – crude composite event rate over time



CV event distributions were predicted using multinomial regression for outcomes of ACS, IS, HF, CV death (IS death and CHD death) in each cohort. The events were also stratified by the time period of follow up (acute versus long-term). For patients without CVD, ECVD was also included as an outcome event. For each cohort and period, the type of outcome was

predicted as a function of age (continuous). Figure 5-6 provides an example for the ACS long-term period and the outcomes distribution with increasing age.

Figure 5-6 ACS long-term period – multinomial model event distribution results by age



ACS, acute coronary syndrome; CV, cardiovascular; HF, heart failure; IS, ischaemic stroke

Calibration was undertaken to estimate the ratio of the observed CV rates to the predicted CV event rates based on Framingham (D'Agostino 2008)¹⁵⁷ and REACH registry²⁶ risk equations for the cohorts. Firstly, predicted probabilities from Framingham (diabetes cohort) and REACH registry (ECVD, ACS, IS and HF cohorts) were calculated at the individual patient-level using their respective published formulas.^{26,165} These probabilities were converted to rates. For each cohort, Poisson regression was used to estimate a rate ratio between the actual event rates seen and the predicted rates at the individual patient-level. The mean rate ratio estimates are used as calibration factors. The calibration factors and their respective 95% CIs, are provided in Table 5-8.

Table 5-8 Calibration estimates applied to Framingham and REACH registry predictions, based on CPRD analysis

Risk estimation tool	CV health state	Fatal or non-fatal CV event	Mean Calibration Factor	Lower bound (95% CI)	Upper bound (95% CI)
Primary CV event (Framingham)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Secondary CV event (REACH Registry)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ACS, acute coronary syndrome; CI, confidence interval; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; REACH, REduction of Atherothrombosis for Continued Health					

With regards to the primary prevention cohort, the Framingham risk equations, on average, slightly over-estimated the CV event risk (calibration factor is 0.92). Authors have suggested that Framingham over-estimates CV event risk,¹⁷⁵ providing additional evidence that the difference between the observed and predicted rates is not unexpected. Of note, the Framingham population mean age was 49, while the CPRD cohort mean age was 63. Therefore, since Framingham includes information from a smaller, younger, US-based diabetic subgroup compared with a larger, older, UK cohort, one would not expect its predictions to be perfectly aligned.

The secondary prevention cohorts appear to have much higher risk for non-fatal and fatal CV events in both the acute and post-acute phases than the REACH registry risk equation predictions (calibration factor is greater than 1). This is likely due to a number of factors, including the selection of patients in CPRD receiving high-intensity statins, which could be indicative of a higher risk group. Perhaps most importantly, the REACH registry did not enrol patients immediately following a CV event. In fact, only about 32% of the cohort had their qualifying CV event within the year prior to enrolment in the registry. There is no information in the registry to describe the time from the qualifying event to enrolment, so it is not possible to fully compare the different selection factors involved in REACH with the CPRD study. However, it is evident from the CPRD study that the first 6 months after an acute event are

critical for capturing further CV events. To the extent that REACH does not include this information, the predicted event rates will underestimate events observed in clinical practice. As an example, for ACS, there is almost a 5-fold decline in the composite CV event rate from 30 days after the index event through the end of the first year. Therefore, because REACH does not systematically include the full risk period, the fact that the calibration factors are so high is not unexpected.

It should also be noted that the REACH study included a broader range of prior events in its inclusion criteria compared with our study using the CPRD data. This is important because each of the secondary prevention cohorts in our study was selected based on very specific inclusion criteria. Although REACH included adjustment factors for HF and the number of vascular beds, this may not be sufficient to estimate the risk accurately for each of the ECVD, ACS, IS and HF cohorts. Therefore, it is reasonable to see variations between the observed and predicted rates. Similar CV event rates to those observed in the CPRD study have been seen in Briffa et al 2011, Chun 2012, and Ezekowitz et al. 2009.¹⁷⁶⁻¹⁷⁸ In Briffa et al. 2011, > 40% of major CHD events were estimated to occur annually in the secondary prevention setting.¹⁷⁶ In Chun 2012, 10-year mortality was 98.8%, with 35,966 hospital readmissions occurring over the lifetime of the cohort.¹⁷⁷

Baseline CV rate calibration for the HeFH population

Patients with FH have a higher baseline CV risk than patients without FH, due to prolonged exposure to elevated LDL-C resulting in early atherosclerotic plaque formation with the subsequent risk of CV events. In the absence of a specific CV risk equation for FH patients, a literature search was undertaken with the objective of quantifying the CV risk in this population (full details are available in Appendix XII).¹⁶⁶

A literature search was undertaken for the period 2004 to 2014 in FH registries, PubMed, and reference citations. All titles and abstracts were screened by two reviewers. FH registries yielded 247 potential publications and the PubMed search yielded 549 potential papers. Fourteen papers met the inclusion criteria and were formally reviewed for evidence of bias after which cardiovascular risk rates were extracted: seven papers were from registries in the UK, Netherlands, Norway, and Spain; three papers were from single hospitals or clinics (Japan, Netherlands, and UK); three publications described the experience of single families; and one publication was from a population survey in Denmark.¹⁶⁶

Quality evaluation showed differences in study outcome and CV event risk. Bias assessment by the Newcastle-Ottawa criteria¹⁷⁹ was used to assess the risk of bias associated with each paper. The study from Benn et al, 2012,¹⁷ showed the least risk of bias by including a direct comparison of FH and non-FH populations in the same study, and collecting both fatal and non-fatal CV events.

An increase in odds for coronary artery disease was reported at 10.3 (95% CI 7.8, 13.8) and 13.2 (95% CI 10.0, 17.4) in patients treated and not treated with lipid-lowering therapy, respectively (relative to non-FH patients not receiving lipid-lowering therapy).¹⁷ The FH rate ratio of 7.1 (95% CI 5.7, 8.7) was calculated by pooling statin and no statin groups to represent real-world treatment practice, accounting for the mix of primary and secondary

prevention patients as well as different treatment paradigms. Therefore, the baseline rate predicted by Framingham and REACH registry is multiplied by a rate ratio of 7.1. The rate ratio was validated through estimation of a 10-year risk of CV events for the RUTHERFORD-2 patient population.

Baseline CV risk for population

The estimated 10-year CV risk for the different patient populations (Table 5-5) on the basis of the risk equations and subsequent CV rate calibration are described in Table 5-9. For example, these indicate a 10-year risk of at least one fatal or non-fatal CV event of 45.5% and 60.5% for patients with existing CVD and HeFH, respectively.

Table 5-9 Baseline CV risk for population

	Hypercholesterolaemia (non-familial) and mixed dyslipidaemia		Heterozygous familial hypercholesterolaemia		
	No history of CVD	History of CVD	All	No history of CVD	History of CVD
Absolute 10-year CV risk ^a	10.3%	46.2%	60.6%	42.9%	76.0%
LDL-C (mmol/L) (mean)	3.37	3.59	4.02	4.00	4.06
^a Estimated 10-year risk of one or more fatal or non-fatal CV events.					
CV, cardiovascular; CVD, cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol					

Applying effects of treatment to the baseline (background treatment) risk

The economic evaluation aims to assess the cost-effectiveness of evolocumab for the prevention of non-fatal and fatal CV events. The CV outcomes study, FOURIER, is currently ongoing to assess the efficacy of evolocumab. In the interim, the phase 3 RCTs provide estimates of LDL-C reduction from baseline, and this surrogate endpoint can be translated to CV events based on the established relationship between LDL-C and CV events.

As such, treatment effectiveness is determined by:

- Treatment effect: Assessing the LDL-C-lowering treatment effect of evolocumab and ezetimibe.
- Translating these LDL-C lowering treatment effects into different rates of CV event rates versus baseline CVD risk.
- Translating CV event rates into risk (transition probabilities) of experiencing various types of CV events.

Treatment effect (LDL-C reduction)

Treatment effects have been taken directly from the head-to-head comparator studies of evolocumab versus ezetimibe (specifically, LAPLACE-2 and GAUSS-2) described in Section 4.7. The observed LDL-C reductions in LAPLACE-2 (evolocumab or ezetimibe in addition to background moderate- to high-intensity statins) and GAUSS-2 (evolocumab or ezetimibe monotherapy) are used directly for the economic evaluation. In the absence of

head-to-head data in HeFH for evolocumab plus statin versus ezetimibe plus statin, and evolocumab monotherapy versus ezetimibe monotherapy, the treatment effects from LAPLACE-2 and GAUSS-2 are deemed to be generalisable to the HeFH population since the treatment effect of evolocumab was consistent regardless of patient population and patient characteristics; evolocumab dosing regimen (140 mg Q2W or 420 mg QM); and presence and type of background lipid-lowering therapy. This approach is supported by the economic evaluation of ezetimibe that was utilised in NICE TA132, in which an assumption was made that the treatment effect of ezetimibe in non-HeFH patients was generalisable to patients with HeFH, in the absence of HeFH-specific effectiveness data. In these RCTs of 12 weeks' duration (LAPLACE-2 and GAUSS-2), the co-primary endpoints were the percent change in LDL-C from baseline at the mean of weeks 10/12 and at week 12. For the purposes of the economic evaluation, the percent change from baseline in LDL-C at the mean of 10/12 weeks is used for evolocumab and ezetimibe since it provides a time-averaged efficacy estimate (see Section 4.3 for further details on rationale for focussing on data at the mean of weeks 10/12). Further, data using the calculated approach to LDL-C assessment are utilised in the economic evaluation to best reflect clinical practice and to align with the evolocumab's SmPC (see Section 4.3 for further details on rationale for focussing on calculated LDL-C data). The observed treatment effect from these 12-week studies are applied for the duration of the model given the confirmatory findings from the ongoing long-term extension studies show that LDL-C reduction is maintained for more than two years (Section 4.7). Table 5-10 summarises the LDL-C reduction treatment effects for evolocumab and ezetimibe applied in the model.

Table 5-10 Mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe when used in combination with statins or as monotherapy

	Evolocumab 140 mg Q2W	Evolocumab 420 mg QM	Ezetimibe 10 mg OD^b
Combination with a statin (based on LAPLACE-2)			
Mean percent change from baseline ^a (95% CI) [SE]	-71.77 (-74.69, -68.85) [1.49] <i>Table 4-13</i>	-69.12 (-73.49, -64.76) [2.23] <i>Table 4-13</i>	-26.56 (-30.70, -22.42) [2.11]
Monotherapy (based on GAUSS-2)			
Mean percent change from baseline ^a (95% CI) [SE]	-57.10 (-60.84, -53.36) [1.90] <i>Table 4-16</i>	-55.82 (-58.88, -52.76) [1.55] <i>Table 4-16</i>	-17.83 (-21.01, -14.65) [1.62]
References: LAPLACE-2 CSR ¹⁰¹ Table 14-4.2.13 and LAPLACE-2 supplementary data table 14-4.6.2 ¹¹⁶ ; GAUSS-2 CSR ¹⁰⁵ Tables 10-4 and 14-4.1.3 and GAUSS-2 supplementary data table 14-4.9.1 ¹⁸⁰			
^a Least squares mean from the repeated measures model which includes treatment group, stratification factors (from IVRS), scheduled visit, dose frequency and the interaction of treatment with scheduled visit as covariates.			
^b Based on <i>post hoc</i> pooled analysis of all ezetimibe arms and all placebo arms in LAPLACE-2 and GAUSS-2, respectively.			
CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; OD, once daily; Q2W, every 2 weeks; QM, monthly; SE, standard error			

Comparative differences in treatment efficacy are modelled between evolocumab and the comparator dependent on whether evolocumab is used in addition to background statin (Scenario 1) or monotherapy (Scenario 2), or when used in combination with ezetimibe, with or without background statin therapy (Scenarios 3 and 4). These are schematically represented in Figure 5-7 and described in

Table 5-11. For the purposes of modelling scenarios 3 and 4, sequential LDL-C reductions are observed based on reduction associated with comparator and then subsequent addition of evolocumab since the baseline represent LDL-C on maximally-tolerated statin therapy. Treatment effects used for scenario 1 (LAPLACE-2) and scenario 2 (GAUSS-2) are also applied in the respective scenario 3 and 4. This is a simplification, as opposed to the sequential modelling of additional lipid-lowering therapies. Different baseline LDL-C levels are modelled (2.5 to 6 mmol/L) for the populations to which the treatment effect for evolocumab and the comparator is applied to estimate the absolute LDL-C reductions. The base case model assumptions are that the patient populations receive treatment continuously over the lifetime, and that treatment has equal efficacy throughout this period in both the intervention and comparator arms.

Figure 5-7 Modelled LDL-C reductions based on evolocumab used in addition to background statin, monotherapy or addition to ezetimibe with or without background statin

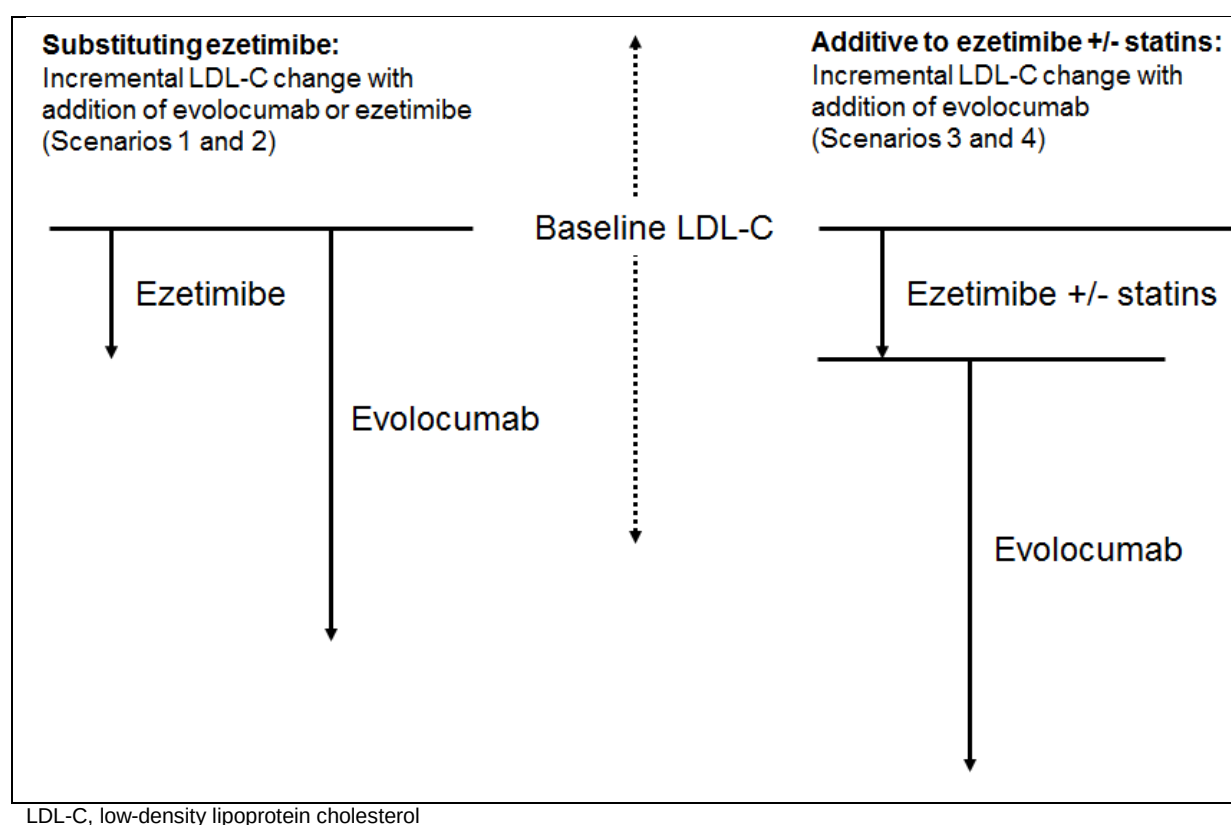


Table 5-11 Treatment effects applied in different modelled scenarios

Scenario		Evolocumab	Ezetimibe	Rationale and comments
1	In combination with statin	LAPLACE-2	LAPLACE-2	• Efficacy from LAPLACE-2 since this relevant RCT assessed efficacy in combination with statin therapy.
2	Monotherapy	GAUSS-2	GAUSS-2	• Efficacy from GAUSS-2 since this relevant RCT assessed efficacy in a statin intolerant (or contraindicated) population.
3	In combination with ezetimibe	GAUSS-2	GAUSS-2	• This comparison was not directly assessed in the relevant RCTs. • Assumed efficacy from GAUSS-2 since this scenario represents a statin intolerant or contraindicated population.
4	In combination with statin and ezetimibe	LAPLACE-2	LAPLACE-2	• This comparison was not directly assessed in the relevant RCTs. • Assumed efficacy from LAPLACE-2 to model the combination of evolocumab, statin and ezetimibe.
RCT, randomised controlled trial				

Translating LDL-C reductions to reductions in CV events

To translate the values in Table 5-10 to changes in CV event rates, estimates from CTTC meta-analysis (first described in Section 3) linking absolute (mmol/L) changes in LDL-C to changes in first CV event rates were utilised.⁴⁷ The CTTC meta-analysis demonstrated that the size of the proportional reduction in CV events is proportional to the absolute LDL-C reduction that is achieved with statins. Across the meta-analysis of 26 trials and 161,138 individuals, a rate ratio of 0.78 (95% CI 0.76 to 0.80, $p < 0.0001$) per mmol/L reduction in LDL-C for any major vascular event was observed. A rate ratio of 0.72 (0.66 to 0.78 $p < 0.0001$) per mmol/L reduction was also observed for any major vascular event in the '*more versus less intensive statin therapy*' meta-analysis (five trials, 39612 individuals, median follow-up 5.1 years). The rate reduction was shown to vary according to CV event type (e.g. non-fatal MI and fatal IS).

As described in Section 4.12, results from a prespecified exploratory analysis of adjudicated CV events in OSLER and OSLER-2 showed statistically significant reductions in CV events of over 50% after approximately 1 year of treatment with evolocumab plus SoC versus SoC alone. These results are consistent with reductions in CV events that could be expected based on the LDL-C reductions seen in Table 5-10 combined with the relationship between LDL-C and CV events as described by CTTC (Table 5-12). The point estimates are also consistent with similar ad-hoc analyses with another PCSK9 inhibitor (alirocumab)¹¹⁴ and a meta-analysis of safety data from randomised clinical trials of PCSK9 inhibitors.¹²⁸

A recent CV outcomes study, IMPROVE-IT, was not included in the CTTC meta-analysis, as it was published after the publication of the CTTC meta-analysis. IMPROVE-IT demonstrated that ezetimibe added to simvastatin further lowered LDL-C and significantly reduced the occurrence of a composite endpoint of CV death, MI, unstable angina requiring hospitalisation, coronary revascularisation, or stroke compared with statin alone

($p = 0.016$).⁶⁴ IMPROVE-IT further confirms the relationship between LDL-C reduction and the reduction in risk of CV events, and demonstrates the incremental benefit of adding non-statin lipid-lowering therapy to a statin. The findings further confirm the relationship between LDL-C reduction and the reduction in risk of CV events.

For the purposes of the economic evaluation, CV event rates have been estimated based on the established LDL-C to CV risk relationship, rather than CV event rates observed in OSLER extension studies and IMPROVE-IT study for evolocumab and ezetimibe, respectively. The CTTC meta-analysis represents a larger and established body of evidence (overall 26 trials, 169,138 individuals; median follow-up 4.9 years) for this relationship. Therefore, in linking LDL-C lowering to non-fatal CV events, the CTTC meta-analysis of '*more versus less intensive statin therapy*' was used rather than the '*statin versus control*' meta-analysis'. The populations and treatment interventions in the studies within this meta-analysis were deemed to be more representative of the high risk CV patients eligible for evolocumab. For every mmol/L lowering of LDL-C (dLDL-C), the rate ratio of CV events is given by the corresponding event specific rate ratio in Table 5-12 to the power of dLDL-C (rate ratio after treatment = CTTC rate ratio^(1/absolute LDL-C reduction)). Based on this modified CV event risk, the consequent impact of treatment on occurrence of CV events, life years, and QALYs are derived.

Table 5-12 Proportion of change in CVD event risk per mmol/L LDL-C change

CV event	Rate ratio (95% CI)	Source	Reference
ACS	0.71 (0.58, 0.87)	Figure 2. More vs. less statins (non-fatal MI)	Baignet 2010 ⁴⁷
Revascularisation	0.66 (0.60, 0.73)	Figure 2. More vs. less statins (any coronary revascularisation)	
IS	0.69 (0.50, 0.95)	Figure 2. More vs. less statins	
HF	0.71 (0.58, 0.87)	Assumption: equal to MI	N/A
CHD death	0.80 (0.74, 0.87)	Figure 5. (CHD)	Baignet 2010 ⁴⁷
Stroke death ^a	1.04 (0.77, 1.44)	Figure 5. (IS)	

^aAssumed rate ratio = 1.

ACS, acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; N/A, not applicable

Several assumptions were used to model this relationship:

- Treatment effect benefits from LDL-C reduction to CV outcomes are modelled from the first cycle (Year 1) based on the findings of the long-term extension studies (Section 4.7).
- The rate ratio for new onset HF is equal to MI. Patients in HF health states (either single or combined) experience no further treatment effect due to LDL-C lowering for risk of recurrent HF since findings suggest lack of benefit for lipid-lowering therapies once patients experience HF on events such as CHD death.
- The treatment effect of ACS has been applied for patients transitioning from 'No CVD' to 'ECVD'.
- A treatment effect for revascularisation procedures has been applied to the 'post-ACS' health state alone.

- The rate ratio for stroke death (fatal IS) is equal to one. This has been assumed since a non-significant effect has been observed for LDL-C reduction for this CV event.
- The relationship between reductions in LDL-C and first event observed CTTC meta-analysis is also representative of corresponding reductions in subsequent CV events.
- The relative reduction in CV event rate per mmol/L in LDL-C is independent of baseline levels.
- The reduction in CV event rate per mmol/L in LDL-C is independent of familial or non-familial hypercholesterolaemia, prognostic factors such as age, gender, co-morbidities (e.g. diabetes), and CV history or burden.
- No reduction in CV event rate associated with LDL-C levels when lower than 1.03mmol/L from baseline (equivalent to 40mg/dL).

Transition probabilities

The treatment- and population-specific transition probabilities are derived from patient characteristics, baseline CV rates, and treatment effects, as described in the previous section. All transition probabilities applied in the model are age-specific. Since there are 24 health states (two entry, three acute, three fatal, three single chronic, and 13 combined chronic health states) for each population and patients can transition between many of those health states, it is not possible to present all transition probabilities in one table (see Figure 5-8 for an overview of all possible transitions). Therefore, an example displaying the transition probabilities for patients who are in the 'ACS' health state to other health states is presented in Table 5-13.

The following assumptions should be considered when interpreting the transition probabilities.

- For secondary risk, assume that the secondary risk is no less than the modelled primary risk.
- Patients who transition from 'ACS' to 'ACS', 'IS', or 'HF' may already have previously experienced these CV events. The model accounts for that by placing such patients in the relevant combined health state.
- The transition probability from a combined health state to 'ACS', 'IS', or 'HF' is defined by the maximum probability of the individual health states transitions to 'ACS', 'IS', or 'HF'
- CVD-related death can be due to CHD or stroke. For 'ACS' and 'post-ACS', an age-specific distribution between CHD and stroke was used.

Table 5-13 Transition probabilities from 'ACS' to other health states

Age (years)	<i>Patients with existing CVD, transitioning from 'ACS' to:</i>						
	'ACS'	'Post-ACS'	'IS + post-ACS'	'HF + post-ACS'	CHD death	IS death	non-CV death
62	0.1187	0.8274	0.0066	0.0117	0.0226	0.0066	0.0064
63	0.1218	0.8215	0.0068	0.0124	0.0241	0.0065	0.0068
64	0.1250	0.8152	0.0070	0.0131	0.0257	0.0064	0.0075
65	0.1283	0.8089	0.0071	0.0139	0.0274	0.0063	0.008
66	0.1316	0.8018	0.0073	0.0147	0.0292	0.0063	0.0091
67	0.1350	0.7948	0.0075	0.0155	0.031	0.0062	0.0099
68	0.1385	0.7877	0.0077	0.0164	0.033	0.0061	0.0107
69	0.1420	0.7796	0.0079	0.0173	0.035	0.006	0.0122
70	0.1456	0.7716	0.0081	0.0183	0.0371	0.0059	0.0133
71	0.1493	0.7633	0.0083	0.0193	0.0394	0.0058	0.0146
72	0.1530	0.7545	0.0085	0.0203	0.0417	0.0057	0.0162
73	0.1568	0.7457	0.0087	0.0215	0.0442	0.0056	0.0175
74	0.1607	0.7359	0.0089	0.0227	0.0467	0.0055	0.0196
75	0.1646	0.7265	0.0092	0.0239	0.0494	0.0054	0.021
76	0.1686	0.7158	0.0094	0.0252	0.0523	0.0053	0.0235
77	0.1726	0.7047	0.0096	0.0266	0.0552	0.0052	0.0261
78	0.1768	0.6926	0.0098	0.028	0.0583	0.0051	0.0293
79	0.1809	0.6804	0.0101	0.0296	0.0615	0.005	0.0326
80	0.1852	0.6680	0.0103	0.0312	0.0649	0.0049	0.0356
81	0.1895	0.6536	0.0106	0.0328	0.0684	0.0048	0.0403
82	0.1938	0.6388	0.0108	0.0346	0.0721	0.0047	0.0452
83	0.1982	0.6230	0.0110	0.0365	0.0759	0.0046	0.0508
84	0.2027	0.6061	0.0113	0.0384	0.08	0.0045	0.057
85	0.2072	0.5891	0.0115	0.0404	0.0842	0.0049	0.0627
86	0.2062	0.5810	0.0115	0.0414	0.0845	0.0052	0.0701
87	0.2052	0.5726	0.0114	0.0425	0.0847	0.0055	0.078
88	0.2042	0.5636	0.0114	0.0435	0.085	0.0059	0.0864
89	0.2032	0.5513	0.0113	0.0446	0.0853	0.0062	0.0981
90	0.2022	0.5408	0.0113	0.0457	0.0855	0.0065	0.1081
91	0.2011	0.5315	0.0112	0.0468	0.0857	0.0069	0.1168
92	0.2000	0.5210	0.0112	0.048	0.0859	0.0072	0.1267
93	0.1989	0.5113	0.0111	0.0491	0.0861	0.0076	0.1358
94	0.1978	0.4946	0.0110	0.0503	0.0862	0.008	0.1521
95	0.1967	0.4737	0.0110	0.0515	0.0864	0.0084	0.1724
96	0.1955	0.4577	0.0109	0.0528	0.0866	0.0088	0.1878
97	0.1943	0.4430	0.0108	0.054	0.0867	0.0092	0.202
98	0.1931	0.4291	0.0108	0.0553	0.0868	0.0096	0.2153
99	0.1919	0.4133	0.0107	0.0566	0.0869	0.01	0.2306
100	0.1906	0.4001	0.0106	0.0579	0.0871	0.0104	0.2433
ACS, acute coronary syndrome; CHD, coronary heart disease; CV, cardiovascular; HF, heart failure; IS, ischaemic stroke							

Figure 5-8 Health state transitions

FROM	TO	NoCVD	ECVD	ACS	IS	HF	PostACS	PostIS	PostHF	CHDdeath	ISdeath	NonCVDdeath	IS +PostACS	PostIS +ACS	PostIS +PostACS	HF +PostACS	PostHF +ACS	PostHF +PostACS	HF +IS	PostHF +IS	PostHF +IS	HF +PostIS	PostHF +PostIS	PostHF +PostIS	PostHF +PostIS
NoCVD		#	TE	TE	TE	TE				TE	T	T													
ECVD			#	TE	TE	TE				TE	T	T													
ACS				TE			#			TE	T	T	TE			TE									
IS					TE			#		TE	T	T		TE					TE						
HF						T			#	TE	T	T					TE			TE					
PostACS				TE			#			TE	T	T	TE			TE									
PostIS					TE			#		TE	T	T		TE					TE						
PostHF						T			#	TE	T	T					TE			TE					
IS+PostACS										TE	T	T	TE	TE	#						TE				
PostIS+ACS										TE	T	T	TE	TE	#						TE				
PostIS+PostACS										TE	T	T	TE	TE	#						TE				
HF+PostACS										TE	T	T				T	TE	#						TE	
PostHF+ACS										TE	T	T				T	TE	#						TE	
PostHF+PostACS										TE	T	T				T	TE	#						TE	
HF+PostIS										TE	T	T							T	TE	#			TE	
PostHF+IS										TE	T	T							T	TE	#			TE	
PostHF+PostIS										TE	T	T							T	TE	#			TE	
HF+PostIS+PostACS										TE	T	T									T	TE	TE		#
PostHF+PostIS+ACS										TE	T	T									T	TE	TE		#
PostHF+PostACS+IS										TE	T	T									T	TE	TE		#
PostHF+PostIS+PostACS										TE	T	T									T	TE	TE		#

Complementary

#

Transition

T

Transition with treatment effect

TE

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; ECVD, established CVD; HF, heart failure; IS, ischaemic stroke.

Transition probabilities for CVD-related death are applied according to the methods described above. Non-CVD death can occur in any health state. Age-specific probabilities of non-CVD death are based on UK life tables, adjusted for the risk of CVD-related death to avoid double-counting.

Adverse events

Analyses of the safety and tolerability data from the evolocumab studies show that evolocumab has a favourable safety and tolerability profile in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. In an integrated safety analysis (of 6,026 patients, representing 7,235 patient-years of exposure), as well as across populations and therapeutic settings in individual studies, adverse events were overall balanced between treatment groups. Most adverse events were mild to moderate in severity, with serious adverse events and adverse events leading to treatment discontinuation infrequently reported. Based on the above findings, the model does not include the incidence of adverse events. This approach is consistent with existing models for statins and ezetimibe.

5.4 Measurement and valuation of health effects

HRQoL data from clinical trials

HRQoL was not assessed in the relevant evolocumab RCTs.

Amgen time trade-off study

A separate Amgen sponsored study¹⁸¹ was conducted to estimate the utility values of health states representing CV events. In this study, six health state descriptions were drafted based on a literature review and clinician interviews, and refined based on a pilot study with 22 respondents.

The six health states described three acute and three chronic CV events, namely: acute stroke, acute ACS, acute HF, chronic stroke, chronic ACS, and chronic HF. The utility values for the acute health states were defined by using a 1-year time trade-off (TTO) method and for the chronic health states a 10-year TTO method was used. A total of 200 healthy participants (≥ 18 years) completed interviews (in two locations in the UK: 107 in Edinburgh, 93 in London; 55% female; mean age 46.6 years; 2% reported CV conditions) in which the health states were rated. Participants were asked to rank the acute and chronic CV health states in order based on their preferences and perform the TTO task.

Based on participants' responses, each health state rated as better than death received a utility value on a scale with the anchors of death (0) to full health (1). The assigned value is calculated based on the choice in which the respondent is indifferent between y years/months in the health state being evaluated and x years/months in full health (followed by y – x years/months dead). The resulting utility estimate (u) is calculated as $u = x/y$.

For TTO ratings of health states considered worse than death, a bounded scoring approach was applied. This approach limits the score range of health states worse than death between 0 and -1. Several methods have been used in previous studies to compute these bounded negative utility values. In this case, the Dolan ¹⁸² method as described by Rowen & Brazier (2011) was used. This method uses the formula “-x/t”, where x is the amount of time in full health, and t is the total life span of alternative 2 in the TTO choice. Alternative 1 is death.

The acute CV event health states with the lowest utility was stroke (1-year with event) (0.327), followed by HF (1-year with acute HF event) (0.602), and ACS (1-year with event) (0.672). Similarly for the chronic CV health states, stroke (long-term effects of prior stroke) (0.524) had the lowest utility, followed by chronic HF (0.571), and ACS (long-term effects of prior ACS) (0.824). These values are summarised in Table 5-14.

Table 5-14 Time trade-off study results

Health state	Absolute utility
ECVD	0.824 ^a
ACS (first year)	0.672
Stroke (first year)	0.327
HF (first year)	0.602
ACS (long-term)	0.824
Stroke (long-term)	0.524
HF (long-term)	0.571
^a ECVD absolute utility assumed equivalent to ACS long-term.	
ACS, acute coronary syndrome; ECVD, established cardiovascular disease; HF, heart failure	

This study showed that both the 1-year TTO and the 10-year TTO methods were able to detect differences among the acute and chronic health states. The results show that acute and chronic stroke were rated lowest compared with the other CV health states, whereas ACS was rated as relatively mild, particularly in the case of the chronic ACS state. For stroke and ACS, the acute CV health state was typically associated with a lower utility value compared with the chronic CV health state. In comparison, the chronic HF health state had a lower utility than the acute HF health state because of the severity of long-term effects after HF.

A limitation of this study is that the resulting utility scores represent specific health states, which are based on clinicians’ descriptions of a typical patient rather than the broad range of symptom severity and outcomes that would be observed in an actual patient sample. The extent to which these utilities might differ from values reported by actual patients living in the health states is not known. Moreover, participants from the general population have been selected from just two locations in the UK. It is therefore possible that the results are not generalisable to the wider UK population. Additionally, due to the extended description of the health states, it is possible that some participants may not have been able to consider all parts of the health states when completing evaluations. There were some respondents who appeared to respond primarily to aspects of impaired functioning that were particularly salient to them, while possibly overlooking other aspects of the health states.

A scenario analysis has been included in which the utilities have been estimated using this TTO study. In the absence of an absolute utility for a long-term 'ECVD' health state, the absolute utility value from the long-term ACS (0.824) has been assumed.

Mapping

HRQoL was not assessed in the relevant evolocumab RCTs, therefore no mapping techniques have been applied.

HRQoL studies

To systematically identify published HRQoL estimates of various CV health states used in the model a SLR was conducted in September 2012 and updated on 23 January 2015. This SLR was designed to identify relevant English language papers indexed in MEDLINE or Embase with an abstract published generating (as a primary source) utility data from 1992 to the date of search.

The databases MEDLINE (via Pubmed) and Embase (via embase.com) were searched for human studies that reported on utility values related to CV events of interest, including stroke (ischaemic, haemorrhagic, and TIA), MI, angina (stable and unstable), CV-related death, HF or revascularisation (including, but not limited to, CABG, coronary bypass, PCI, stenting, angioplasty, and catheterisation) in an adult population. The search syntax used is presented in Appendix XIII.

Additionally, conference proceedings and HTA websites were searched for documents, proceedings and abstracts reporting utility measures related to the CV events of interest and published since July 2012. For conference proceedings the following websites were consulted:

- International Society For Pharmacoeconomics and Outcomes Research (www.ispor.org/)
- American Heart Association (www.heart.org/)
- American College of Cardiology (<http://www.acc.org/>)
- European Society of Cardiology (<http://www.acc.org/>)
- European Atherosclerosis Society (www.eas-society.org/).

The search strategy for the conference proceedings was based on keywords from the MEDLINE and Embase searches. Details of the search strategy for the selected conferences are available in Appendix XIII.

For HTA documents the following websites were consulted:

- NHS EED (www.crd.york.ac.uk/CRDWeb)
- National Institute for Health and Care Excellence (<http://www.nice.org.uk/>)
- Scottish Medicines Consortium (<http://www.scottishmedicines.org.uk/>)
- Canadian Agency for Drugs and Technologies in Health (<http://cadth.ca/>).

The search strategy was based on keywords from the MEDLINE and Embase searches. Details of the search strategy for the selected HTAs are presented in Appendix XIII.

After identifying potential relevant studies through the database searches, a three-stage screening procedure was applied to collect relevant studies based on the inclusion and exclusion criteria outlined in

Duplicate records identified in the search were removed prior to application of the inclusion/exclusion process in stage 1. In the first stage titles and abstracts of the publications obtained from the literature search strategy were manually reviewed by one reviewer and studies were included if the title and/or abstract met the inclusion criteria or if the abstract was not reported. All papers accepted during title and abstract screenings (stage 1) were reviewed in full text (stage 2) against the inclusion and exclusion criteria by two independent investigators, as presented in Table 5-15. The studies were only included if they met all of the inclusion criteria and none of the exclusion criteria. The specific reason for exclusion was recorded for each excluded full-text article.

The bibliographies of included articles were examined to identify additional articles noted as relevant by prior reviewers. Published studies considered eligible after full-text review of the database search and considered eligible from the HTAs, the conference proceedings, and the bibliographies were selected for data extraction in stage 3.

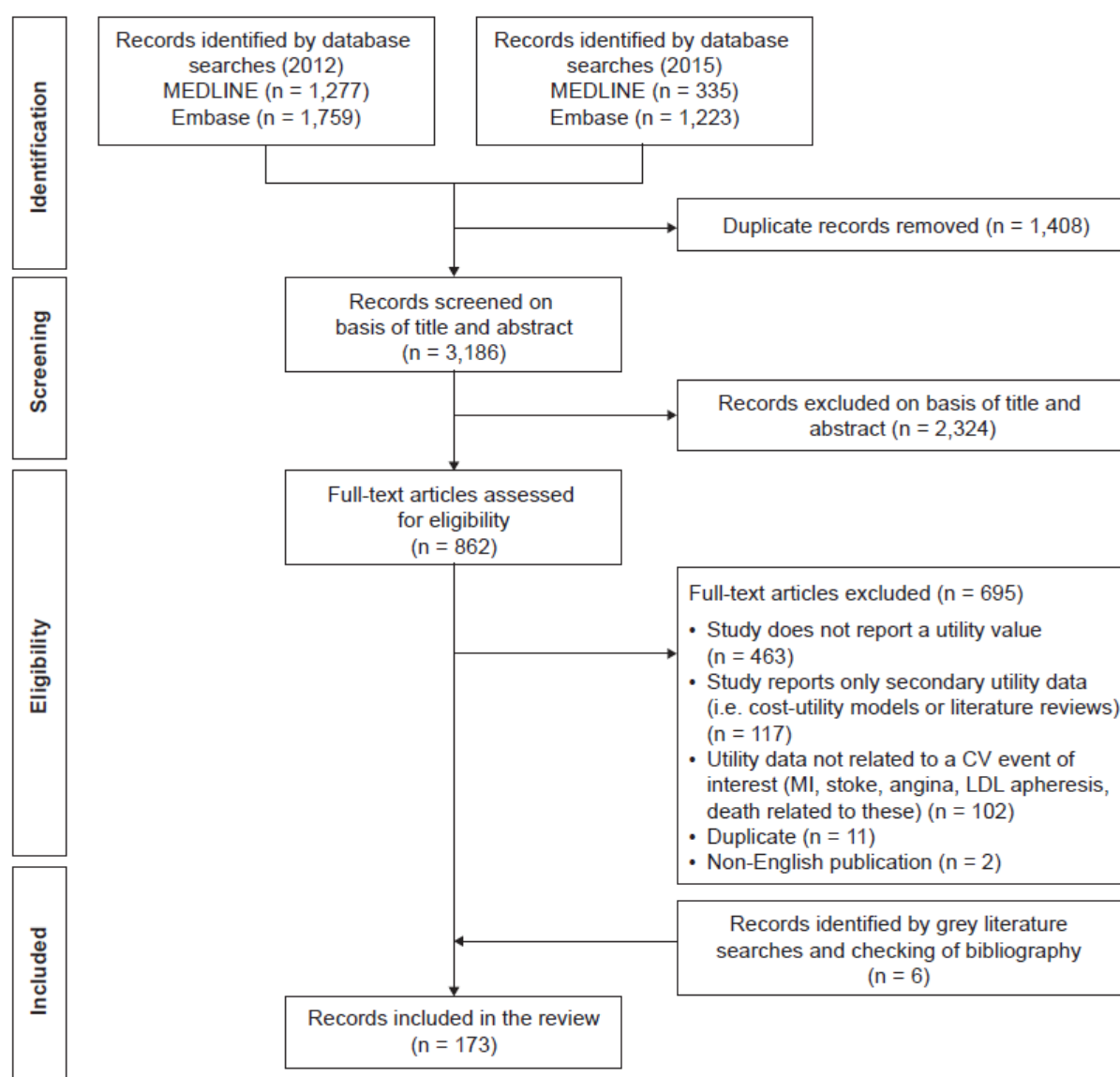
Table 5-15 Eligibility criteria used in the HRQoL SLR

Parameter	Inclusion	Exclusion	Rationale/comments
Population	• Human adults (≥ 18 years)	• Children (< 18 years) • Non-humans	Studies assessing the cost-effectiveness of statins and ezetimibe only in children were excluded in accordance with the scope of CG181 ⁷⁷
Intervention	• Any treatment	• No restrictions	No specific treatment of interest
Therapeutic area/conditions of interest	• Stroke (ischaemic or TIA) • MI • Angina (stable and unstable) • CV-related death • HF • Revascularisation (including, but not limited to, CABG, coronary bypass, PCI, stenting, angioplasty, and catheterization)	• Study not related to a CV event	This submission will focus only on CV events.
Outcomes	• Any health utility value	• No health utility value reported	
Study Design	• Any study design • Primary source studies	• Not primary source studies	
Language restrictions	• English language	• Non-English language	
Country restrictions (HTAs only)	• HTA documents from the UK, the US, and Canada		
Date restrictions	• Database: 1992 to February 2015 • Conference proceedings and HTAs: July 2012 to February 2015	• Database search: published before 1992 • Conference proceedings and HTAs: published before July 2012	
ACS, acute coronary syndromes; CABG, coronary artery bypass graft; CV, cardiovascular; HF, heart failure; HTA, Health Technology Assessment; HRQoL, health-related quality of life; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; PCI, percutaneous coronary intervention; SLR, systematic literature review; TIA, transient ischaemic attack			

In the SLR conducted in 2012, a total of 1277 citations were obtained from MEDLINE and 1759 from Embase. The database literature search for the updated SLR identified 335 additional citations from Medline and 1223 citations from Embase. In total, 1408 articles were duplicates and subsequently removed from the review for a total of 3186 unique articles that could proceed to stage 1 of the inclusion/exclusion process. A list of the duplicate studies can be found in Appendix XIII. Of the unique citations, 2324 were excluded after a review of titles/abstracts (stage 1).

After full-text review, during which a further 695 studies were excluded, a total of 167 studies from the database search were included for data extraction. A full list of the 695 excluded studies from the full-text review can be found in Appendix XIII. For the final data extraction 171 studies were included, 165 identified through database searches and 6 additional hand-searched articles were included from the conference proceedings, HTAs, and the bibliography check. The PRISMA flow chart of the inclusion and exclusion criteria of the HRQoL search is presented in Figure 5-9.

Figure 5-9 PRISMA flow diagram for HRQoL SLR from the database search



CV, cardiovascular; HRQoL, health-related quality of life; LDL, low-density lipoprotein; MI, myocardial infarction; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review

Of the 171 papers extracted, 123 reported utility data for stroke, 56 for MI, and 40 for angina. Only one paper explicitly estimated the utility for CV death. Many papers reported utilities for multiple CV health states.

The papers most commonly reported on observational studies in North America and Europe. Sixty-three papers reported on cross-sectional surveys, 57 on prospective cohort studies, 35 on clinical trials, and the remaining 18 papers reported on post-hoc analyses that generated new utility data or were unclear in the design of the study. Papers most commonly reported on studies conducted in the UK (33), US (28), Canada (19), Germany (12), and Sweden (10); 11 papers reported on multinational studies. Utility data were also available for Australia, Belgium, Brazil, China, France, India, Israel, Japan, Mexico, Netherlands, Nigeria, Norway, Poland, Singapore, South Korea, Spain, Taiwan, and Thailand.

Regarding the types of utility measures used, 115 provided 5-dimension European Quality of Life questionnaire (EQ-5D) data, 17 used a standard gamble, 16 used a TTO method, 13 used the Short Form–Six Dimensions, 12 used a Health Utilities Index measure, and 13 used other less common measures; 21 studies captured utilities using more than one measure.

A full list of studies reporting relevant utilities and the main items included during data extraction are presented in Appendix XIII. Study data were extracted by a single investigator and validated by a second investigator.

HRQoL summary data extraction tables

Table 5-16 highlights the data extracted from UK-based studies that use EQ-5D as the method of elicitation. In addition, the studies elicited utilities from at least two of the following: (1) patients or caregivers; (2) in a clinical trial; (3) using UK tariffs. For the full data extraction table see Appendix XIII.

Table 5-16 HRQoL summary data extraction table of UK studies using EQ-5D as utility methods of elicitation

First author, year	Country, recruitment and study type	Interventions	Population tariff used	Respondent population and sample size	Absolute utility values	Relative utility values	Events reported
Ali, 2013 ¹⁸³	Country: UK Recruitment: Recruited patients from the University of North Staffordshire between October 2004 and April 2008 Study type: RCT	Routine oxygen supplementation vs. control	Weighting scheme derived from the UK (the EuroQol Group, 1990)	Population: Patients who had experienced acute stroke Sample size: N = 301; EQ-5D scores were obtained for 110 (74%) and 112 (79%) participants, in the oxygen and control groups, respectively	Covariate adjusted mean EQ-5D for patients with stroke: oxygen = 0.50 at 6 months, control = 0.49 at 6 months Unadjusted mean EQ-5D for patients with stroke: oxygen = 0.50 at 6 months, control = 0.50 at 6 months	NR	Stroke
Alva, 2014 ¹⁸⁴	Country: UK Recruitment: Recruited patients through the United Kingdom Prospective Diabetes Study Study type: Regression analysis	Not an interventional study	Utility values were taken from the UK preference set (Dolan et al., 1996)	Population: Patients with diabetes Sample size: N = 5102; 3380 participants (66%) completed at least one EQ-5D questionnaire Age: Mean 67.7 years, SD 9.3 years	NR	EQ-5D regression coefficients Ordinary least squares with attrition MI (year before): -0.112 MI (prior history): -0.037 Stroke: -0.180 Heart failure: -0.175 FE with attrition MI (year before): -0.110 MI (prior history): -0.014 Stroke: -0.165 Heart failure: -0.133	Stroke, MI

First author, year	Country, recruitment and study type	Interventions	Population tariff used	Respondent population and sample size	Absolute utility values	Relative utility values	Events reported
Bowen, 2012 ¹⁸⁵	Country: UK Recruitment: Recruited patients from 12 English NHS hospital and community stroke services between December 2006 and January 2010 Study type: RCT	Speech and language therapy vs. attention control	UK population tariff	Population: Stroke survivors Sample size: Attention control group: N = 66, Speech and language therapy group: N = 74 82% of those evaluated reported a utility score (66+74/85+85) 30% above retirement age 53% female	Mean EQ-5D for patients with stroke: Treated with attention control: 0.47 Treated with speech and language therapy: 0.51	NR	Stroke
Calvert, 2012 ¹⁸⁶	Country: UK Recruitment: Recruited patients through the 2001 Census ethnic group classifications from 20 health centres in Birmingham Recruitment: Cross-sectional study	Not an interventional study	A set of weighted preferences from the UK population was used	Population: General population Sample size: N = 5354; Age: Mean 60.8 years, SD 11.1 years Male: 47.5%	NR	EQ-5D disutility for medical history of angina: -0.039 EQ-5D disutility for medical history of stroke or TIA: -0.135	Stroke, angina
Clarke, 2002 ¹⁸⁷	Country: UK Recruitment: Patients with newly	N/A	Dolan et al. 1996	Population: Patients with newly diagnosed	NR	Marginal effect (95% CI) on EQ-5D based on Tobit model:	Stroke, MI

First author, year	Country, recruitment and study type	Interventions	Population tariff used	Respondent population and sample size	Absolute utility values	Relative utility values	Events reported
	diagnosed type 2 diabetes were recruited at 23 hospitals in the UK from 1977 to 1997 as part of the United Kingdom Prospective Diabetes Study Study type: Prospective cohort study of patients enrolled in a trial			type 2 diabetes Patients were excluded from the trial if they had HF, angina, or more than one major vascular event, if they had had an MI in the previous year, or if they had another illness that was likely to limit lifespan Sample size: N = 3192		MI: -0.055 (-0.067, -0.042) Stroke: -0.164 (-0.222, -0.105) Marginal effect (95% CI) on EQ-5D based on censored least absolute deviations regression analysis: MI: -0.035 (-0.061, -0.008) Stroke: -0.090 (-0.147, -0.032)	
Dennis, 2014 ¹⁸⁸	Country: UK Recruitment: Recruited patients from 94 hospital centres from days 0 (admission) to 3 in hospital between December 2008 and September 2012 Study type: Secondary analyses of a RCT	Intermittent pneumatic compression group vs. no intermittent pneumatic compression group	UK	Population: Patients with acute stroke Sample size: N = 2876 Intermittent pneumatic compression: N = 1438 No intermittent pneumatic compression: N = 1,438)	Median EQ-5D for intermittent pneumatic compression after stroke: 0.26 (IQR -0.07 to 0.66) Median EQ-5D for no intermittent pneumatic compression after stroke: 0.27 (IQR -0.06 to 0.64)	NR	Stroke
Kim,	Country: UK	Patients were	Based on a	Population:	Mean (SE) EQ-5D in patients with	Difference from baseline in	MI,

First author, year	Country, recruitment and study type	Interventions	Population tariff used	Respondent population and sample size	Absolute utility values	Relative utility values	Events reported
2005 ¹⁸⁹	Recruitment: Patients who had experienced chest pain and had previous arteriographic evidence of coronary artery disease or chest pain were recruited for the RITA-3 Trial in England and Scotland from 1997 to 2001 Study type: RCT	randomised either to an early interventional strategy (i.e. maximal medical therapy plus early coronary arteriography with possible myocardial revascularisation) or to a more conventional strategy (i.e. maximal medical therapy plus ischaemia- or symptom-provoked angiography and revascularisation)	sample of 3395 persons in the UK (Dolan et al., 1995)	Patients with unstable angina or nSTEMI Sample size: At 4 months since study entry: Interventional strategy: N = 839, conventional strategy: N = 853 At 1 year since study entry: interventional strategy: N = 806, conventional strategy: N = 820	unstable angina or nSTEMI: At 4 months with conservative strategy: 0.71 (0.10) At 4 months with interventional strategy: 0.75 (0.01) At 1 year with conservative strategy: 0.74 (0.01) At 1 year with interventional strategy: 0.75 (0.01)	EQ-5D in patients with unstable angina or nSTEMI (95% CI): At 4 months with conservative strategy: 0.041 (0.009) At 4 months with interventional strategy: 0.077 (0.009) At 1 year with conservative strategy: 0.063 (0.009) At 1 year with interventional strategy: 0.079 (0.009)	angina
Logan, 2014 ¹⁹⁰	Country: UK Recruitment: Patients were recruited from 15 sites including primary care therapy teams, general practices, community stroke teams, or outpatient clinics and were recruited	Outdoor mobility therapy (up to 4-month period) or control group (no further therapy) Outdoor mobility therapy sought to improve outdoor mobility, helping patients overcome physical and	York A1 tariff from the UK Dolan et al., 1997	Population: Patients who had experienced a stroke at least 6 weeks prior Sample size: N = 568; Mean (SD) age: 71 (12.1) years	Mean (95% CI) EQ-5D for stroke patients who received intervention: Baseline: 0.408 (95% CI -0.182 to 0.848) 6 months: 0.398 (95% CI -0.181 to 0.848) 12 months: 0.384 (95% CI -0.182 to 0.850) Mean (95% CI) EQ-5D for stroke patients who were in the control	EQ-5D mean (95% CI) change from baseline to 12 months for stroke survivors in the following groups: Intervention: -0.022 (95% CI -0.570 to 0.435) Control: 0.022 (95% CI -0.531 to 0.651)	Stroke

First author, year	Country, recruitment and study type	Interventions	Population tariff used	Respondent population and sample size	Absolute utility values	Relative utility values	Events reported
	through the GP database or stroke register across the UK between November 2009 and August 2011 Study type: Prospective RCT	psychological barriers		% female: Intervention: 53% Control: 57.8%	group: Baseline: 0.420 (95% CI -0.124 to 0.850) 6 months: 0.436 (95% CI -0.181 to 0.883) 12 months: 0.447 (95% CI -0.164 to 1.000)		
Longworth, 2005 ¹⁹¹	Country: UK Recruitment: Patients recruited from UK cardiac outpatient clinics Study type: Cross-sectional study	Not an interventional study 43% had undergone at least one PTCA and 21% had undergone at least one bypass graft	UK general population Dolan et al., 1997	Population: Patients either had CAD with symptoms of angina or had previously undergone revascularisation procedures; patients chosen to be representative of patients from the RITA-2 trial Sample size: N = 510; Median age: 61 years; 81.8% male	Mean EQ-5D for patients with angina evaluated using CCS scores: CCS 0: 0.81 CCS 1: 0.75 CCS 2: 0.60 CCS 3: 0.41 CCS 4: 0.36	Regression model to predict EQ-5D scores in patients with angina (coefficient, standard error): CCS 1: -0.028, 0.026 CCS 2: -0.147, 0.031 CCS 3: -0.252, 0.044 CCS 4: -0.263, 0.058	Angina
Luengo-Fernandez, 2013 ¹⁹²	Country: UK Recruitment: Patients with stroke or TIA were recruited from April 2002 to	Not an interventional study	UK population valuations Dolan et al.,	Population: Patients with stroke defined by WHO definition for	Mean (SD) EQ-5D for all stroke patients at the following time points: 1 month (N = 445): 0.64 (0.33) 6 months (N = 339): 0.70 (0.29) 12 months (N = 418): 0.70 (0.27)	Expected mean (95% CI) EQ-5D utility gain at 1 month for patients with stroke or TIA: Stroke: -0.017 (-0.061 to	Stroke, MI, angina

First author, year	Country, recruitment and study type	Interventions	Population tariff used	Respondent population and sample size	Absolute utility values	Relative utility values	Events reported
	March 2007 into the Oxford Vascular Study Study type: Prospective cohort study		1997	stroke or TIA Sample size: Stroke patients: N = 748 TIA patients: N = 440 Mean age (SD): Stroke = 75 (12) years, TIA = 73 (13) years % male: Stroke = 49%, TIA = 44%	24 months (N = 263): 0.66 (0.29) 60 months (N = 269): 0.68 (0.31)	0.028) MI: 0.041 (-0.018 to 0.098) Angina: 0.023 (-0.028 to 0.069) Recurrent stroke: -0.150 (-0.228 to -0.073) Expected mean (95% CI) utility gain at 5 years for patients with stroke or TIA: Stroke: -0.067 (-0.138 to 0.002) MI: -0.003 (-0.077 to 0.063) Angina: -0.040 (-0.133 to 0.061) Recurrent stroke: -0.068 (-0.118 to -0.023)	
Peters, 2014 ¹⁹³	Country: UK Recruitment: A cohort of patients with long-term conditions was recruited from 33 primary care practices in London and Northwest England from September 2010 to April 2012. Data were collected at baseline and 1-year follow-up Study type: Prospective cohort	NR	Valued against the general population UK (EQ-5D York tariff) Rabin et al., 2001	Population: Patients with long-term conditions including stroke, asthma, chronic obstructive pulmonary disease, epilepsy, HF, and diabetes Sample size: EQ-5D for stroke based on N = 93 patients	Mean (95% CI) EQ-5D for stroke patients: Baseline: 0.67 (0.61 to 0.74) 12-month follow-up: 0.67 (0.60 to 0.73)	Mean (95% CI) change in EQ-5D for stroke patients from 12-month follow-up to baseline: -0.008 (-0.31 to 0.13)	Stroke

First author, year	Country, recruitment and study type	Interventions	Population tariff used	Respondent population and sample size	Absolute utility values	Relative utility values	Events reported
	study						
Rivero-Arias, 2010 ¹⁹⁴	Country: UK Recruitment: Patients registered with 9 general practices across Oxfordshire who had been monitored for the incidence of stroke and TIA were recruited from the Oxford Vascular Study Study type: Cohort study	Not an interventional study	UK tariff (derived from a large representative sample of the British population using TTO and regression)	Population: Stroke patients stratified by mRS, where a score of 5 indicates high severity of stroke symptoms Sample size: N = 1,283; Mean age: 72.8 years; 47% male	Mean $\pm$ SD EQ-5D at 1 month after stroke: mRS score 0 = 0.909 ± 0.153 mRS score 1 = 0.819 ± 0.181 mRS score 2 = 0.694 ± 0.220 mRS score 3 = 0.589 ± 0.280 mRS score 4 = 0.252 ± 0.301 mRS score 5 = -0.112 ± 0.195 Mean $\pm$ SD EQ-5D at 6 months after stroke: mRS score 0 = 0.931 ± 0.117 mRS score 1 = 0.803 ± 0.194 mRS score 2 = 0.682 ± 0.220 mRS score 3 = 0.547 ± 0.308 mRS score 4 = 0.236 ± 0.313 mRS score 5 = 0.101 ± 0.519 Mean $\pm$ SD EQ-5D at 12 months after stroke: mRS score 0 = 0.961 ± 0.118 mRS score 1 = 0.832 ± 0.178 mRS score 2 = 0.684 ± 0.190 mRS score 3 = 0.547 ± 0.275 mRS score 4 = 0.323 ± 0.277 mRS score 5 = -0.069 ± 0.137	NR	Stroke

First author, year	Country, recruitment and study type	Interventions	Population tariff used	Respondent population and sample size	Absolute utility values	Relative utility values	Events reported
					Mean $\pm$ SD EQ-5D at 24 months after stroke: mRS score 0 = 0.959 ± 0.074 mRS score 1 = 0.812 ± 0.181 mRS score 2 = 0.656 ± 0.218 mRS score 3 = 0.545 ± 0.277 mRS score 4 = 0.248 ± 0.281 mRS score 5 = 0.020 ± 0.046 Mean $\pm$ SD EQ-5D after stroke (total follow-up): mRS score 0 = 0.936 ± 0.127 mRS score 1 = 0.817 ± 0.183 mRS score 2 = 0.681 ± 0.211 mRS score 3 = 0.558 ± 0.284 mRS score 4 = 0.265 ± 0.294 mRS score 5 = -0.054 ± 0.264		
Ryan, 2006 ¹⁹⁵	Country: UK Recruitment: Consecutive patients aged 65 or over recovering from stroke or hip fracture and not suffering from a concomitant disease (e.g. Parkinson's disease or dementia) were	Intensive vs. non-intensive rehabilitation following stroke or hip fracture	NR	Population: Post-stroke Sample size: N = 89 Age: Total population = 78.6; stroke less intensive = 77.3 (6.4 SD); stroke intensive = 76.4 (6.1 SD)	Median (IQR) EQ-5D for patients with stroke: Non-intensive intervention: At baseline = 0.52 (0.26–0.75) At 3 months = 0.54 (0.26–0.73) Intensive intervention: At baseline: 0.56 (0.28–0.72) At 3 months: 0.71 (0.59–0.81)	Mean change score (SD) for patients with stroke from baseline to follow-up at 3 months: Non-intensive intervention : 0 (0.25) Intensive intervention: 0.14 (0.25)	Stroke

First author, year	Country, recruitment and study type	Interventions	Population tariff used	Respondent population and sample size	Absolute utility values	Relative utility values	Events reported
	contacted by the research team within 5 working days of discharge from hospital Study type: RCT						
Stafford, 2012 ¹⁹⁶	Country: UK Recruitment: Data from the Health Survey for England from 2003 and 2006 Study type: Cross-sectional survey	NR	UK tariffs Dolan et al., 1996	Population: Non-institutionalised persons in the UK Sample size: N = 26,104 % of patients with the following conditions: Angina: 3% Heart attack: 2.3% Stroke: 1.8% % by age group (years): 16-24: 13.9 25-34: 16.8 35-44: 20.0 45-54: 16.4 55-64: 14.8 65-74: 10.2 ≥ 75: 8.0 % female: 49.8	Age-adjusted mean (95% CI) EQ-5D for the following conditions: Angina: 0.711 (0.659 to 0.763) Heart attack: 0.636 (0.602 to 0.669) Stroke: 0.680 (0.619 to 0.741)	Mean (SE) difference EQ-5D considering this condition alone (ignoring comorbidity): Angina: -0.141 (0.011) Heart attack: -0.139 (0.013) Stroke: -0.160 (0.015) Mean (SE) difference EQ-5D considering all predisposing conditions together (predisposing conditions included BMI ≥ 30 kg/m ² , hypertension, diabetes, angina, heart attack, and stroke): Angina: -0.090 (0.012) Heart attack: -0.060 (0.014) Stroke: -0.101 (0.015)	Stroke, MI, angina

First author, year	Country, recruitment and study type	Interventions	Population tariff used	Respondent population and sample size	Absolute utility values	Relative utility values	Events reported
Whynes, 2013 ¹⁹⁷	Country: Multinational (16 countries) Recruitment: Regression analysis on DIF within EQ-5D instrument using data from the ENOS trial	N/A	UK	Population: Patients around 90-days post-stroke Sample size: N = 1,462	EQ-5D around 90 days post-stroke: 0.53 (0.37)	NR	Stroke
Whynes, 2013 ¹⁹⁸	Country: UK Recruitment: Pooled records of 4 controlled clinical trials including men and women with several conditions. Study type: Regression analysis (data pooled from several controlled clinical trials, one for stroke – see Additional Notes)	N/A	UK	Population: Patients in recovery following a stroke event Sample size: N = 655; Mean age: 69.9 (11.4) years	EQ-5D for approximately 3 months post-stroke: 0.571 (0.545 to 0.596)	NR	Stroke
BMI, body mass index; CI, confidence interval; EQ-5D, 5-dimension European Quality of Life questionnaire; HF, heart failure; HRQoL, health-related quality of life; IQR, interquartile range; MI, myocardial infarction; N/A, not applicable; NR, not reported; nSTEMI, non-ST-segment elevation myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; RCT, randomised controlled trial; SD, standard deviation; SE, standard error; TIA, transient ischaemic attack; WHO, World Health Organization							

The relevance of considered health states and the consistency with the NICE reference case of the extracted studies was assessed. All studies were given a rating based on whether the health states of interest were reported and whether the utility elicitation method is in agreement with the preferred NICE reference case (EQ-5D elicited from patients or caregivers in a clinical trial using UK tariffs). Further details of the study assessment and the assessment tables are available in Appendix XIII.

HRQoL data used in cost-effectiveness analysis

For this appraisal HRQoL measures that are mostly in agreement with the utility values used in the NICE CG181 were used, as those values have been deemed robust and suitable for a UK assessment of lipid-lowering therapy. Most of the utilities presented in CG181 were identified following a systematic review conducted by Ward in 2005.¹⁶⁷ The utilities are derived from various published sources in which the HRQoL measures were mainly patient-reported, using the EQ-5D questionnaire, and collected in the UK. Nineteen of the papers identified in the HRQoL SLR described above provided utility data that were reported directly or indirectly (cited through other secondary sources) in the NICE CG181 on lipid modification.

A minor adjustment was made to the utilities used in CG181 in order to reflect the health states in the current model. In the model, an 'ACS' health state is used, which combines patients with MI or UA. The utility multipliers used for acute MI and UA were 0.760 and 0.770, respectively. An assumption regarding the utility of patients in acute ACS was made by applying the higher estimate (0.770). For 'post-MI' and 'post-UA', the utility multipliers were both 0.880; therefore no adjustment was made for the 'post-ACS' health state. For the 'ECVD' health state which encompasses a number of prior CV events (excluding ACS, IS and HF), the utility multiplier for ACS was selected. The estimate was selected since it provides greater face validity for the 'ECVD' health state. The utility multiplier for stable angina (acute and post are both 0.808) is lower than that of post-MI (0.880) and post-unstable angina (0.880) which would not be expected since these events are more severe than stable angina. The utility multipliers for the health states included in the model are presented in Table 5-17.

Table 5-17 Utility multipliers of health states

State	Mean utility value (SE)	95% CI (lower bound)	95% CI (upper bound)	Justification
No CVD	1	-	-	NICE 2014
ECVD	0.8800 (0.018)	0.8447	0.9153	NICE 2014 ^a
First year: ACS (UA/MI)	0.7700 (0.018)	0.7347	0.8053	NICE 2014 ^b
First year: IS	0.6280 (0.040)	0.5496	0.7064	NICE 2014
First year: HF	0.6830 (0.020)	0.6438	0.7222	NICE 2014
Subsequent years: ACS (UA/MI)	0.8800 (0.018)	0.8447	0.9153	NICE 2014
Subsequent years: IS	0.6280 (0.040)	0.5496	0.7064	NICE 2014
Subsequent years: HF	0.6830 (0.020)	0.6438	0.7222	NICE 2014
CVD death	0	-	-	NICE 2014
Non-CVD death	0	-	-	NICE 2014
^a Assumed ACS subsequent years utility multiplier for ECVD. ^b Assumed UA first year utility multiplier for ACS first year. ACS, acute coronary syndrome; CI, confidence interval; CVD, cardiovascular disease; ECVD, established CVD; HF, heart failure; IS, ischaemic stroke; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; SE, standard error; UA, unstable angina				

Although the utility multipliers presented in Table 5-17 are sourced from different studies, conducted in different settings, they are assumed to be the best available figures available at this time, as such they have been considered suitable estimates to inform the economic evaluation within the recent NICE CG (CG181).⁷⁷

In line with the approach in NICE CG181,⁷⁷ which referred to the methods applied by Ward,¹⁶⁷ the baseline utilities have been corrected for age. In her methods, Ward analysed data from Kind et al. 1998¹⁹⁹ and found a uniform linear relationship between age and utility. Ward estimated the utility at 40 years to be 0.890 and that this declined by 0.00425 per year to 0.635 at the age of 100 years. Furthermore (as applied in NICE CG181) the age-adjusted baseline utilities were multiplied by health state utility multipliers throughout the model for this submission.

Ezetimibe is an oral agent, administered daily, while evolocumab is a subcutaneously injectable drug (patients use a prefilled pen that auto-injects the drug when pressed). It is assumed that there is no difference in disutility between patients receiving ezetimibe and evolocumab, since evolocumab only needs to be administered once every 2 weeks or monthly, instead of daily, which is the case for ezetimibe. The prefilled pen offers an appropriate way of administering the drug with minimal effort. As such, no disutilities associated with treatment administration are included in the model.

5.5 *Cost and healthcare resource use identification, measurement, and valuation*

Resource identification, measurement, and valuation studies

To identify direct cost estimates for the treatment of specific CV events, a SLR of existing peer-reviewed journal articles and conference posters/abstracts (i.e. published studies only) was conducted. Cost-effectiveness studies, randomised controlled trials, and prospective and retrospective data analyses formed the basis of this search. Eligible studies provided patient-level direct cost estimates (either short- or long-term, from acute hospitalisation through lifetime costs) for the treatment of one or more CV events of interest (unstable angina, ACS, MI, HF, ischaemic stroke, myocardial revascularisation [PCI/CABG]). Only cost studies specific to care of patients with identified dyslipidaemia or elevated LDL-C in 13 European countries (the UK, Germany, France, Italy, Spain, Norway, Denmark, Finland, Iceland, Sweden, Belgium, Switzerland, and Netherlands) were selected. Based on previous research and prior literature reviews on the cost of CV events, it was anticipated that eligible studies would report cost estimates in a number of patient subpopulations (e.g. patients with diabetes, prior history of CV event, or more than one CV event). Due to anticipated breadth of literature, the SLR was focused on direct medical costs only. The SLR focussed on studies published between 1 January 2000 and 31 March 2015 in the English language. Indirect and population-level costs were not considered.

The databases MEDLINE, Embase, and Econlit were searched for studies reporting on the cost of CV events through the OVID interface. The NHS EED database was searched through the University of York CRD website. The searches were conducted on 31 March 2015.

The search strategy used was formulated using terms focussing on (i) the dyslipidaemic population, (ii) CV conditions, and (iii) economic studies. Medical Subject Headings, Emtree headings and text words used were queried based on a modified version of the filters utilized in evidence summaries of NICE CG181.⁷⁷ Modifications to the NICE CG181 filters were made to ensure that studies of CV events not relevant to the current model – ineligible event (e.g. haemorrhagic stroke, peripheral arterial disease) would likely be excluded from the search results. Animal studies, case studies, pilot studies, editorials, letters, and comments were excluded for all searches. The search syntax used for the database searches are presented in Appendix XIV.

To identify more recently completed research that has yet to be published, a targeted search was conducted for relevant conference abstracts from the ISPOR, AHA, ACC, ESC, and EAS conferences during 2013 and 2014. All conferences were indexed through the OVID interface. For details of the search strategy for the selected conferences, please see Appendix XIV.

After the studies were identified and obtained from the databases, and the conference abstract search, a three-stage screening procedure was applied to collect relevant studies based on the inclusion and exclusion criteria outlined in Table 5-18. Duplicate records identified in the search were removed prior to application of the inclusion/exclusion process

at stage 1. In the first stage, abstracts of the obtained publications from the literature search strategy were manually reviewed and studies were included if the abstract met the inclusion criteria. Titles without an abstract were excluded from the selection process.

All papers included during abstract screening (stage 1) were reviewed in full text (stage 2) against the inclusion and exclusion criteria, as presented in Table 5-18. The articles were only included if they met all of the inclusion criteria and none of the exclusion criteria. The specific reason for exclusion was recorded for each excluded full-text article. Cost estimates from cost-effectiveness studies were reviewed for inclusion and, if relevant, the primary source of the cost estimate was extracted. Both the abstract and full-text review were conducted by two independent reviewers. Any disagreements were adjudicated by discussion.

No specific HTA search was conducted. HTA documents that met the search criteria and were identified in the database search results were retrieved, but not extracted unless the document included a *de novo* economic model or primary cost data. Reference sections of HTA documents and of the NICE CG181 were hand searched for original cost source data fitting within the identified time frame. All other review articles were excluded from review. Published studies considered eligible after full-text review proceeded to data extraction (stage 3).

Study data were extracted by one researcher. A random sample (30%) of extractions was reviewed by a second reviewer to assess each entry for completeness and standardisation.

Table 5-18 Eligibility criteria used in the cost and resource use SLR

Domain	Criteria for inclusion	Criteria for exclusion	Rationale/comments
Population	• Human adults (≥ 18 years) with identified dyslipidaemia or elevated LDL-C	• Children (< 18 years) • Animals • Hypertensive patients without specified co-occurring dyslipidaemia • Diabetic patients without specified co-occurring dyslipidaemia	Based on previous research and prior literature review on cost of CVEs, it is anticipated that eligible studies will report cost estimates in a number of patient subpopulations (e.g. patients with diabetes, patients with prior history of CVE, patients with more than one CVE)
Intervention	• Primary or secondary prevention of cardiovascular events	• Primary prevention interventions not aimed at lowering cholesterol (e.g. smoking cessation) • Diagnostics or imaging • Telehealth or remote health • Provider or patient education • Sedation or antibiotics • Transplantation	
Therapeutic Area/ Conditions of Interest	• Unstable angina • Myocardial infarction • Acute coronary syndrome • Heart failure • Ischaemic stroke • Myocardial revascularisation (PCI/CABG)	• Congenital heart conditions • Traumatic brain injuries • Brain aneurysms • Atrial fibrillation • Peripheral arterial disease • Haemorrhagic stroke or TIA • Studies that report costs on broad categories: “cardiovascular disease”, “ischaemic disease”, and “coronary heart disease”	
Outcomes	• Direct medical costs (modelled or primary) of one or more CVE conditions	• Indirect medical costs (e.g. absenteeism, disability, caregiver burden) • Population-level costs	
Study Design	• Burden of disease analyses • Economic substudies of	• Case studies • Pilot studies • Disease management	

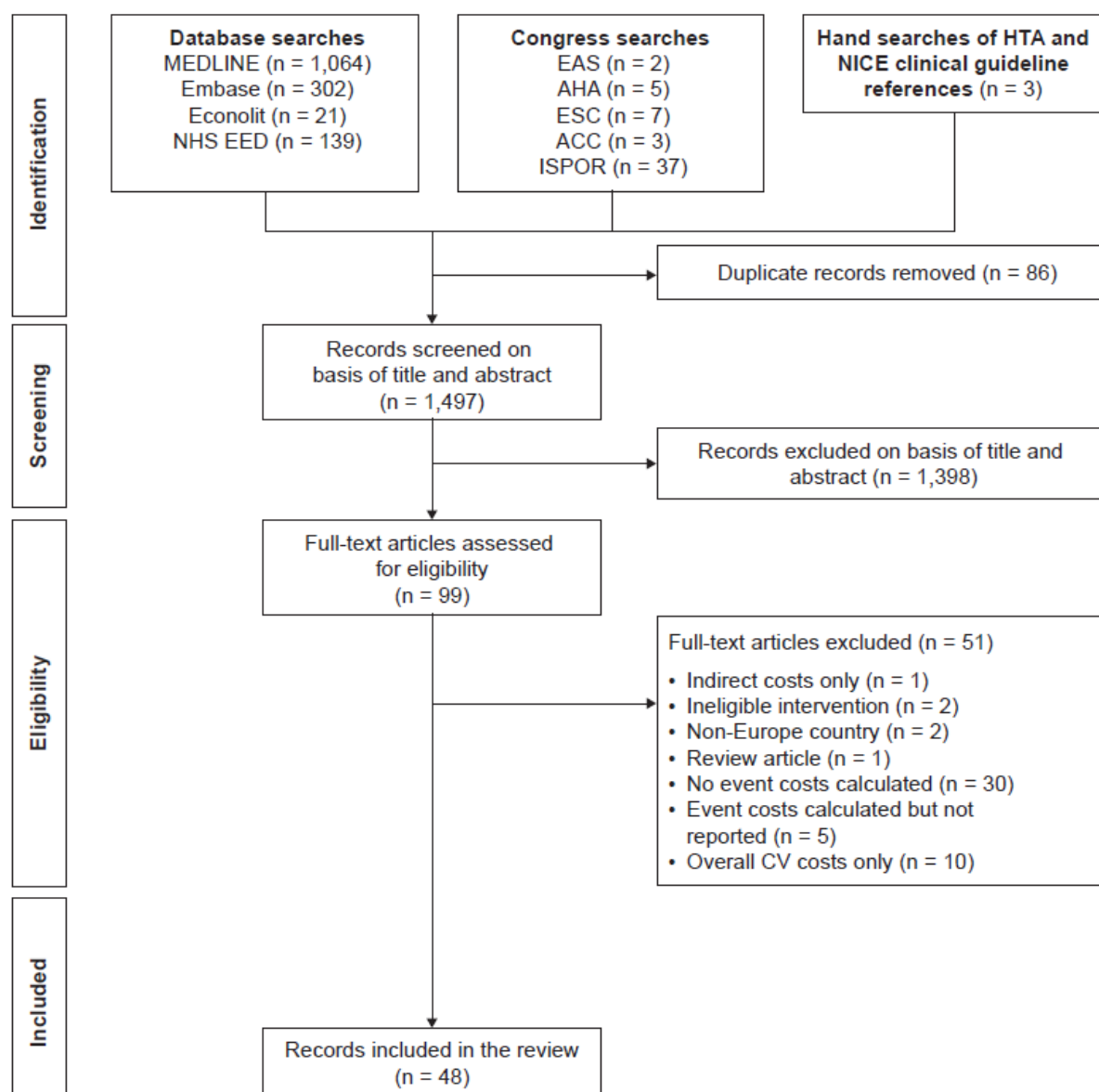
	- controlled trials • Cohort studies • Cost-effectiveness studies • Randomized controlled trials • Prospective or retrospective observational studies • Systematic reviews, meta-analyses, and economic evaluations (for hand searching primary articles) • Conference proceedings	- studies • Screening or monitoring trials • Systematic or non-systematic reviews • Editorials • Letters • Comments	
Language restrictions	• English language	• Non-English language	
Country restrictions	• UK, Germany, France, Italy, Spain, Denmark, Finland, Iceland, Norway, Sweden, Belgium, Switzerland, Netherlands	• Countries with cost estimates not specific to the UK, Germany, France, Italy, Spain, Denmark, Finland, Iceland, Norway, Sweden, Belgium, Switzerland, Netherlands	
Date restrictions	• Database search: 01 January 2000 to 31 March 2015 • Conference proceedings: 01 January 2013 to 31 December 2014	• Database search: published before 2000 • Conference proceedings: published before 2013	
CABG, coronary artery bypass graft; cardiovascular event; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; SLR, systematic literature review			

The database literature search (in MEDLINE, Embase, Econlit and NHS EED), conference proceedings (in EAS, AHA, ESC, ACC, and ISPOR) and hand search of HTA and NICE CG references identified 1583 potentially relevant citation results. Of these, 86 articles were duplicates and subsequently removed from the review for a total of 1497 unique articles that could proceed to phase stage 1 of the inclusion/exclusion process. A list of the duplicate studies can be found in Appendix XIV. Of the unique articles, 1398 were excluded after a review of titles/abstracts (stage 1).

After full-text review, during which a further 51 studies were excluded, a total of 48 studies from the database search were included for data extraction. A full list of the 51 excluded studies in the full-text review can be found in Appendix XIV.

The PRISMA flow chart of the inclusion and exclusion of the cost and resource use studies from the database search is presented in Figure 5-10.

Figure 5-10 PRISMA flow diagram for costs and resources SLR from the database search



ACC, American College of Cardiology; AHA, American Heart Association; CV, cardiovascular; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; HTA, Health Technology Assessment; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; NHS EED, National Health Service Economic Evaluations Database; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review

An overview of the countries from which the 48 included studies report cost data is presented in Table 5-19. Studies evaluating costs in the UK comprised the majority of the studies (15 studies on unstable angina, 21 on MI, 10 on HF, 19 on ischaemic stroke, 4 on ACS, and 11 on cardiovascular revascularisation).

Table 5-19 Summary of represented countries in cardiovascular event studies

Country	UA	MI	HF	IS	ACS	Revasc
Belgium	2	2	1	3	2	1
Denmark	-	1	-	-	-	-
Finland	1	3	1	1	1	-
France	2	2	3	3	2	1
Germany	4	4	2	2	-	2
Italy	2	2	2	2	3	1
Netherlands	1	2	-	-	-	1
Norway	1	2	-	-	-	-
Spain	5	4	4	4	-	4
Sweden	3	6	-	6	-	3
Switzerland	-	1	-	1	-	1
UK	15	21	10	19	4	11
Note: A single article may report on more than one country population.						
ACS, acute coronary syndrome; HF, heart failure; IS, ischaemic stroke; MI, myocardial infarction; Revasc, revascularisation; UA, unstable angina						

A full list of studies reporting relevant costs and the main items included during data extraction are presented in Appendix XIV.

Cost summary data extraction tables.

Table 5-20 highlights the data extracted from the cost studies with a UK focus. Studies included in the table present costs from the past 10 years in order to ensure the data are still relevant. For the full data extraction table see Appendix XIV.

Table 5-20 Cost summary data extraction of UK studies, presenting a Markov model with a lifetime time horizon

Study	Study design	Intervention	Source for costing data	Cost type	Currency (source data) year
Ara 2008 ¹³⁴	CE model	Ezetimibe monotherapy vs. no treatment for patients with statin intolerance	Angina/MI: Ward 2007 HTA ⁵ report; 2004 glycoprotein HTA report; Stroke: Youman 2003 ⁶	Annual	2006 (2004)
Ara 2008 ¹³⁵	CE model	Ezetimibe + statin vs. statin alone	Angina/MI: Ward 2007 HTA ⁵ report; 2004 glycoprotein HTA report; Stroke: Youman 2003 ⁶	Annual	2006 (2004)
Ara 2009 ²⁰⁰	CE Model	HTA assessment of statin therapies in prevention of CV events in ACS patients	HRG costs for angina/MI/revascularisation; Stroke: Youman 2003 ⁶	Annual	2007 (2003-2007)
Ara 2012 ¹³³	CE model	Atorvastatin vs. rosuvastatin vs. simvastatin in ACS patients	Ara 2008 ezetimibe/statin CE model, based on 2004 data	Annual	2007 (2004)
Barton 2011 ¹⁴⁹	CE model	Lipid-lowering therapy, blood-pressure lowering therapy, dietary interventions	Not clearly cited by author	Annual	2008
McConnachie 2014 ²⁰¹	CE model	Pravastatin vs. placebo	Acute costs: NHS HRG codes; Follow-up based on Ward 2007 ¹⁴² HTA inflated to 2011	Follow-up	2011 (2007-2011)

Nherera 2010 ¹³⁹	CE model	High and low-intensity statins in treatment of FH	NHS reference costs, NICE clinical guideline and NICE statin TA94	Annual	2008-2009
NICE 2014 ²⁰²	CE model	Statin therapies for primary and secondary prevention of CV events	NHS reference costs	Annual	2014 (2012-2014)
Reckless 2010 ¹⁴⁰	CE model	Ezetimibe/statin vs. statin alone	NICE technical report and assumption	Annual	2009 (2002-2004)
Roze 2007 ²⁰³	CE model	Statin + nicotinic acid vs. statin alone	Previous CE models based on 1998 Nottingham Attack Register resource use	Annual	2005 (1998)
ACS, acute coronary syndrome; CE, cost-effectiveness; CV, cardiovascular; FH, familial hypercholesterolaemia; HRG, Healthcare Resource Group; HTA, Health Technology Assessment; MI, myocardial infarction; NHS, National Health Service; NICE, National Institute for Health and Care Excellence					

The quality of the extracted publications was assessed by one reviewer using the Cochrane instrument for randomised trials, a modified Newcastle-Ottawa scale for case-control and cohort studies, the ISPOR checklist for retrospective database analyses, and the Drummond-Jefferson checklist for economic evaluations and cost-effectiveness studies. A second reviewer reassessed study quality for a sample (30%) of extracted studies to ensure accurate bias assessment. Disagreements were adjudicated by discussion.

Intervention and comparators' drug acquisition costs and resource use

Drug acquisition costs

Drug acquisition costs were obtained from the NHS Drug Tariff for ezetimibe and statins.²⁰⁴ Atorvastatin 20 mg and 80 mg daily was selected as the high-intensity statin in accordance with recommendations from CG181⁷⁷ for primary and secondary prevention, respectively. Atorvastatin 80 mg daily was assumed as the statin for the management of patients with HeFH. As presented in Section 2, evolocumab is self-administered as a subcutaneous injection of 140 mg Q2W or 420 mg QM. The evolocumab drug acquisition is £170.10 per 140 mg prefilled pen or syringe. Assuming a continuous treatment course, the annual cost per patient year is £4,422.60 for 140 mg Q2W in the model base case. Scenario analysis including the 420 mg QM dosing is presented. The annual drug acquisition cost for ezetimibe is £342.97 (10 mg daily) and the annual drug acquisition cost for atorvastatin 20 mg and 80 mg is £18.38 (20 mg daily) and £35.33 (80 mg daily), respectively. The impact of alternative costs of statins is assessed in univariate sensitivity analysis. Table 5-21 summarises the drug acquisition costs in the model.

Table 5-21 Unit costs associated with the technology in the economic model

Medicine	Formulation	Dosing description	Cost per pack	Units per pack	Doses per year	Annual cost
Evolocumab	140 mg PFP	140 mg Q2W	£340.20	2	26	£4,422.60
	140 mg PFP	420 mg QM	£340.20	2	36	£6,123.60
Ezetimibe	10 mg tablet	10 mg daily	£26.31	28	365	£342.97
Atorvastatin	20 mg tablet	20 mg daily	£1.41	28	365	£18.38
	80 mg tablet	80 mg daily	£2.71	28	365	£35.33
PFP, prefilled pen; Q2W, every 2 weeks; QM, monthly; SC, subcutaneous.						

Patients receiving evolocumab will receive training for self-administration by a nurse at treatment initiation. In the model, it is assumed that patients receive 1 hour of nurse training, which is included as a one-off cost at the start of the first year. The cost of training is £84.00 based on the per hour cost for a nurse (day ward, including staff nurse) derived from the Personal Social Services Research Unit 2014.²⁰⁵

Monitoring

No additional monitoring is required for patients receiving evolocumab over and above those which are part of routine clinical practice (Section 2.4). Since evolocumab is anticipated to be initiated in secondary care (e.g. specialist lipid clinics), it has been assumed that patients

will require an initial appointment for initiation and a subsequent follow-up in the lipid clinic to assess treatment efficacy and tolerability (two appointments in first year). Thereafter, it is assumed patients are discharged to primary care for ongoing care (one appointment in first year). Therefore the monitoring costs associated with tests and appointments following discharge have been included based on assumptions made by the Guideline Development Group for CG181.²⁰² Costs for activity are based on Personal Social Services Research Unit (PSSRU) and NHS Reference Costs.^{205,206} These are considered with regards first year and subsequent years (Table 5-22). Therefore the annual monitoring costs for the first year and subsequent years are £238.72 and £101.08, respectively.

Table 5-22 Monitoring resource use and costs

Activity	Healthcare resource use		Unit cost	Source
	Year 1	Year 2+		
Lipid clinic	2	0	£87.77	NHS Reference Costs 2013/14 (Chemical pathology CLOA [822])
GP appointment	1	2	£45.00	PSSRU 2013
HCA appointment	1	1	£6.46	PSSRU 2013
Blood tests				
Total cholesterol	3	2	£1.18	NHS Reference Costs (DAPS04)
HDL cholesterol	3	1	£1.18	NHS Reference Costs (DAPS04)
LFT	2	1	£1.18	NHS Reference Costs (DAPS04)
HbA _{1c} test	1	1	£1.18	NHS Reference Costs (DAPS04)
Total cost for monitoring in year 1: £238.72				
Total cost for monitoring in subsequent years: £101.08				
CLOA, consultant led outpatient appointment; GP, general practitioner; HbA _{1c} , haemoglobin A _{1c} ; HCA, healthcare assistant; HDL, high-density lipoprotein; LFT, liver function test; NHS, National Health Service; PSSRU, Personal Social Services Research Unit				

Health state unit costs and resource use

The health state unit costs as presented in CG181⁷⁷ are the most recently published cost estimates for CV events in the UK. The health state costs used in CG181 are based on expert opinion from the Guideline Development Group with regards resource use. Since these costs are based on expert opinion, additional evidence generation was undertaken through a retrospective longitudinal observational cohort study⁴⁴ (using CPRD and HES data) to estimate acute and long-term health care resource use and costs for first and subsequent CV events (Appendix XV). CV events were defined as hospitalisations with a primary diagnosis code for UA, MI, IS, HF or TIA, or hospitalisations that included CABG or percutaneous transluminal coronary angioplasty, based on ICD-10-CM codes. Since subsequent CV events could be related to the initial CV event, all CV events within 30 days of the initial event were identified and treated as a single event. When there were multiple events within 30 days, the event that was highest in the following hierarchy was used to classify the event: MI, UA, IS, CABG, PTCA, HF, TIA. This process was followed for the first CV event as well as the subsequent CV events, which, by definition, had to occur more than 30 days after the first event. See Appendix XV for a list of the specific codes used and

additional details regarding the process of attributing events within 30 days of the initial event.

Between January 2006 and March 2012, the study followed a cohort of 24,093 patients (≥ 18 years), who were hospitalised for their first CV event, had received at least two prescriptions for lipid-lowering therapy (statins, ezetimibe, fibrates, nicotinic acid, or bile acid sequestrants) in the 180 days prior to the event and for whom at least 12 months of data prior to the index date and 30 days afterward were available from both the CPRD and HES, to estimate the direct medical resource use before and after CV events, and hence be able to calculate incremental cost associated with CV events.⁴⁴

Patients were divided into two cohorts based on diagnosis of conditions (diabetes, peripheral arterial disease, ischaemic heart disease (excluding MI or UA), or angina pectoris) (cohort 1: CV high risk, N = 17,685) or absence of those conditions (cohort 2: low risk, N = 6408). In addition, patients from both cohorts experiencing a second CV event were included in a third, separate cohort (cohort 3: CV event history). Therefore, patients were included in two cohorts if they experienced a second event (N = 5274).

Patients were followed from the date of the first CV event until 31 March 2012 or until a subsequent CV event, death, or loss to follow-up, whichever occurred first. The average duration of follow-up for all patients was 81 months (6.75 years). The mean age at the time of CV event was 72.7 years, and the proportion of men ranged from 56% in the CV low-risk cohort to 60% in the CV high-risk cohort.

CV event-related costs were estimated by attributing unit costs to the identified resource use for each individual patient during the baseline (12 months prior to an event), acute (6 months after an event), and long-term (subsequent 30 months) periods. Intervals were selected to align with timeframes estimated in the economic evaluation in NICE CG181.⁷⁷ A pre-post design was implemented to correct event costs for confounding costs associated with other underlying chronic diseases. The long-term costs were corrected for the mean follow-up time and converted to annualised costs for use in the cost-effectiveness analysis.

Resource use in the study included healthcare visits to general practitioners, referrals to specialists (as reported in CPRD), CV and non-CV hospitalisations (intensive care unit, cardiovascular ward/clinic, general ward, surgical procedures, and emergency room visits, all as reported by HES), and prescriptions for medications (including lipid-lowering therapy, antihypertensive therapy, antithrombotic therapy, and anti-diabetic therapy).

Unit costs were taken from UK NHS price lists; PSSRU Unit Costs of Health & Social Care for costs of services provided in the community.²⁰⁵ Costs for outpatient referrals were assigned using NHS Reference Costs (2013/2014)²⁰⁶ according to speciality type. Costs for hospitalisations were based on Healthcare Resource Group reference costs. All hospitalisations in the HES data were assigned a cost using the 2013/2014 Healthcare Resource Group 4+ Reference Costs Grouper software. The costs of drugs administered for events were taken from the NHS Drug Tariff. Generic prices were used where available.

CV event costs summary

CV event costs were estimated for the acute and long-term periods per CV event type. For comparison, the mean 6-month (acute) CV event costs and annual event costs for the long-term period from the CPRD study and NICE CG181²⁰² are presented in Table 5-23. For CPRD study derived CV costs, drug costs (lipid-lowering therapy, antihypertensive therapy, antithrombotic therapy, and anti-diabetic) were excluded from the CV event costing to prevent double counting. For NICE CG181, the CV event costs were based on expert opinion from the Guideline Development Group (GDG) regarding the resource use associated with each CV event. The NICE CG181 cost estimates have been updated with the current NHS Reference Costs (2013/14)²⁰⁶ whilst maintaining the GDG assumptions regarding healthcare resource use for each CV event. To adjust to the 1-year cycle length for acute CV event costs, a combined first year cost was estimated from the acute period cost and 6 months of the long-term period cost for use in the model.

Table 5-23 CV event costs for acute and long-term period from the CPRD study

CV Event	CPRD Study			NICE CG181		
	Acute event cost (6 months)	Acute event cost (annual)	Long-term cost	Acute event cost (6 months)	Acute event cost (annual)	Long-term cost
Myocardial infarction	██████	██████	██████	£2,856.15	£3,251.13	£789.95
Unstable angina	██████	██████	██████	£2,832.71	£3,025.05	£384.68
ACS	██████	██████	██████	£2,841.76 ^b	£3,104.61 ^b	£525.71 ^b
TIA	██████	██████	██████	£580.70	£642.51	£123.62
Ischaemic stroke	██████	██████	██████	£4,516.62	£4,234.30	£155.35
Heart failure	██████	██████	██████	£2,426.48	£3,799.49	£2,746.00
Revascularisation	██████	██████	██████	Health state dependent	Health state dependent	N/A
Ischaemic stroke death	██████	██████	██████	£1,197.55	N/A	N/A
CHD death	██████	██████	██████	£1,197.55	N/A	N/A
^a ACS health state costs based on aggregation of myocardial infarction and unstable angina from CPRD. ^b ACS health state costs calculated based on proportions observed from CPRD study. ACS, acute coronary syndrome; CHD, coronary heart disease; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; NICE, National Institute for Health and Care Excellence; TIA, transient ischaemic attack						

ACS, UA and MI events

The model includes an 'ACS' health state (UA and MI) as opposed to the individual UA and MI health states. The acute and long-term costs for ACS were estimated directly from the CPRD study based on the observed proportions of UA and MI events during these two

periods. These proportions were then used to estimate 'ACS' health state cost for NICE CG181 using the costs for MI and UA.

Revascularisation procedures

The average cost of revascularisation procedures was estimated to be £5648.60 based on the findings of the CPRD study. Application of this cost to the CV health states was done in accordance with the assumptions made by the GDG for NICE CG181.²⁰² This was based on the following assumptions:

- All patients in the 'ACS' health state undergo a revascularisation procedure.
- Ten percent of patients in the 'post-ACS' health state undergo a revascularisation procedure annually.
- The GDG assumed that all patients with stable angina (acute health state) would undergo a revascularisation procedure. Stable angina is a CV condition within the composite 'ECVD' health state of the model. Therefore, since 'ECVD' is considered as a long-term health state, it is assumed that all patients would have already undergone a revascularisation procedure in the secondary prevention population modelling. This assumption is conservative when considered in the primary prevention population based on transitioning from 'No CVD' to 'ECVD'.

CVD death and non-CVD death

The cost of fatal IS and CHD was estimated from the CPRD study to be £717.96 and £1847.92, respectively. NICE CG181 based costs are estimated to be £1197.55.

5.6 *Summary of base case de novo analysis inputs and assumptions*

Summary of base case *de novo* analysis inputs

The input values used in the base case analysis are presented in Table 5-24. The input variables are separated into different categories for ease of reading and are presented with their 95% CIs.

For the combined health states, a conservative approach is taken whereby the event costs are assumed to equal the highest cost of the individual events and the event utility is assumed to equal to the lowest utility of the individual events, as explained in detail in Section 5.2. Therefore, for ease of presentation, costs and utilities associated with combined health states are not presented in Table 5-24.

Table 5-24 Summary of deterministic variables applied in the economic model

Category	Variable	Value (reference to appropriate table or figure in submission)	Lower 95% CI	Upper 95% CI	Reference to section in submission
Annual treatment cost	Evolocumab Q2W PFP	£4,448.60	-	-	5.5
	Evolocumab QM PFP	£6,123.60	-	-	5.5
	Ezetimibe	£342.97	-	-	5.5
	Atorvastatin 80 mg	£35.33	-	-	5.5
	Atorvastatin 20 mg	£18.38	-	-	5.5
Training	Self-administration training (1 hour)	£84.00	-	-	5.5
Monitoring	First year	£238.72	-	-	5.5
	Subsequent years	£101.08	-	-	5.5
Health state costs	No CVD	£0	-	-	5.5
	ECVD	████████	████████	████████	5.5
	ACS (year 1)	████████	████████	████████	5.5
	IS (year 1)	████████	████████	████████	5.5
	HF (year 1)	████████	████████	████████	5.5
	Post-ACS	████████	████████	████████	5.5
	Post-IS	████████	████████	████████	5.5
	Post-HF	████████	████████	████████	5.5
	CHD death	████████	████████	████████	5.5
	Stroke death	████████	████████	████████	5.5
	Revascularisation	████████	████████	████████	5.5
	Non-CVD death	£0	-	-	5.5
Utility multiplier	No CVD	1.0000	-	-	5.4
	Established CVD	0.8800	0.8447	0.9153	5.4
	ACS (year 1)	0.7700	0.7347	0.8053	5.4
	IS (year 1)	0.6280	0.5496	0.7064	5.4
	HF (year 1)	0.6830	0.6438	0.7222	5.4
	Post-ACS	0.8800	0.8447	0.9153	5.4
	Post-IS	0.6280	0.5496	0.7064	5.4
	Post-HF	0.6830	0.6438	0.7222	5.4
	CHD death	0.0000	-	-	5.4
	Stroke death	0.0000	-	-	5.4
	Non-CVD death	0.0000	-	-	5.4
Relative reduction LDL-C	Evolocumab Q2W	0.7177	0.6885	0.7469	5.3
	Evolocumab Q2W SI	0.5710	0.5336	0.6084	5.3
	Evolocumab QM	0.6912	0.6476	0.7349	5.3
	Evolocumab QM SI	0.5582	0.5276	0.5888	5.3

Category	Variable	Value (reference to appropriate table or figure in submission)	Lower 95% CI	Upper 95% CI	Reference to section in submission
	Ezetimibe	0.2656	0.2242	0.3070	5.3
	Ezetimibe SI	0.1783	0.1465	0.2101	5.3
CTTC rate ratio (per mmol/L reduction)	ACS	0.71	0.58	0.87	5.3
	IS	0.69	0.50	0.95	5.3
	HF	0.71	0.58	0.87	5.3
	CHD death	0.80	0.74	0.87	5.3
	Stroke death	1.00	0.77	1.00	5.3
	Revascularisation	0.66	0.60	0.73	5.3
Discount	Cost	0.035	0.000	0.06	5.2
	Outcomes	0.035	0.000	0.06	5.2
Time horizon	Time horizon	To 100 years	5 years	To 100 years	5.2
Treatment duration	Treatment duration	To 100 years	5 years	To 100 years	5.2
Baseline CV rate ratio calibration	Rate ratio calibration for CV events	Yes (see Table 5-8)	Lower bounds	Upper bounds	
Baseline CV rate ratio for HeFH	Rate ratio calibration for HeFH population	7.1	5.7	8.7	
Risk capping age	Risk capping age	85 years	75 years	95 years	
CVD utilities approach	CVD utilities approach	Utility multipliers	Absolute utilities	Utility multipliers	
ACS, acute coronary syndromes; CHD, coronary heart disease; CI, confidence interval; CTTC, Cholesterol Treatment Trialists' Collaboration; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; PFP, prefilled pen; SP, secondary prevention; SI, statin intolerant; Q2W, every 2 weeks; QM, monthly					

The model inputs varied in the probabilistic sensitivity analysis are presented in Table 5-25. This table also presents details of the distribution specified around each parameter for probabilistic sensitivity analysis sampling.

Table 5-25 Summary of the variables applied in the probabilistic sensitivity analysis of the economic model

Category	Variable	Value	Lower 95% CI	Upper 95% CI	Distribution	SE	Alpha	Beta	Mu	Sigma	Reference to section in submission
Cost	Established CVD	██████	██████	██████	Gamma	66.20	62.2573	8.3900	6.2504	0.1262	5.5
	ACS (year 1)	██████	██████	██████	Gamma	56.93	3,286.3928	0.9931	8.0904	0.0174	5.5
	IS (year 1)	██████	██████	██████	Gamma	160.20	643.4234	6.3156	8.3090	0.0394	5.5
	HF (year 1)	██████	██████	██████	Gamma	176.61	323.8655	9.8137	8.0626	0.0555	5.5
	Post-ACS	██████	██████	██████	Gamma	66.20	62.2573	8.3900	6.2504	0.1262	5.5
	Post-IS	██████	██████	██████	Gamma	262.19	11.4535	77.4724	6.7464	0.2893	5.5
	Post-HF	██████	██████	██████	Gamma	301.20	12.8155	84.1369	6.9455	0.2741	5.5
	CHD death	██████	██████	██████	Gamma	20.06	1,280.8429	0.5605	6.5760	0.0279	5.5
	Stroke death	██████	██████	██████	Gamma	72.85	643.4234	2.8720	7.5210	0.0394	5.5
	Revascularisation	██████	██████	██████	Gamma	85.26	4,389.2568	1.2869	8.6390	0.0151	5.5
Utility multiplier	Established CVD	0.9000	0.8500	0.9500	Beta	0.026	123.5633	13.7293	-	-	5.4
	ACS (year 1)	0.7700	0.7347	0.8053	Beta	0.018	420.1158	125.4891	-	-	5.4
	IS (year 1)	0.6280	0.5496	0.7064	Beta	0.040	84.4805	69.2318	-	-	5.4
	HF (year 1)	0.6830	0.6438	0.7222	Beta	0.020	369.0095	171.2680	-	-	5.4
	Post-ACS	0.8800	0.8447	0.9153	Beta	0.018	285.9348	38.9911	-	-	5.4
	Post-IS	0.6280	0.5496	0.7064	Beta	0.040	90.8604	37.7644	-	-	5.4
	Post-HF	0.6830	0.6438	0.7222	Beta	0.020	369.0095	171.2680	-	-	5.4
Relative reduction LDL-C	EvoMab Q2W	0.7177	0.6885	0.7469	Beta	0.0149	654.4119	257.4063	-	-	5.3
	EvoMab Q2W SI	0.5710	0.5336	0.6084	Beta	0.0190	383.5628	288.1759	-	-	5.3
	EvoMab QM	0.6912	0.6476	0.7349	Beta	0.0223	296.7577	132.5793	-	-	5.3

Category	Variable	Value	Lower 95% CI	Upper 95% CI	Distribution	SE	Alpha	Beta	Mu	Sigma	Reference to section in submission
	EvoMab QM SI	0.5582	0.5276	0.5888	Beta	0.0156	564.1950	446.5449	-	-	5.3
	Ezetimibe	0.2656	0.2242	0.3070	Beta	0.0211	115.8483	320.3276	-	-	5.3
	Ezetimibe SI	0.1783	0.1465	0.2101	Beta	0.0247	99.0551	456.4979	-	-	5.3
CTTC rate ratio	ACS	0.71	0.58	0.87	Lognormal	0.1034	-	-	-0.3530	0.1449	5.3
	IS	0.69	0.50	0.95	Lognormal	0.1637	-	-	-0.3985	0.2341	5.3
	HF	0.71	0.58	0.87	Lognormal	0.1034	-	-	-0.3530	0.1449	5.3
	CHD death	0.80	0.74	0.87	Lognormal	0.0413	-	-	-0.2245	0.0516	5.3
	Revascularisation	0.66	0.60	0.73	Lognormal	0.0500	-	-	-0.4184	0.0757	5.3
HeFH	CVD rate ratio	7.10	5.70	8.70	Lognormal	0.1079	-	-	1.9601	0.1079	5.3
ACS, acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval; CTTC, Cholesterol Treatment Trialists' Collaboration; CVD, cardiovascular disease; ECVD, established cardiovascular disease; EvoMab, evolocumab; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; SE, standard error; SI, statin intolerant; Q2W, every 2 weeks; QM, monthly											

Assumptions

A list of assumptions applied in the model is presented in Table 5-26.

Table 5-26 Model assumptions used in defining the cost-effectiveness of evolocumab for LDL-C reduction

	Assumption	Source/rationale
1	Combined health states: The transition probability from a combined health state to an event is defined by the maximum of the individual (ACS, IS or HF) health state transitions to that event.	No current data are available specifying the transition probability from a combined health state. This assumption is conservative with regards the CV risk for patients with a number of prior CV events, compared with those with one prior CV event.
2	Combined health states: The utility of a combined health state is defined by the lowest utility of the individual included health states.	No current data are available specifying these combined health state utilities. This assumption is conservative with regards the utility for patients with a number of prior CV events, compared with those with one prior CV event.
3	Combined health states: The cost for a combined health state is defined by the highest of the costs for the individual health states.	No current data are available specifying these combined health state costs. This assumption is conservative with regards the potential cost for a patient with a number of prior CV events, compared with those with one prior CV event.
4	Non-CVD death costs: Costs for 'Non-CVD death' are assumed to be zero.	These costs are anticipated to be equivalent to those in the general population, therefore no costs have been included.
5	'ACS' state: The ACS health state is a combination of MI and UA, to which the higher utility of UA has been applied.	The utility multipliers used for acute MI and UA were 0.760 and 0.770, respectively. A conservative assumption regarding the utility of patients in acute ACS was made by assuming the higher estimate (0.770). For post-MI and post-UA, the utility multipliers were both 0.880; therefore no adjustment was made for the post-ACS health state.
6	'ECVD' state: Established CVD health state captures less severe CV events, including: TIA, PVD, SA, carotid stenosis, revascularisation in absence of MI, and abdominal aortic aneurism. Patients cannot experience the individual CV events, captured in ECVD, as separate health states.	The rationale for the use of a catch-all health state (ECVD) as an entry state is that data were lacking to inform the current model to this level of granularity.
7	'ECVD' costs: this long term health states comprises minor CVD events which are not incorporated in the CE model as health states, like angina pectoris or transient	No current data are available on the costs for established CVD. Therefore, it was chosen to align these costs with the health state which

	ischemic attack. Costs associated with these minor events are assumed to be equal to costs related to the long term ACS (MI+UA) health state.	it is clinically most equal to (ACS).
8	Revascularisations costs: Revascularisation may involve either PCI or CABG.	Revascularisation costs are based on the distribution between PCI and CABG derived from CPRD, and costs based on NHS reference costs for PCI and CABG.
9	Treatment duration: The patient population receive treatment (for the intervention and comparator arm) continuously over the patient's lifetime.	In accordance with MAs and clinical intent to manage hypercholesterolaemia.
10	LDL-C reduction: The treatment effect is maintained throughout the time horizon in both the intervention and comparator arm.	Long-term extension studies demonstrate maintained LDL-C reductions.
11	Evolocumab self-administration: Patients need an average of one hour of nurse training to be able to self-administer.	A plausible time associated with nurse training for a patient to self-administer using the auto-injector device.
12	Time horizon: It is assumed that lifetime is an age of 100 years.	It is expected to be realistic that all patients have died before or at the age of 100 years.
13	Quality of life: It is assumed that there is no impact of treatment on quality of life.	Evolocumab is self-administered once every 2 weeks or monthly, instead of daily which is the case for ezetimibe.
ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; CPRD, Clinical Practice Research Database; CV, cardiovascular; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; MA, marketing authorisation; MI, myocardial infarction; NHS, National Health Service; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SA, stable angina; SE, standard error; SI, statin intolerant; Q2W, every 2 weeks; QM, monthly; TIA, transient ischaemic attack; UA, unstable angina		

5.7 Base case results

The cost-effectiveness analysis has been conducted for the relevant populations within the decision problem according to the four treatment scenarios. Treatment scenarios for evolocumab and statin versus ezetimibe and statin (scenario 1), and evolocumab alone versus ezetimibe alone (scenario 2) are presented in full in this section. For brevity, the cost-effectiveness analyses for evolocumab and ezetimibe versus ezetimibe alone (scenario 3), and evolocumab, statin, and ezetimibe versus statin and ezetimibe (scenario 4) are presented as scenario analyses (Section 5.11). Summary details of these analyses are provided in Table 5-27.

Table 5-27 Modelled intervention and comparator for patients with and without existing CVD, and patients with HeFH

Pop.	Intervention	Comparator	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Analysis, Section, Tables
Without existing CVD	Evolocumab and statin	Ezetimibe and statin	N/A	N/A	N/A	Analysis A (threshold) according to LDL-C, Table 5-28 and Table 5-29
	Evolocumab alone	Ezetimibe alone	N/A	N/A	N/A	Analysis B (threshold) according to LDL-C, Table 5-30 and Table 5-31
	Evolocumab and ezetimibe	Ezetimibe alone	N/A	N/A	N/A	Not conducted
	Evolocumab, ezetimibe, and statin	Ezetimibe and statin	N/A	N/A	N/A	Not conducted
Existing CVD	Evolocumab and statin	Ezetimibe and statin	■	0.44	■	Analysis C, Table 5-32 to Table 5-36
	Evolocumab alone	Ezetimibe alone	■	0.42	■	Analysis D, Table 5-37 to Table 5-41
	Evolocumab and ezetimibe	Ezetimibe alone	■	0.49	■	Analysis E, Table 5-60
	Evolocumab, ezetimibe, and statin	Ezetimibe and statin	■	0.44	■	Analysis F, Table 5-61
HeFH	Evolocumab and statin	Ezetimibe and statin	■	1.20	■	Analysis G, Table 5-42 to Table 5-46
	Evolocumab alone	Ezetimibe alone	■	1.10	■	Analysis H, Table 5-47 to Table 5-51
	Evolocumab and ezetimibe	Ezetimibe alone	■	1.29	■	Analysis I, Table 5-62
	Evolocumab, ezetimibe, and statin	Ezetimibe and statin	■	1.26	■	Analysis J, Table 5-63
CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SP, secondary prevention						

Additionally step-wise subgroup cost-effectiveness analyses for evolocumab and statin versus ezetimibe and statins (scenario 1) are presented in Section 5.13 for patients with existing CVD at high residual risk due to additional risk factors (based on risk factors described in Section 3 and Table 3-5).

5.8 Without existing CVD

For patients without existing CVD, threshold analyses were conducted for various baseline LDL-C levels (2.5 mmol/L to 4.5 mmol/L) to establish the minimum 10-year CVD risk (measured using a risk assessment tool such as QRISK2) at which treatment with evolocumab in accordance with its MA would be deemed a cost-effectiveness use of NHS resources according to willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained.

Analysis A: Evolocumab and statin versus ezetimibe and statin

Threshold analyses for evolocumab and statin versus ezetimibe and statin presented in Table 5-28 and Table 5-29 indicate the minimum 10-year CVD risk required for defined willingness-to-pay thresholds. A minimum 10-year risk could not be appropriately estimated based on the proposed price of evolocumab for defined willingness-to-pay thresholds.

Table 5-28 Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin)

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
2.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	79%		6.74			
	Evolocumab and statin			8.15		1.41	
4	Ezetimibe and statin	73%		7.40			
	Evolocumab and statin			8.95		1.55	
4.5	Ezetimibe and statin	70%		7.83			
	Evolocumab and statin			9.46		1.63	
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year							

Table 5-29 Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin)

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
2.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4	Ezetimibe and statin	-*	N/A	N/A			

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year							

Analysis B: Evolocumab alone versus ezetimibe alone

Threshold analyses for evolocumab alone versus ezetimibe alone presented in Table 5-30 and Table 5-31 indicate the minimum 10-year CVD risk required for defined willingness-to-pay thresholds.

Table 5-30 Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone)

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
2.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	81%		6.27			
	Evolocumab and statin			7.58		1.31	
4	Ezetimibe and statin	75%		6.90			
	Evolocumab and statin			8.34		1.44	
4.5	Ezetimibe and statin	71%		7.38			
	Evolocumab and statin			8.92		1.54	

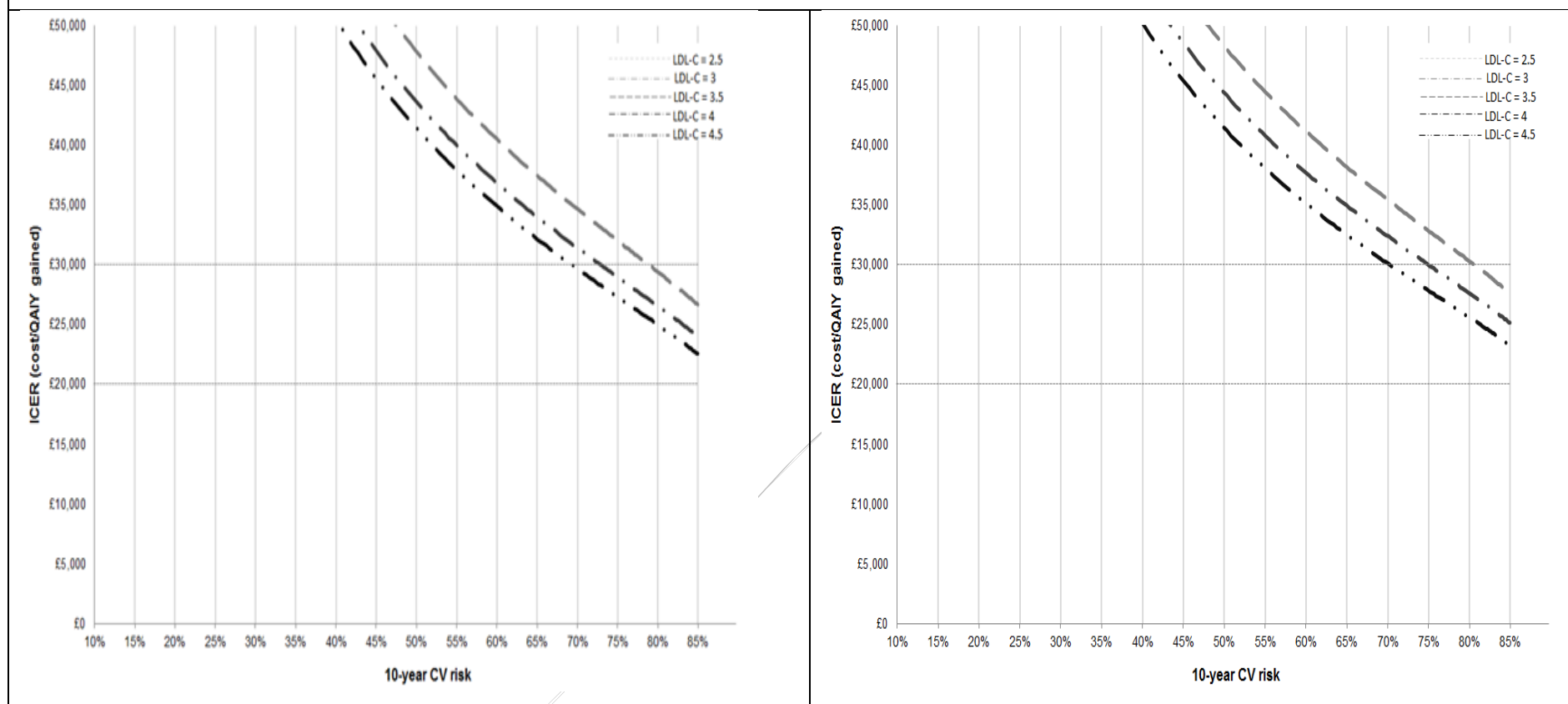
Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year							

Table 5-31 Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone)

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
2.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year							

Threshold analyses for various baseline LDL-C levels (2.5 mmol/L to 4.5mmol/L) for the cost-effectiveness of evolocumab and statin compared with ezetimibe and statin, and evolocumab alone compared with ezetimibe alone are presented in Figure 5-11.

Figure 5-11 Threshold analysis for different baseline LDL-C for scenarios 1 and 2



CV, cardiovascular; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year

5.9 Existing CVD

Analysis C: Evolocumab and statin versus ezetimibe and statin

Base case incremental cost-effectiveness results

The incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin in patients with existing CVD is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 0.44 (Table 5-32).

Table 5-32 Analysis C: Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab and statin versus ezetimibe and statin)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£17,959	7.28				
Ezetimibe and statin	£20,302	7.62	£2,343	0.34	£6,917	
Evolocumab and statin	[REDACTED]	8.06	[REDACTED]	0.78	[REDACTED]	[REDACTED]

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Clinical outcomes – CV events

The base case undiscounted CV event rates for the secondary population for evolocumab in combination with statin versus ezetimibe in combination with statin are presented in Table 5-33. This indicates that evolocumab and statin is anticipated to prevent approximately 0.41 CV events compared with ezetimibe and statin.

Table 5-33 Analysis C: Base case undiscounted CV event rates

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.84	0.62	0.37	-0.25	0.25	60%
IS	0.14	0.10	0.06	-0.04	0.04	10%
HF	0.25	0.23	0.21	-0.02	0.02	6%
CHD death	0.43	0.37	0.27	-0.09	0.09	23%
IS death	0.10	0.11	0.11	0.01	0.01	2%
Total	1.77	1.43	1.02	-0.41	0.42	100%

ACS, acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; IS, ischaemic stroke

Disaggregated results – QALY gains by health state

Disaggregated QALYs for statin, ezetimibe and statin, and evolocumab and statin are presented in Table 5-34. This indicates a total QALY gain of 0.44 for evolocumab and statin compared with ezetimibe and statin.

Table 5-34 Analysis C: Base case summary of QALYs by health state

Health state	QALY: Statin	QALY: Ezetimibe and statin (comparator)	QALY: Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.30	0.22	0.13	-0.09	0.09	14%
IS	0.04	0.03	0.02	-0.01	0.01	2%
HF	0.08	0.07	0.06	-0.01	0.01	1%
ECVD	3.00	3.29	3.68	0.40	0.40	61%
Post-acute	3.87	4.02	4.17	0.15	0.15	23%
No CVD	0.00	0.00	0.00	0.00	0.00	0%
Total	7.28	7.62	8.06	0.44	0.66	100%

ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke

Disaggregated results – costs by health state

The base case disaggregated costs show that there is an anticipated saving of £[REDACTED] associated with evolocumab and statin versus ezetimibe and statin when considering the health states. These savings are attributable to a reduction in ACS, IS, HF, CHD death, and revascularisation costs (Table 5-35).

Table 5-35 Analysis C: Base case summary of costs by health state

Health state	Cost: Statin	Cost: Ezetimibe and statin (comparator)	Cost: Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	£1,755	£1,281	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IS	£336	£240	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HF	£496	£452	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CHD death	£191	£160	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IS death	£108	£111	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ECVD	£2,337	£2,573	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Post-acute	£4,905	£5,089	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Revasc	£6,087	£4,351	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total	£16,216	£14,257	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke ;Revasc Revascularisation

Summary of predicted resource use by category of cost

The resource use estimations show increased costs of £[REDACTED] associated with evolocumab and statin compared with ezetimibe and statin over the time horizon (Table 5-36). The summary indicates that these are due to additional costs for medication, and monitoring and training for evolocumab.

Table 5-36 Analysis C: Base case summary of resource use by health state

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£418	£4,667	████████	████████	████████	████████
Monitoring and training	£1,326	£1,379	████████	████████	████████	████████
Health states	£16,216	£14,257	████████	████████	████████	████████
Total	£17,959	£20,302	████████	████████	████████	████████

Analysis D: Evolocumab alone versus ezetimibe alone*Base case incremental cost-effectiveness results*

The incremental cost per QALY gained for evolocumab alone versus ezetimibe alone in patients with existing CVD and whom are statin intolerant or contraindicated is £████████ based on incremental costs of £████████ and incremental QALYs of 0.42 (Table 5-37).

Table 5-37 Analysis D: Base case incremental cost, incremental QALYs and ICER for patients with existing CVD

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
No lipid-lowering therapy	£17,542	7.28	████████	████████	████████	████████
Ezetimibe alone	£20,371	7.52	£2,829	0.23	£12,071	████████
Evolocumab alone	████████	7.94	████████	0.66	████████	████████
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Clinical outcomes – CV events

The base case undiscounted CV event rates for patients with existing CVD and whom are statin intolerant or contraindicated are presented in Table 5-38. This indicates that evolocumab alone is anticipated to prevent approximately 0.41 CV events compared with ezetimibe alone.

Table 5-38 Analysis D: Base case undiscounted CV event rates

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.84	0.62	0.37	-0.25	0.25	60%
IS	0.14	0.10	0.06	-0.04	0.04	10%
HF	0.25	0.23	0.21	-0.02	0.02	6%
CHD death	0.43	0.37	0.27	-0.09	0.09	23%
IS death	0.10	0.11	0.11	0.01	0.01	2%
Total	1.77	1.43	1.02	-0.41	0.42	100%
ACS, acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – QALY gains by health state

Disaggregated QALYs for ezetimibe alone and evolocumab alone are presented in Table 5-39. This indicates a total QALY gain of 0.42 for evolocumab alone compared with ezetimibe alone.

Table 5-39 Analysis D: Base case summary of QALYs by health state

Health state	QALY: No lipid-lowering therapy	QALY: Ezetimibe alone (comparator)	QALY: Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.30	0.24	0.15	-0.09	0.09	14%
IS	0.04	0.03	0.02	-0.01	0.01	2%
HF	0.08	0.07	0.07	-0.01	0.01	1%
ECVD	3.00	3.20	3.57	0.38	0.38	59%
Post-acute	3.87	3.98	4.13	0.15	0.15	24%
No CVD	0.00	0.00	0.00	0.00	0.00	0%
Total	7.28	7.52	7.94	0.42	0.64	100%
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – costs by health state

The base case disaggregated costs show that there is an anticipated saving of £ [REDACTED] associated with evolocumab alone versus ezetimibe alone. These savings are attributable to a reduction in ACS, IS, HF, CHD death and revascularisation costs (Table 5-40).

Table 5-40 Analysis D: Base case summary of costs by health state

Health state	Cost: No lipid-lowering therapy	Cost: Ezetimibe alone (comparator)	Cost: Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	£1,755	£1,421				
IS	£336	£268				
HF	£496	£465				
CHD death	£191	£170				
IS death	£108	£110				
ECVD	£2,337	£2,499				
Post-acute	£4,905	£5,035				
Revasc	£6,087	£4,864				
Total	£16,216	£14,832				
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; Revasc Revascularisation						

Summary of predicted resource use by category of cost

The resource use estimations show increased costs associated with evolocumab alone compared with ezetimibe alone. The summary in Table 5-41 indicates that these are due to additional costs for medication, and monitoring and training for evolocumab.

Table 5-41 Analysis D: Base case summary of resource use by health state

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment	Absolute increase	Absolute increment
Medication	£0	£4,176				
Monitoring and training	£1,326	£1,362				
Health states	£16,216	£14,832				
Total	£17,542	£20,371				

5.10 Heterozygous familial hypercholesterolaemia

Analysis G: Evolocumab and statin versus ezetimibe and statin

Base case incremental cost-effectiveness results

The incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin in patients with HeFH is £ based on incremental costs of £ and incremental QALYs of 1.20 (Table 5-42).

Table 5-42 Analysis G: Base case incremental cost, incremental QALYs and ICER for the HeFH population (evolocumab and statin vs. ezetimibe and statin)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£17,244	8.04				
Ezetimibe and statin	£18,697	8.86	£1,453	0.81	£1,791	
Evolocumab and statin		10.05		2.01		
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Clinical outcomes – CV events

The base case undiscounted CV event rates for the HeFH population for evolocumab in combination with statin versus ezetimibe in combination with statin are presented in Table 5-43. This indicates that evolocumab and statin is anticipated to prevent approximately 0.69 CV events compared with ezetimibe and statin over the lifetime horizon.

Table 5-43 Analysis G: Base case undiscounted CV event rates

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	1.47	1.13	0.68	-0.45	0.45	59%
IS	0.30	0.23	0.13	-0.09	0.09	12%
HF	0.31	0.28	0.23	-0.05	0.05	6%
CHD death	0.72	0.65	0.52	-0.13	0.13	17%
IS death	0.15	0.17	0.21	0.04	0.04	5%
Total	2.95	2.46	1.78	-0.69	0.76	100%
ACS, acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – QALY gains by health state

Disaggregated QALYs for statin, ezetimibe and statin, and evolocumab and statin are presented in Table 5-44. This indicates a total QALY gain of 1.20 for evolocumab and statin compared with ezetimibe and statin.

Table 5-44 Analysis G: Base case summary of QALYs by health state

Health state	QALY: Statin	QALY: Ezetimibe and statin (comparator)	QALY: Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.54	0.40	0.23	-0.17	0.17	9%
IS	0.09	0.06	0.03	-0.03	0.03	2%
HF	0.09	0.08	0.06	-0.02	0.02	1%
ECVD	1.56	1.79	2.12	0.33	0.33	17%
Post-acute	2.43	2.48	2.36	-0.13	0.13	7%
No CVD	3.33	4.04	5.25	1.22	1.22	64%
Total	8.04	8.86	10.05	1.20	1.90	100%
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – costs by health state

The base case disaggregated costs show that there is an anticipated saving of £[REDACTED] associated with evolocumab and statin compared with ezetimibe and statin. These savings are attributable to a reduction in ACS, IS, HF, CHD death and revascularisation costs (Table 5-45).

Table 5-45 Analysis G: Base case summary of costs by health state

Health state	Cost: Statin	Cost: Ezetimibe and statin (comparator)	Cost: Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	% absolute increment
ACS	£3,009	£2,223	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IS	£731	£521	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HF	£563	£486	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CHD death	£306	£264	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IS death	£159	£170	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ECVD	£1,138	£1,316	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Post-acute	£2,446	£2,509	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Revasc	£7,218	£5,165	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total	£15,570	£12,655	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; Revasc, revascularisation						

Summary of predicted resource use by category of cost

The resource use estimations show increased costs of £[REDACTED] associated with evolocumab and statin compared with ezetimibe and statin over the time horizon. The summary in Table 5-46 indicates that these are due to additional costs for medication, and monitoring and training for evolocumab.

Table 5-46 Analysis G: Base case summary of resource use by health state

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£399	£4,664	████████	████████	████████	████████
Monitoring and training	£1,275	£1,378	████████	████████	████████	████████
Health states	£15,570	£12,655	████████	████████	████████	████████
Total	£17,244	£18,697	████████	████████	████████	████████

Analysis H: Evolocumab alone versus ezetimibe alone*Base case incremental cost-effectiveness results*

The incremental cost per QALY gained for evolocumab alone versus ezetimibe alone in patients with HeFH is £████████ based on incremental costs of £████████ and incremental QALYs of 1.10 (Table 5-47).

Table 5-47 Analysis H: Base case incremental cost, incremental QALYs, and ICER for the HeFH population

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
No lipid-lowering therapy	£16,845	8.04	████████	████████	████████	████████
Ezetimibe alone	£19,005	8.60	£2,161	0.55	£3,913	████████
Evolocumab alone	████████	9.69	████████	1.65	████████	████████
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Clinical outcomes – CV events

The base case undiscounted CV event rates for the HeFH population (statin intolerant or contraindicated) for evolocumab alone compared with ezetimibe alone are presented in Table 5-48. This indicates that evolocumab alone is anticipated to prevent approximately 0.64 CV events compared with ezetimibe alone.

Table 5-48 Analysis H: Base case undiscounted CV event rates

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	1.47	1.24	0.81	-0.43	0.43	61%
IS	0.30	0.25	0.16	-0.09	0.09	13%
HF	0.31	0.29	0.25	-0.04	0.04	6%
CHD death	0.72	0.67	0.57	-0.11	0.11	16%
IS death	0.15	0.17	0.20	0.03	0.03	5%
Total	2.95	2.62	1.98	-0.64	0.70	100%
ACS, acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – QALY gains by health state

Disaggregated QALYs for statin, ezetimibe and statin, and evolocumab and statin are presented in Table 5-49. This indicates a total QALY gain of 1.10 for evolocumab alone compared with ezetimibe alone.

Table 5-49 Analysis H: Base case summary of QALYs by health state

Health state	QALY: No lipid-lowering therapy	QALY: Ezetimibe alone (comparator)	QALY: Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.54	0.44	0.28	-0.17	0.17	10%
IS	0.09	0.07	0.04	-0.03	0.03	2%
HF	0.09	0.08	0.07	-0.02	0.02	1%
ECVD	1.56	1.71	2.02	0.31	0.31	19%
Post-acute	2.43	2.48	2.42	-0.06	0.06	4%
No CVD	3.33	3.80	4.87	1.06	1.06	64%
Total	8.04	8.60	9.69	1.10	1.65	100%
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established CVD; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – costs by health state

The base case disaggregated costs show that there is an anticipated saving of £ [REDACTED] associated with evolocumab alone versus ezetimibe alone when considering the health states. These savings are attributable to a reduction in ACS, IS, HF, CHD death and revascularisation costs (Table 5-50).

Table 5-50 Analysis H: Base case summary of costs by health state

Health state	Cost: No lipid-lowering therapy	Cost: Ezetimibe alone (comparator)	Cost: Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	£3,009	£2,462	████████	████████	████████	████████
IS	£731	£583	████████	████████	████████	████████
HF	£563	£511	████████	████████	████████	████████
CHD death	£306	£278	████████	████████	████████	████████
IS death	£159	£166	████████	████████	████████	████████
ECVD	£1,138	£1,258	████████	████████	████████	████████
Post-acute	£2,446	£2,502	████████	████████	████████	████████
Revasc	£7,218	£5,783	████████	████████	████████	████████
Total	£15,570	£13,544	████████	████████	████████	████████
ACS, acute coronary syndrome; CHD, coronary heart disease; ECVD, established; CHF, heart failure; IS, ischaemic stroke; Revasc, Revascularisation						

Summary of predicted resource use by category of cost

The resource use estimations show increased costs associated with evolocumab alone compared with ezetimibe alone (£████████). The summary in Table 5-51 indicates that these are due to additional costs for medication, and monitoring and training for evolocumab.

Table 5-51 Analysis H: Base case summary of resource use by health state

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment vs. comparator	Absolute increase	Absolute increment
Medication	£0	£4,117	████████	████████	████████	████████
Monitoring and training	£1,275	£1,345	████████	████████	████████	████████
Health states	£15,570	£13,544	████████	████████	████████	████████
Total	£16,845	£19,005	████████	████████	████████	████████

5.11 Sensitivity analyses**Probabilistic sensitivity analysis**

The probabilistic sensitivity analysis was run with 1,000 simulations. Probabilistic sensitivity analysis outputs are represented graphically by plotting incremental cost and effectiveness pairs on the cost-effectiveness plane and presenting the likelihood of evolocumab being the optimal strategy across different maximum willingness-to-pay thresholds. The results of the various baseline LDL-C levels and corresponding 10-year CVD risk are presented in

Table 5-28 to Table 5-31 for scenarios 1 and 2. The results of the probabilistic sensitivity analysis depicted as scatter plots are presented in the figures below for patients with existing CVD and HeFH based on scenarios 1 and 2 (Figure 5-12 to Figure 5-15). The ellipses represent the 95% CI and the gradients represent £20,000 and £30,000 incremental cost per QALY gained on the scatterplots.



Table 5-52 Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Probability of optimal strategy at MAICER of £30,000 per QALY
2.5	Ezetimibe and statin	-*	N/A	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	79%	■	6.74				
	Evolocumab and statin		■	8.15	■	1.41	■	37.5%
4	Ezetimibe and statin	73%	■	7.40				
	Evolocumab and statin		■	8.95	■	1.55	■	40.6%
4.5	Ezetimibe and statin	70%	■	7.83				
	Evolocumab and statin		■	9.46	■	1.63	■	36.6%

*Not achievable based on threshold analysis for defined willingness-to-pay thresholds
CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Table 5-53 Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Probability of optimal strategy at MAICER of £20,000 per QALY
2.5	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
4	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds								
CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Analysis B: Evolocumab alone versus ezetimibe alone

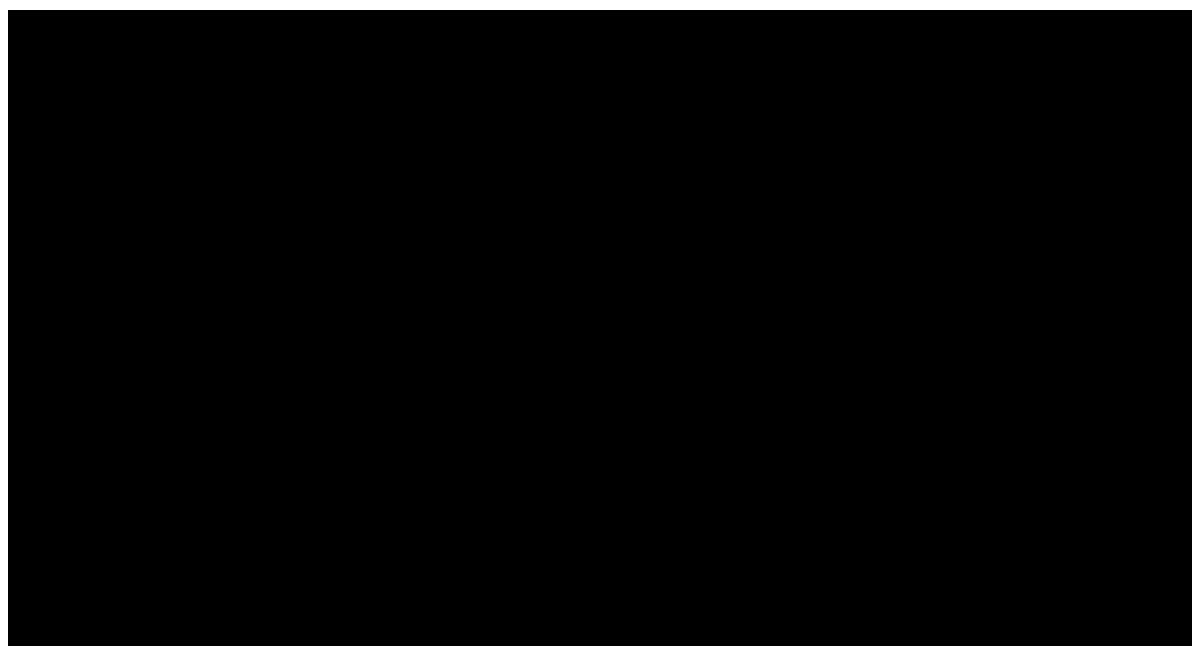
Table 5-54 Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone) [scenario 2]

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Probability of optimal strategy at MAICER of £20,000 per QALY
2.5	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
3	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe alone	81%		6.27				
	Evolocumab alone			7.58		1.31		41.8%
4	Ezetimibe alone	75%		6.90				
	Evolocumab alone			8.34		1.44		43.0%
4.5	Ezetimibe alone	71%		7.38				
	Evolocumab alone			8.92		1.54		42.4%
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Table 5-55 Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone) [scenario 2]

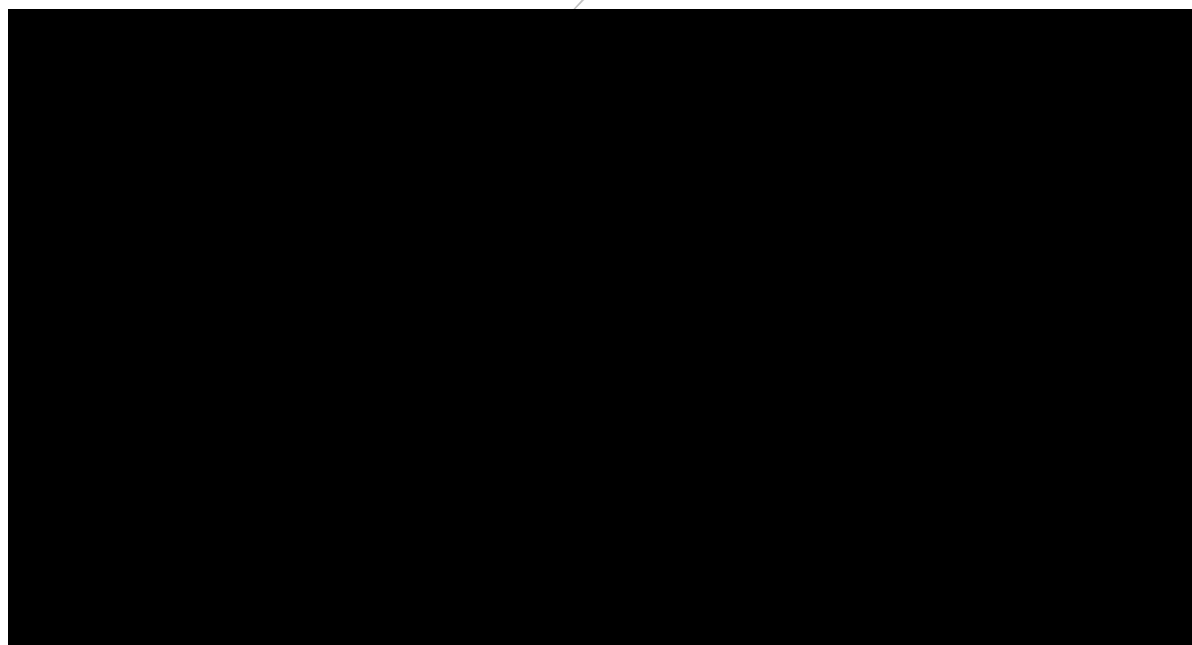
Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Probability of optimal strategy at MAICER of £20,000 per QALY
2.5	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
3	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
4	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds								
CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Figure 5-12 Scatterplot for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1]



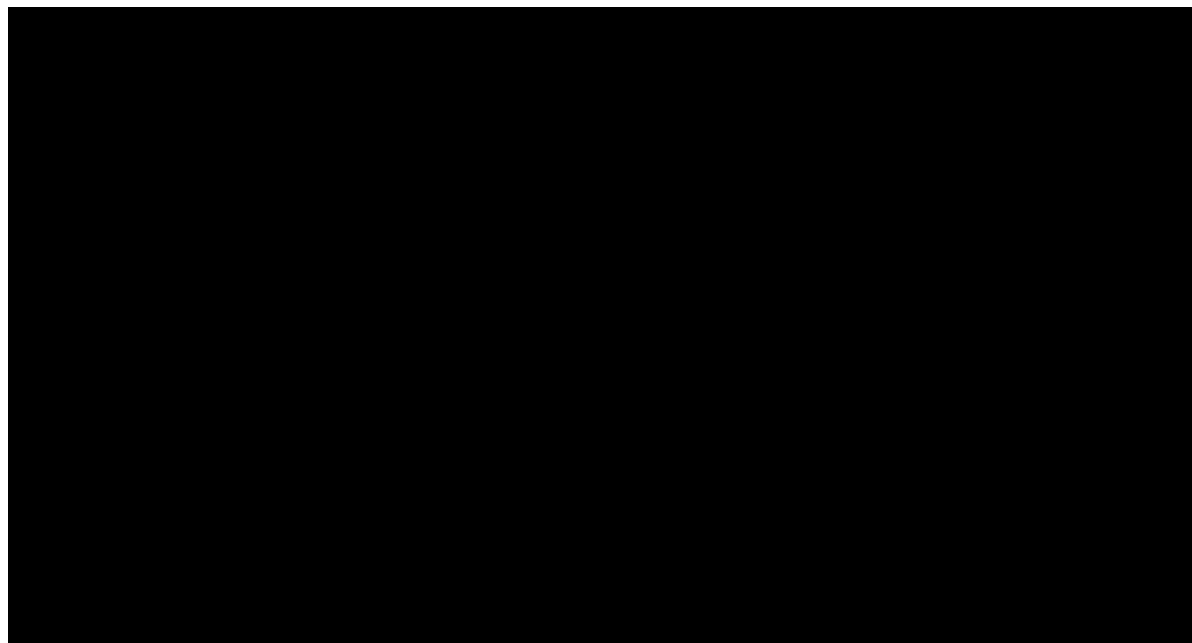
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention

Figure 5-13 Scatterplot for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2]



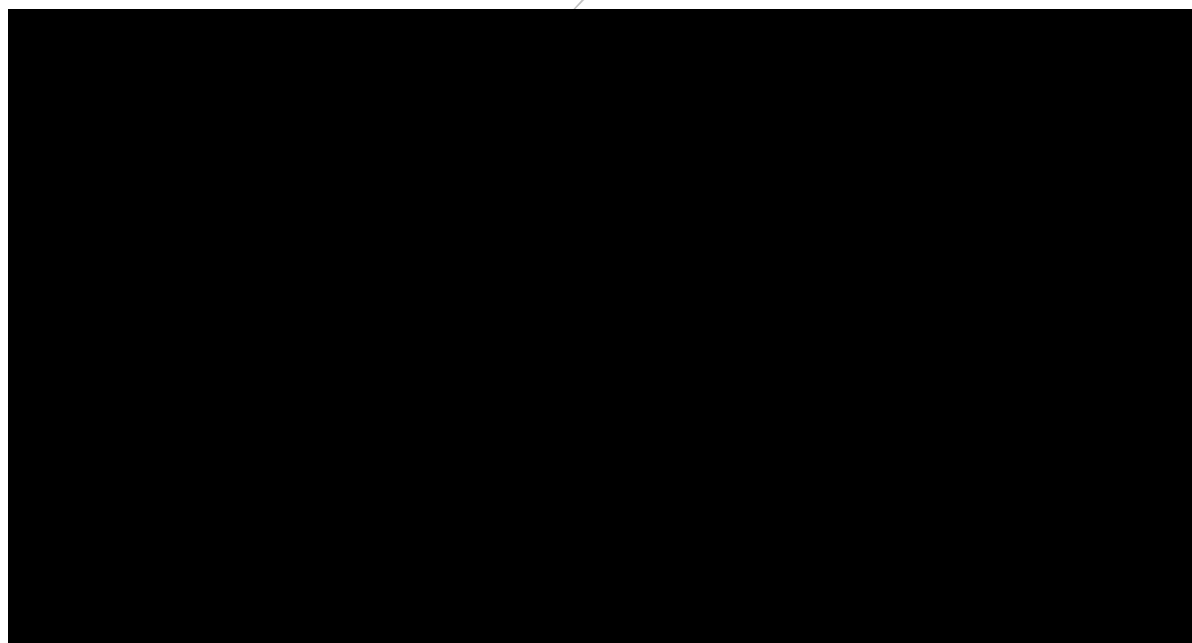
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention

Figure 5-14 Scatterplot for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

Figure 5-15 Scatterplot for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2]

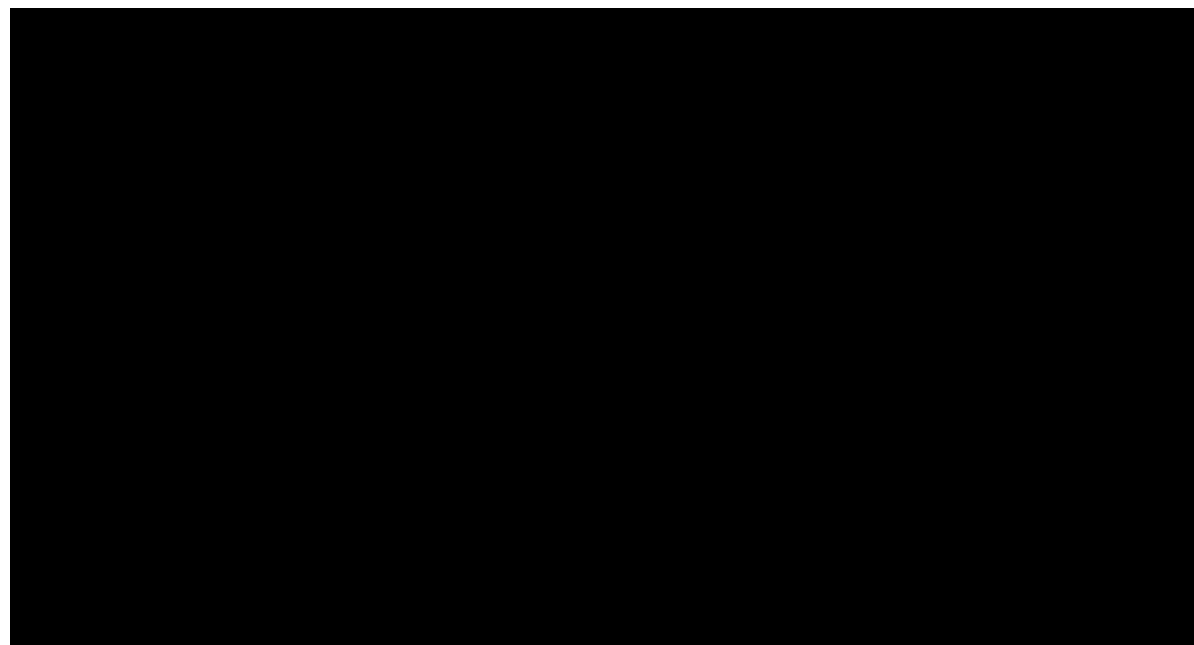


HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

In addition, cost-effectiveness acceptability curves were used to assess the proportion of simulations whereby the different treatment strategies for specific maximum acceptable ICERs. These are presented in Figure 5-16 to Figure 5-19 and summarised in Table 5-56. Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

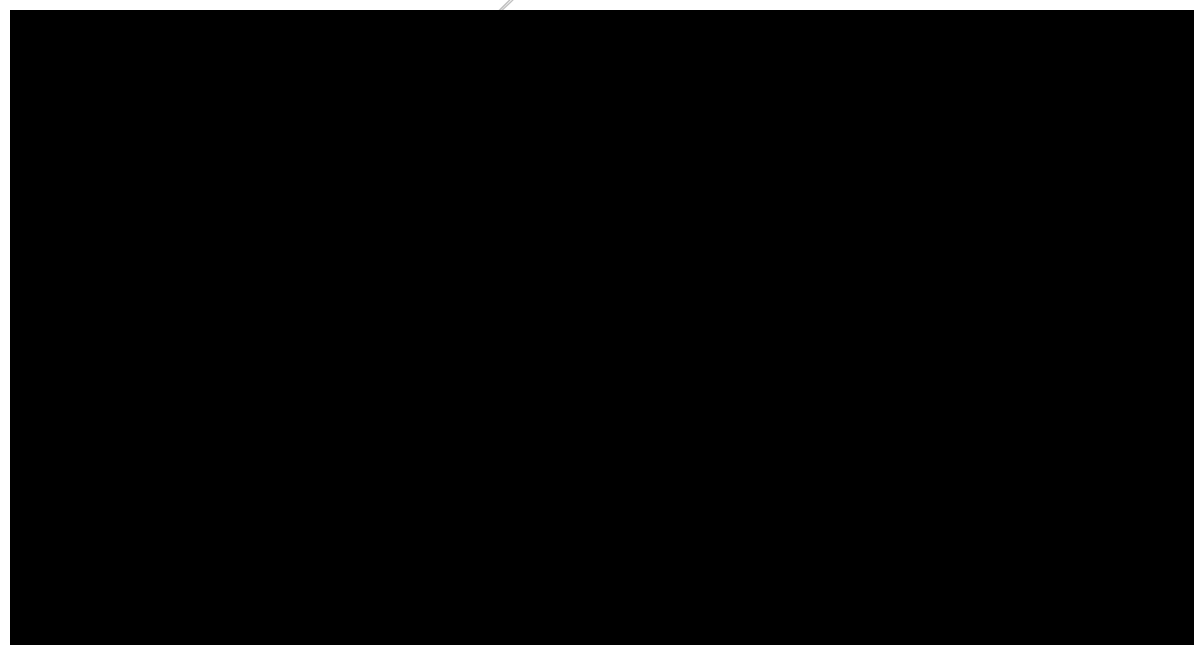
Furthermore, a comparison of the base case results for the deterministic and probabilistic analyses are presented in Table 5-57.

Figure 5-16 Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1]



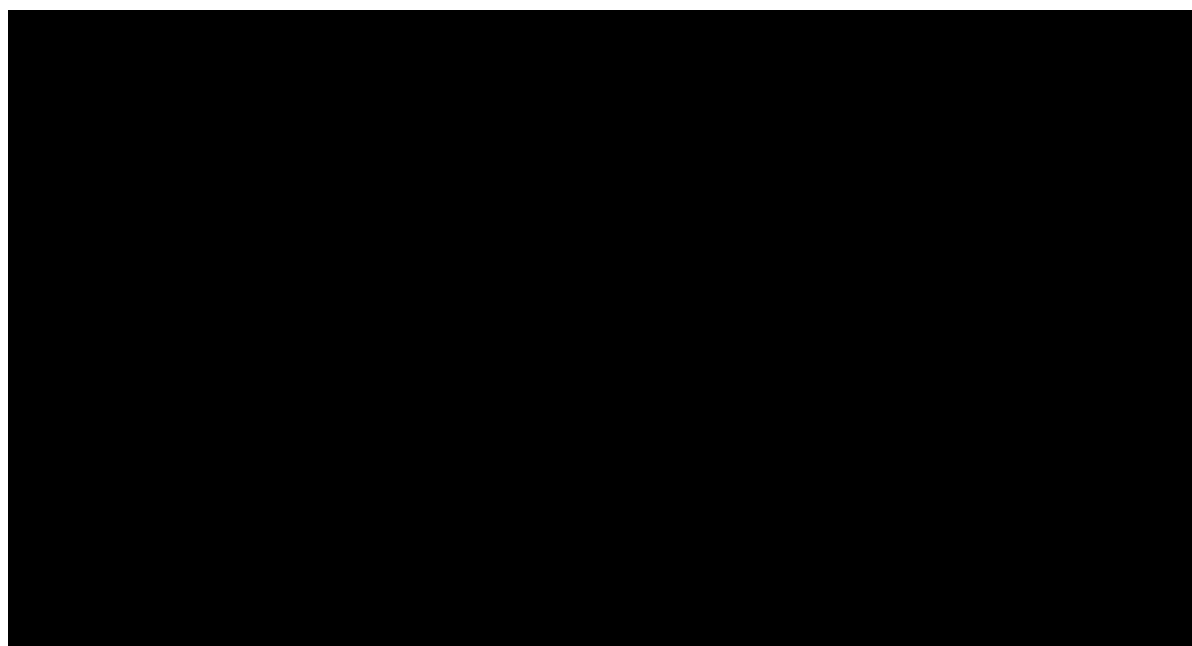
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 5-17 Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2]



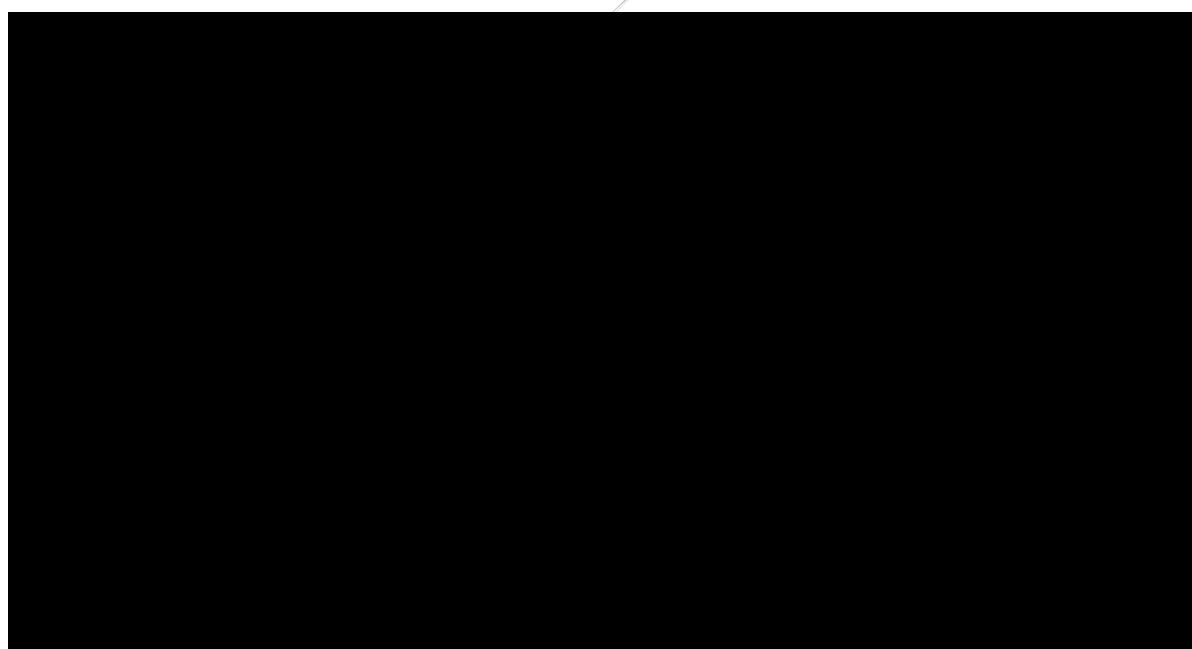
LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 5-18 Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol

Figure 5-19 Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol

Table 5-56 Probability of cost-effectiveness for evolocumab in different populations and maximum acceptable incremental cost-effectiveness ratios [scenarios 1 and 2]

Population	Intervention	Comparator	MAICER

Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

			£20,000 per QALY	£30,000 per QALY
Existing CVD	Evolocumab and statin	Ezetimibe and statin		
	Evolocumab alone	Ezetimibe alone		
HeFH	Evolocumab and statin	Ezetimibe and statin		
	Evolocumab alone	Ezetimibe alone		
HeFH; heterozygous familial hypercholesterolaemia; MAICER maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year				

Table 5-57 Deterministic and probabilistic incremental cost-effectiveness ratios

Pop.	Intervention	Comparator	ICER	
			Deterministic	Probabilistic
Existing CVD	Evolocumab and statin	Ezetimibe and statin		
	Evolocumab alone	Ezetimibe alone		
HeFH	Evolocumab and statin	Ezetimibe and statin		
	Evolocumab alone	Ezetimibe alone		
HeFH; heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio MAICER maximum acceptable incremental cost-effectiveness ratio; Pop., population; QALY, quality-adjusted life-year				

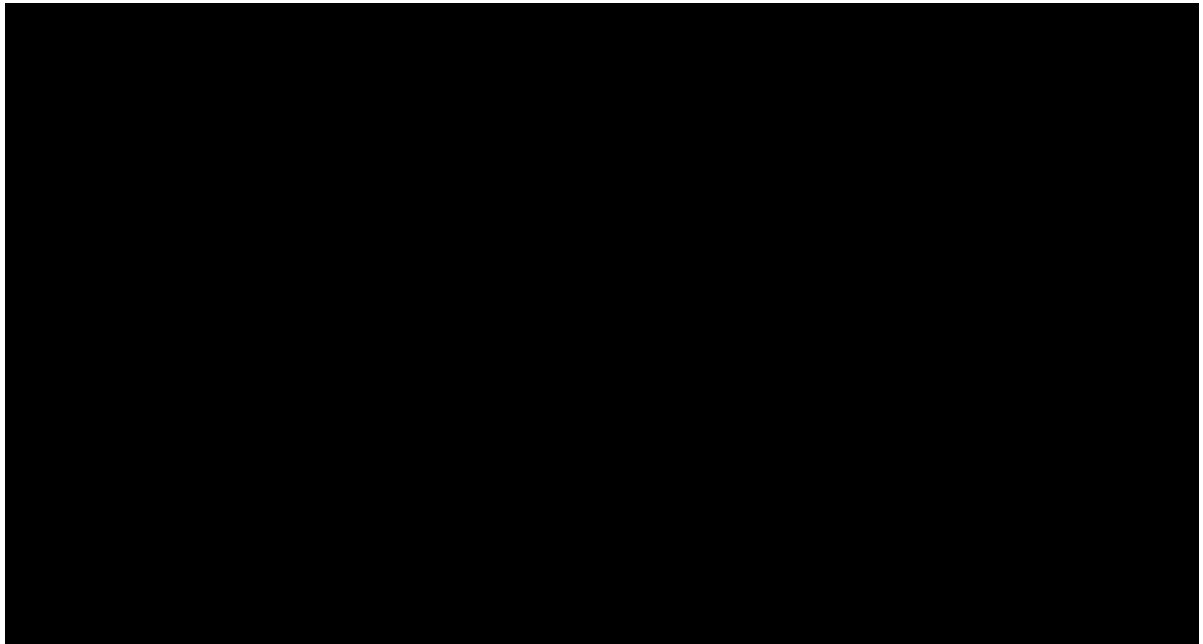
Deterministic sensitivity analysis

Deterministic sensitivity analyses were performed by means of one-way sensitivity analyses, where one parameter was varied relative to its base case value. The method adopted and the parameters tested are described in Section 5.6. A summary of the results is presented below for patients with and without existing CVD and patients with HeFH for evolocumab and statin versus ezetimibe and statin (scenario 1). The additional scenarios are not presented as the results were not sensitive to the different treatment strategies covered in scenarios 2 to 4. All parameters where the incremental cost per QALY gained was sensitive by > 1% are presented in Tornado plots (Figure 5-20 to Figure 5-22).

The Tornado plots that indicate the most sensitive parameters for cost-effectiveness of evolocumab versus ezetimibe were:

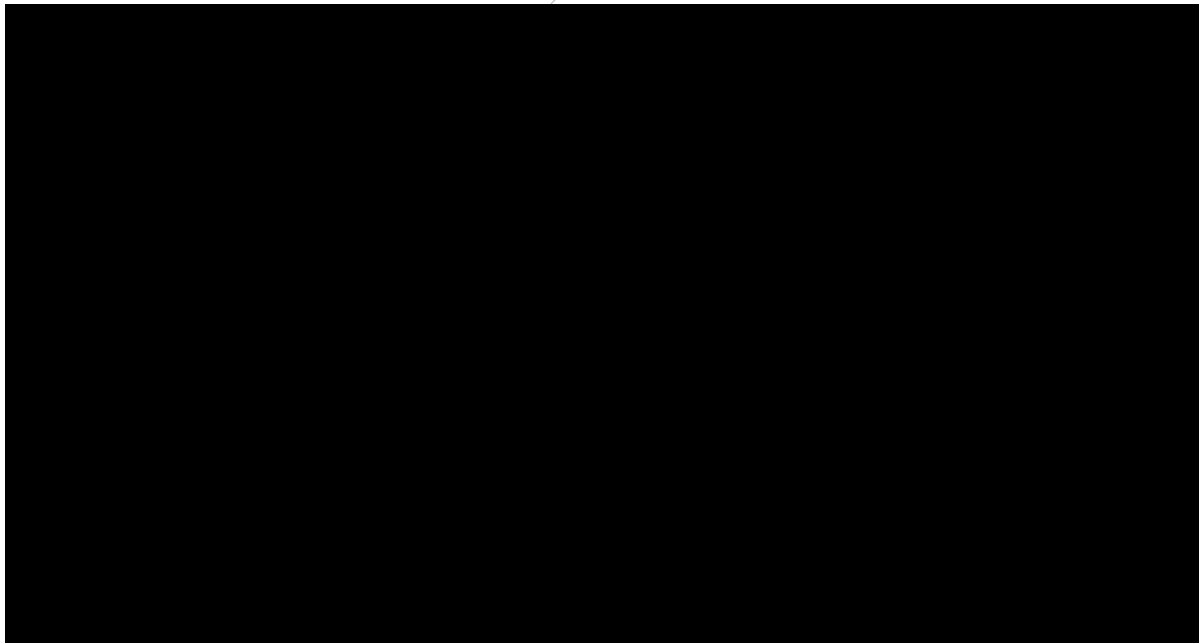
- CV event rate ratio (HeFH alone)
- CPRD ratio ratios (secondary prevention alone)
- treatment duration
- effect of LDL-C reduction on CV events
- ezetimibe treatment effect
- evolocumab treatment effect
- 'ECVD' and 'post-ACS' health state utility multiplier.

Figure 5-20 Tornado plot: evolocumab and statin versus ezetimibe and statin in patients without existing CVD (based on LAPLACE-2) [scenario 1]



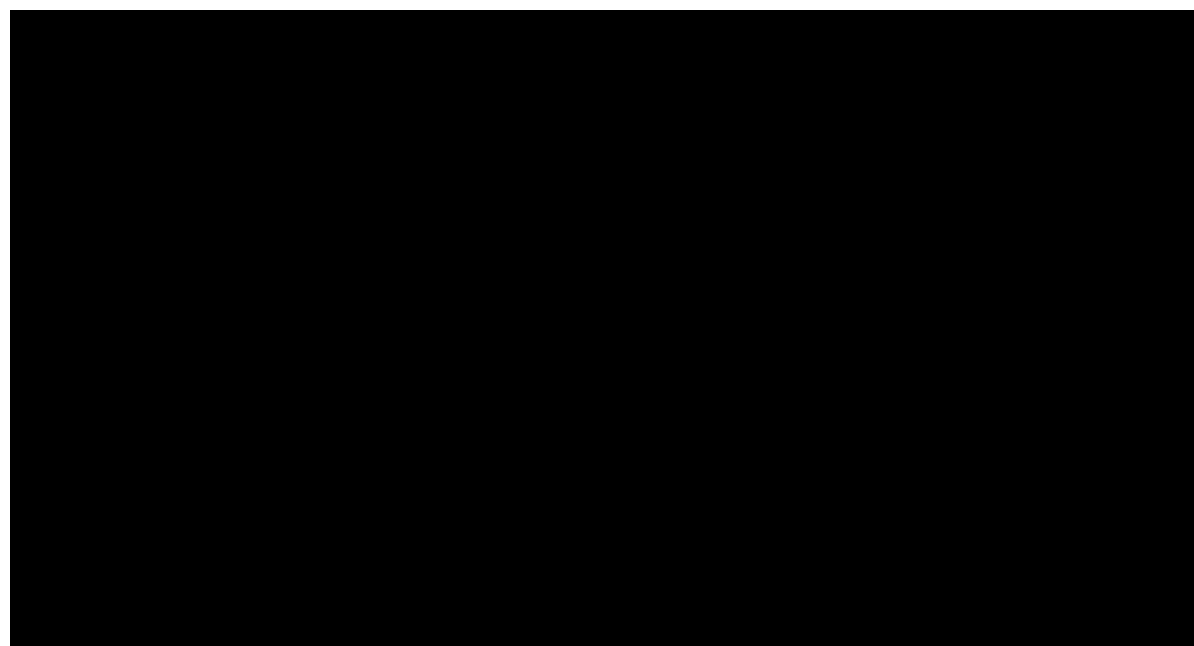
ACS, acute coronary syndrome; CI, confidence interval; CHD, coronary heart disease; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 5-21 Tornado plot: evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1]



ACS, acute coronary syndrome; CI, confidence interval; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 5-22 Tornado plot: evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]



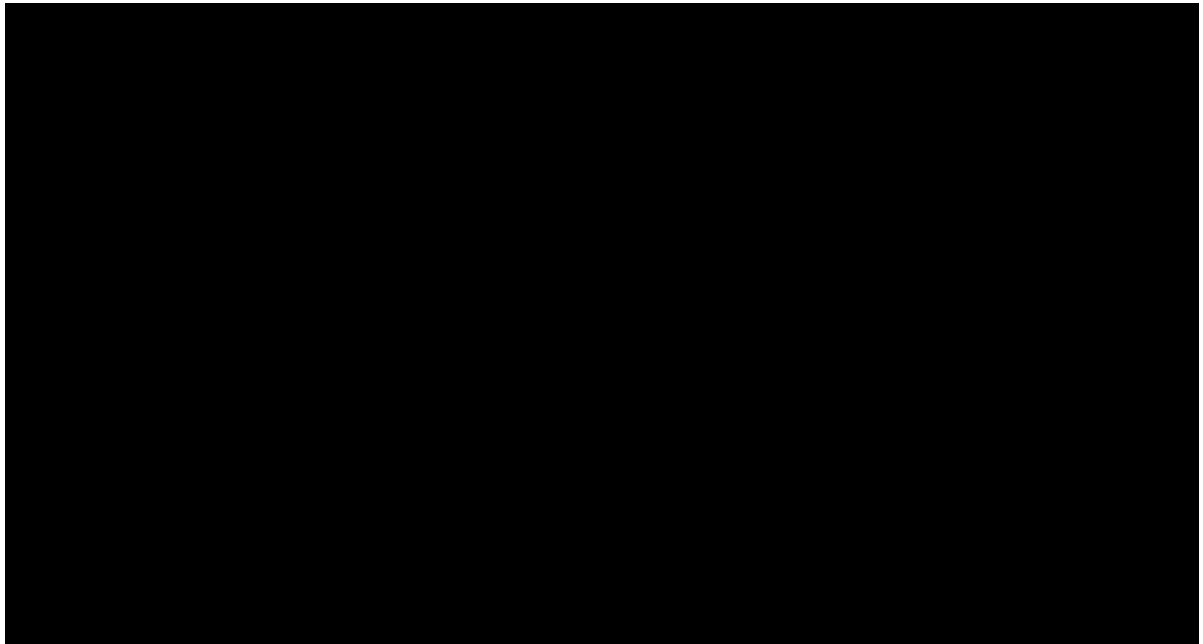
ACS, acute coronary syndrome; CI, confidence interval; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol

5.12 Scenario analysis

Existing CVD and severity of hypercholesterolaemia

For the existing CVD population, the impact of severity of hypercholesterolaemia has been assessed on the basis of the baseline LDL-C level when treatment with evolocumab or ezetimibe would be initiated. Results from scenario 1 (evolocumab and statin vs. ezetimibe and statin) are presented in Figure 5-23 and Table 5-58 indicate that the incremental cost per QALY gained is £[REDACTED] to £[REDACTED] based on a baseline LDL-C range of 3.0 mmol/L to 6.0 mmol/L. Additional analyses for scenarios 2 to 4 have not been presented given the same anticipated trend with respect to cost-effectiveness and severity of hypercholesterolaemia.

Figure 5-23 Existing CVD: Incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin according to severity of hypercholesterolaemia



CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

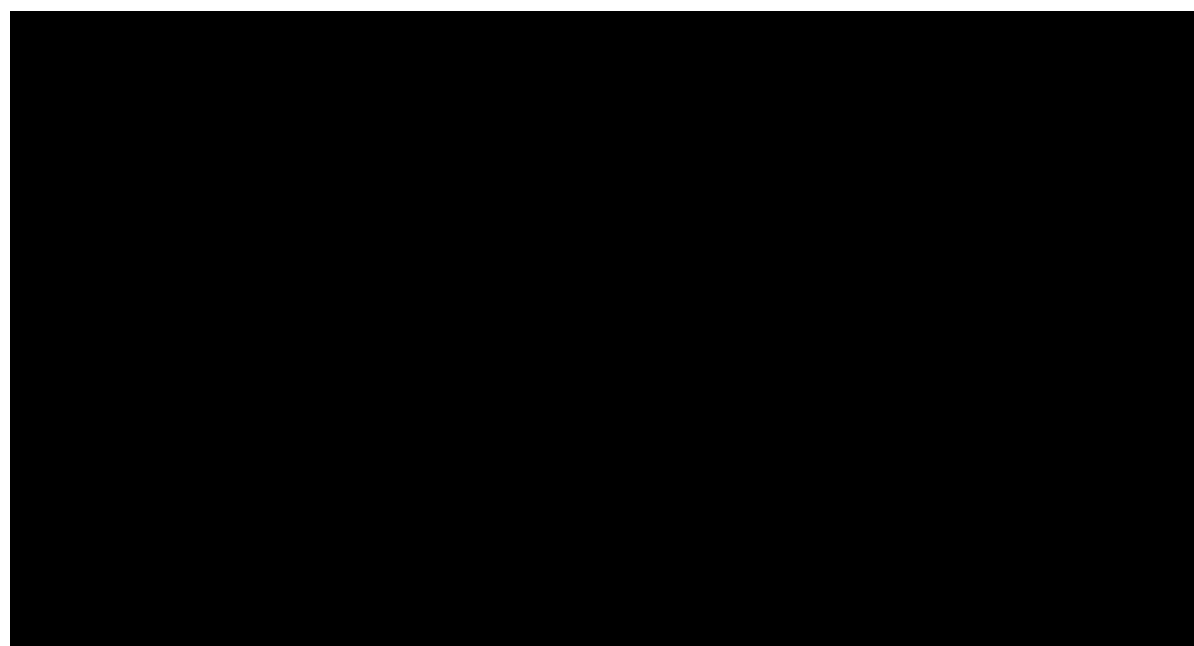
Table 5-58 Scenario analyses: Existing CVD and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Baseline LDL-C	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
3.0 mmol/L	██████	£20,544	██████	7.92	7.57	0.35	██████
3.5 mmol/L	██████	£20,338	██████	8.04	7.61	0.43	██████
4.0 mmol/L	██████	£20,142	██████	8.13	7.66	0.48	██████
4.5 mmol/L	██████	£19,956	██████	8.21	7.70	0.51	██████
5.0 mmol/L	██████	£19,779	██████	8.28	7.74	0.54	██████
5.5 mmol/L	██████	£19,611	██████	8.34	7.78	0.56	██████
6.0 mmol/L	██████	£19,452	██████	8.40	7.82	0.59	██████
CVD, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year							

HeFH and severity of hypercholesterolaemia

For the HeFH population, the impact of severity of hypercholesterolaemia has been assessed on the basis of the baseline LDL-C level when treatment with evolocumab or ezetimibe would be initiated (scenario 1 modelled). The HeFH population modelled on the basis of RUTHERFORD-2 had a baseline LDL-C of 4.0 mmol/L (Table 5-5). In the UK, the National Audit of Familial Hypercholesterolaemia indicated that the median LDL-C is 3.3 mmol/L⁹⁰ (Figure 3-1). Scenario analysis indicates that evolocumab is anticipated to be a cost-effective treatment option when considering baseline LDL-C in accordance with the UK HeFH population (Figure 5-24 and Table 5-59). As for patients with existing CVD, scenarios 2 to 4 have not been presented based on severity of hypercholesterolaemia.

Figure 5-24 HeFH: Incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin (scenario 1) according to severity of hypercholesterolaemia



HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

Table 5-59 Scenario analyses: HeFH and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Baseline LDL-C	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
3.0 mmol/L	██████	£19,257	██████	9.48	8.66	0.82	██████
3.5 mmol/L	██████	£18,978	██████	9.80	8.75	1.05	██████
4.0 mmol/L	██████	£18,708	██████	10.04	8.85	1.19	██████
4.5 mmol/L	██████	£18,446	██████	10.25	8.95	1.30	██████
5.0 mmol/L	██████	£18,193	██████	10.44	9.04	1.40	██████
5.5 mmol/L	██████	£17,949	██████	10.63	9.14	1.49	██████
6.0 mmol/L	██████	£17,713	██████	10.80	9.23	1.57	██████
EvoMab; evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year							

Additional scenario analyses

The following scenario analyses were performed for patients without existing CVD, patients with existing CVD and patients with HeFH.

Treatment scenarios for evolocumab: In the base case, it is assumed that evolocumab will be used either in combination with statin or alone in patients who are statin intolerant or contraindicated. In these scenarios the cost-effectiveness of evolocumab and ezetimibe

versus ezetimibe alone (scenario 3), and evolocumab, statin and ezetimibe versus statin and ezetimibe (scenario 4) are assessed.

Treatment duration: In the base case analysis, a lifetime treatment duration (to a maximum age of 100 years) is assumed. In these scenario analyses the treatment duration is shortened to 5, 10, and 20 years.

Discounting: In the base case, discount rates of 3.5% were applied to both costs and health effects. Here the discount rates are changed to (1) 0% for both costs and health effects, and (2) 0% for costs and 6% for health effects.

Risk capping at age 75 years: As CVD patients age, the risk of CV events increases. In this scenario it is assumed that the risk of CV events does not increase any more after patients have reached the age of 75 years (versus 85 years assumed in the base case).

CV cost data based on NICE CG181: In the base case CV, costs were based on the CPRD study. In this scenario the costs for CV events as presented in NICE CG181 are used.²⁰²

Utilities based on TTO study: In the base case, utilities as presented in NICE CG181⁷⁷ were used. In this scenario analysis, utilities from the TTO study described in Section 5.4 are used. This analysis uses the absolute utility modelling approach, not the multiplicative approach applied in the base case.

Nursing time evolocumab self-administration training: In the base case it is assumed that 1 hour of nurse time will be needed for evolocumab self-administration training. As this is an assumption, the impact of using half and double the time is investigated.

Analysis E: Evolocumab and ezetimibe versus ezetimibe alone in secondary prevention

The incremental cost per QALY for evolocumab and ezetimibe versus ezetimibe alone in patients with existing CVD is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 0.49 (Table 5-60).

Table 5-60 Analysis E: Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab and ezetimibe versus ezetimibe alone)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Ezetimibe	£20,371	7.52			
Evolocumab and ezetimibe	[REDACTED]	8.01	[REDACTED]	0.49	[REDACTED]
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Analysis F: Evolocumab, statin and ezetimibe versus statin and ezetimibe in secondary prevention

The incremental cost per QALY for evolocumab, statin, and ezetimibe versus statin and ezetimibe in patients with existing CVD is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 0.44 (Table 5-61).

Table 5-61 Analysis F: Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab, statin and ezetimibe versus statin and ezetimibe)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Statin and ezetimibe	£20,302	7.62			
Evolocumab, statin and ezetimibe	[REDACTED]	8.06	[REDACTED]	0.44	[REDACTED]
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Analysis I: Evolocumab and ezetimibe versus ezetimibe alone in HeFH

The incremental cost per QALY for evolocumab and ezetimibe versus ezetimibe alone in patients with HeFH is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 1.29 (Table 5-62).

Table 5-62 Analysis I: Base case incremental cost, incremental QALYs and ICER for patients with HeFH (evolocumab and ezetimibe versus ezetimibe alone)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Ezetimibe	£19,005	8.60			
Evolocumab and ezetimibe	[REDACTED]	9.88	[REDACTED]	1.29	[REDACTED]
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Analysis J: Evolocumab, statin, and ezetimibe versus statin and ezetimibe in HeFH

The incremental cost per QALY for evolocumab, statin, and ezetimibe versus statin and ezetimibe in patients with HeFH is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 1.26 (Table 5-63).

Table 5-63 Analysis J: Base case incremental cost, incremental QALYs, and ICER for patients with HeFH (evolocumab, statin and ezetimibe vs. statin and ezetimibe)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Statin and ezetimibe	£18,697	8.86			
Evolocumab, statin and ezetimibe		10.11		1.26	
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Table 5-64 Scenario analyses – without existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
Base case	██████	£9,868	██████	12.15	11.84	0.31	██████
Evolocumab QM PFP	██████	£9,868	██████	12.15	11.84	0.31	██████
5-year treatment duration	██████	£5,295	██████	11.70	11.63	0.07	██████
10-year treatment duration	██████	£6,758	██████	11.83	11.69	0.14	██████
20-year treatment duration	██████	£8,716	██████	12.03	11.78	0.25	██████
Discounting: 0% costs, 0% effects	██████	£16,741	██████	19.22	18.52	0.70	██████
Discounting: 0% costs, 6% effects	██████	£16,741	██████	9.33	9.14	0.19	██████
Risk capping 75 years	██████	£9,810	██████	12.19	11.90	0.29	██████
NICE CG181 CV costs	██████	£10,097	██████	12.15	11.84	0.31	██████
TTO study utilities	██████	£9,868	██████	12.32	12.08	0.24	██████
Nurse training 30 minutes	██████	£9,868	██████	12.15	11.84	0.31	██████
Nurse training 2 hours	██████	£9,868	██████	12.15	11.84	0.31	██████
CV, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

Table 5-65 Scenario analyses – existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
Base case	██████	£20,302	██████	8.06	7.62	0.44	██████
Evolocumab QM PFP	██████	£20,302	██████	8.04	7.62	0.42	██████
5-year treatment duration	██████	£17,173	██████	7.52	7.39	0.13	██████
10-year treatment duration	██████	£18,461	██████	7.72	7.48	0.24	██████
20-year treatment duration	██████	£19,864	██████	7.97	7.59	0.38	██████
Discounting: 0% costs, 0% effects	██████	£30,241	██████	11.80	10.96	0.84	██████
Discounting: 0% costs, 6% effects	██████	£30,241	██████	6.44	6.15	0.30	██████
Risk capping 75 years	██████	£20,364	██████	8.15	7.72	0.43	██████
NICE CG181 CV costs	██████	£23,587	██████	8.06	7.62	0.44	██████
TTO study utilities	██████	£20,302	██████	9.79	9.21	0.58	██████
Nurse training 30 minutes	██████	£20,302	██████	8.06	7.62	0.44	██████
Nurse training 2 hours	██████	£20,302	██████	8.06	7.62	0.44	██████
CV, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

Table 5-66 Scenario analyses – HeFH population (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
Base case	██████	£18,697	██████	10.05	8.86	1.20	██████
Evolocumab QM PFP	██████	£18,697	██████	9.99	8.86	1.13	██████
5-year treatment duration	██████	£16,338	██████	8.61	8.30	0.30	██████
10-year treatment duration	██████	£17,299	██████	9.08	8.51	0.57	██████
20-year treatment duration	██████	£18,357	██████	9.72	8.76	0.96	██████
Discounting: 0% costs, 0% effects	██████	£29,576	██████	15.04	12.64	2.40	██████
Discounting: 0% costs, 6% effects	██████	£29,576	██████	7.96	7.18	0.78	██████
Risk capping 75 years	██████	£18,759	██████	10.11	8.89	1.22	██████
NICE CG181 CV costs	██████	£19,315	██████	10.05	8.86	1.20	██████
TTO study utilities	██████	£18,697	██████	10.84	9.57	1.26	██████
Nurse training 30 minutes	██████	£18,697	██████	10.05	8.86	1.20	██████
Nurse training 2 hours	██████	£18,697	██████	10.05	8.86	1.20	██████
CV, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

5.13 Subgroup analysis

Existing CVD and additional risk factors

As described in Section 3, there are a number of risk factors that are relevant for identifying patients with existing CVD at enhanced risk, which were identified based on ESC/EAS guidelines, a targeted literature review of recurrent CVD risk equations, and expert clinical opinion. A step-wise approach has been taken to assess the impact of these risk factors (Table 5-67) on the cost-effectiveness of evolocumab, whereby:

- CV risk factors assessed individually using the LAPLACE-2 population with existing CVD characteristics
- Combining CV risk factors with age and gender whilst maintaining other cohort characteristics from LAPLACE-2
- Combining two or more risk factors whilst maintaining other cohort characteristics from LAPLACE-2.

All other clinical parameters and variables have been applied as per the base case for the cost-effectiveness analysis of the overall populations. Severity of hypercholesterolaemia has also been included on the basis of baseline LDL-C in the analyses. Baseline cholesterol was not identified as a significant predictor in the REACH registry; however, treatment with statins (yes or no) was identified as a significant predictor of CV death or next CV event. Treatment with statins was associated with HRs of 0.80 (95% CI 0.70, 0.91) and 0.75 (95% CI 0.69, 0.82) for the risk of CV death or next CV event, respectively. The REACH registry

cites the explanation for baseline cholesterol not being a significant predictor being the very common use of statins (74% at baseline). Furthermore, the survey form used in the study only queried whether the cholesterol level was > 200 mg/dL (approximately 5.0 mmol/L), and information on the actual cholesterol level at baseline was not available at baseline for all participants. Thereby cholesterol was not identified as a predictive factor in this analysis.

Scenario 1 (evolocumab and statin versus ezetimibe and statin) has been assessed in this step-wise approach considering the impact of CV risk factors on the cost-effectiveness. The analyses were not repeated for scenarios 2 to 4, since the impact of these CV risk factors on the cost-effectiveness will be independent of the treatment scenarios.

Table 5-67 Patient characteristics relevant for identifying patients with existing CVD at enhanced risk

Source	Risk factor	Impact on CV risk HR (95% CI)
ESC/EAS guidelines for the management of dyslipidaemias 2011 ²	•Patients with type 2 diabetes mellitus and patients with type 1 diabetes mellitus with target organ damage (such as microalbuminuria)	•Non-fatal and fatal CV event risk as per REACH registry
<i>Patients classified as very high risk</i>	•Patients with moderate to severe CKD (eGFR < 60 mL/min/1.73 m ²)	•Assumed equivalent to diabetes (REACH registry)
REACH registry ²⁶ <i>Risk factors for recurrent CV events^a</i>	•Age (years)	•CV death: 1.05 (1.04, 1.06) •Next CV event: 1.03 (1.03, 1.04)
	•Male gender	•CV death: 1.28 (1.12, 1.46) •Next CV event: 1.11 (1.03, 1.21)
	•Diabetes mellitus	•CV death: 1.59 (1.40, 1.80) •Next CV event: 1.46 (1.34, 1.58)
	•2 vascular beds affected	•CV death: 1.28 (1.15, 1.43) •Next CV event: 1.35 (1.26, 1.46)
	•3 vascular beds affected	•CV death: 1.64 (1.32, 2.06) •Next CV event: 1.83 (1.35, 2.13)
	•CV ^a event in previous year	•CV death: 1.31 (1.15, 1.49) •Next CV event: 1.46 (1.35, 1.59)
	•Congestive heart failure	•CV death: 2.46 (2.15, 2.82) •Next CV event: 1.68 (1.53, 1.85)
	•Atrial fibrillation	•CV death: 1.53 (1.32, 1.78) •Next CV event: 1.30 (1.17, 1.46)
Clinician opinion <i>Additional clinically-relevant risk factors for recurrent CV events</i>	•≥ 2 documented acute ischaemic CV events or revascularisation procedures	•Assumed equivalent to diabetes (REACH registry)
	•Elevated plasma Lp(a) ≥ 77 mg/dL (≥ 90% centile)	•Assumed equivalent to diabetes (REACH registry) •Threshold based on findings of

Source	Risk factor	Impact on CV risk HR (95% CI)
		Copenhagen City Heart Study. HR of MI for 90 th –95 th centile (77–117 mg/dL): 1.9 (1.2, 3.0)
^a MI, cerebrovascular disease, or CV mortality. CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HR, hazard ratio; Lp(a), lipoprotein (a); MI, myocardial infarction; REACH, REduction of Atherothrombosis for Continued Health		

Individual risk factors for patients with existing CVD

The impact of the individual risk factors on the cost-effectiveness (evolocumab and statin versus ezetimibe and statin) has been assessed individually whilst maintaining the baseline population characteristics from LAPLACE-2 (Table 5-68). The cost-effectiveness analysis indicates that the risk factors with the greatest impact are number of vascular beds, diabetes mellitus, baseline LDL-C > 6.0 mmol/L, AF, ACS and HF. The cost-effectiveness analyses also indicated that patients starting in either an acute IS or post-IS health state are associated with reduced QALYs gained, whilst the total costs were relatively similar to the base case.

Table 5-68 Cost-effectiveness analysis of evolocumab and statin versus ezetimibe and statin in patients with existing CVD and additional risk factors

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER	Difference
Base case	██████	£20,302	██████	8.06	7.62	0.44	██████	0
Baseline LDL-C								
3.0 mmol/L	██████	£20,544	██████	7.92	7.57	0.35	██████	██████
3.5 mmol/L	██████	£20,338	██████	8.04	7.61	0.43	██████	██████
4.0 mmol/L	██████	£20,142	██████	8.13	7.66	0.48	██████	██████
4.5 mmol/L	██████	£19,956	██████	8.21	7.70	0.51	██████	██████
5.0 mmol/L	██████	£19,779	██████	8.28	7.74	0.54	██████	██████
5.5 mmol/L	██████	£19,611	██████	8.34	7.78	0.56	██████	██████
6.0 mmol/L	██████	£19,452	██████	8.40	7.82	0.59	██████	██████
Gender								
Male	██████	£19,813	██████	7.85	7.41	0.44	██████	██████
Female	██████	£21,392	██████	8.52	8.09	0.43	██████	██████
Diabetes mellitus = Yes	██████	£19,959	██████	7.56	7.00	0.55	██████	██████
Vascular beds = 2	██████	£20,511	██████	7.79	7.28	0.51	██████	██████
Vascular beds = 3	██████	£20,848	██████	7.38	6.77	0.61	██████	██████
AF = Yes	██████	£19,561	██████	7.55	7.00	0.55	██████	██████
CV event in the past year								
ECVD	██████	£17,239	██████	8.90	8.49	0.41	██████	██████
ACS	██████	£26,767	██████	8.46	7.93	0.53	██████	██████
Post-ACS	██████	£22,697	██████	8.61	8.11	0.50	██████	██████
IS	██████	£20,843	██████	5.84	5.62	0.22	██████	██████
Post-IS	██████	£19,326	██████	5.92	5.69	0.23	██████	██████
HF	██████	£23,300	██████	5.94	5.43	0.52	██████	██████
Post-HF	██████	£22,420	██████	6.02	5.53	0.49	██████	██████
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; ECVD, established cardiovascular disease; EvoMab; evolocumab; EZE, ezetimibe; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TTO, time trade off								

Combination of risk factors with baseline LDL-C, age, and gender

Secondly, the impact of combining one of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 5-69). The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000. These results indicate that evolocumab can be considered a cost-effective treatment option in patients with a baseline LDL-C of 3.5 mmol/L and one the following risk factors, when age and gender are taken into consideration:

- diabetes mellitus
- CV risk factors deemed at equivalent risk to diabetes mellitus:
 - moderate to severe CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²)
 - two or more documented acute ischaemic CV events or revascularisation procedures
 - Elevated plasma Lp(a) ≥ 77 mg/dL (≥ 90% centile)
- three vascular beds
- acute coronary syndrome (ACS) in the past 12 months
- other CV conditions that significantly elevate risk of further CV events: atrial fibrillation

Table 5-69 Cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin with specific CV risk factors

Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
3.5 mmol/L	Cohort	Cohort												
		+5												
		+10												
	Male	Cohort												
		+5												
		+10												
	Female	Cohort												
		+5												
		+10												

Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
4.0 mmol/L	Cohort	Cohort												
		+5												
		+10												
	Male	Cohort												
		+5												
		+10												
	Female	Cohort												
		+5												
		+10												
Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
4.5 mmol/L	Cohort	Cohort												
		+5												
		+10												
	Male	Cohort												
		+5												
		+10												
	Female	Cohort												
		+5												
		+10												
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; PACS, post-acute coronary syndrome; PHF, post-heart failure; PIS, post-IS; QALY, quality-adjusted life year; SP, secondary prevention; VB, vascular beds														

Combination of two risk factors with baseline LDL-C, age, and gender

Thirdly, the impact of combining two of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 5-70). The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000. These results indicate that evolocumab can be considered a cost-effective treatment option in patients with a baseline LDL-C of 3.0 mmol/L and two of the following risk factors, when age and gender are taken into consideration:

- diabetes mellitus
- CV risk factors deemed at equivalent risk to diabetes mellitus:
 - moderate to severe CKD (eGFR < 60 mL/min/1.73 m²)
 - two or more documented acute ischaemic CV events or revascularisation procedures
 - Elevated plasma Lp(a) ≥ 77 mg/dL (≥ 90% centile)
- two or more vascular beds
- ACS in the past 12 months
- other CV conditions that significantly elevate risk of further CV events: heart failure (HF) and atrial fibrillation

Table 5-70 Cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin with two specific CV risk factors

Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB
3.0 mmol/L	Cohort	Cohort							
		+5							
		+10							
	Male	Cohort							
		+5							
		+10							
	Female	Cohort							
		+5							
		+10							
Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB

3.5 mmol/L	Cohort	Cohort							
		+5							
		+10							
	Male	Cohort							
		+5							
		+10							
	Female	Cohort							
		+5							
		+10							
Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB
4.0 mmol/L	Cohort	Cohort							
		+5							
		+10							
	Male	Cohort							
		+5							
		+10							
	Female	Cohort							
		+5							
		+10							
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention; VB, vascular beds									

5.14 Validation

Validation of de novo cost-effectiveness analysis

The model was validated by comparing the estimated rate ratio reduction of non-fatal and fatal CV events with CTTC rate ratios by event type over 5 years. This time horizon was chosen since the median follow-up of the 26 trials used from the CTTC meta-analysis was 4.9 years. The results indicate that the model provides consistent, and in instances, conservative estimates. The rate ratios per mmol/L reduction ranged from 0.72 to 0.80 for any major event (excluding HF) compared with 0.72 (95% CI 0.66, 0.78; $p < 0.0001$) per mmol/L reduction as observed for any major vascular event in the '*more versus less intensive statin therapy*' meta-analysis. Additional analyses for the lifetime horizon also indicate that the results remain conservative for major events. Table 5-71 presents the predicted rate ratio by CVD event for evolocumab versus high-intensity statin alone.

Table 5-71 Model validation: Predicted rate ratio by CVD event for evolocumab versus high-intensity statin

	Rate ratio per mmol/L reduction, CTTC 2010	Rate ratio per mmol/L reduction, predicted (5 years)	Rate ratio per mmol/L reduction, predicted (lifetime)	Rate ratio per mmol/L reduction, CTTC 2010	Rate ratio per mmol/L reduction, predicted (5 years)	Rate ratio per mmol/L reduction, predicted (lifetime)
	Existing CVD			HeFH		
Any major event	0.72	0.73	0.76	0.72	0.72	0.80
ACS	0.71	0.70	0.72	0.71	0.70	0.77
IS	0.69	0.68	0.71	0.69	0.68	0.75
HF	0.71	0.92	0.93	0.71	0.79	0.91
CHD death	0.80	0.80	0.83	0.80	0.80	0.90
IS death	1.00	0.99	1.04	1.00	0.95	1.12
Revascularisation	0.66	0.69	0.70	0.66	0.69	0.74
ACS, acute coronary syndrome; CHD, coronary heart disease; CTTC, Cholesterol Treatment Trialists' Collaboration; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; IS, ischaemic stroke						

As an extension of the external validation, the model prediction of CVD events can be compared after matching the model population to available study population characteristics.

On completing a trial of evolocumab (parent trial), patients could enrol into one of two longer-term extension trials, OSLER-1 for patients completing phase 2 trials, and OSLER-2 for those completing phase 3 trials. The OSLER-1 and OSLER-2 trials were designed to gather longer-term data on safety, side-effect profile, and LDL-C reduction, and also included a pre-specified exploratory analysis on adjudicated cardiovascular outcomes.

Model predictions were validated by considering the patient characteristics and the relative reduction (61%) reported in OSLER. The rate ratio of cardiovascular events and procedures

Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

of evolocumab added to statins versus statins was computed in a 1-year time horizon, matching the duration of OSLER. A rate ratio of 0.48, meaning a 52% percent reduction in fatal and non-fatal cardiovascular events and revascularisations, was obtained from the model. This compares favourably to the hazard ratio of 0.47 (95% CI 0.28, 0.78; $p = 0.003$), meaning a 53% reduction in outcomes, presented in OSLER. The reduction in CV events in the economic model and OSLER are therefore well aligned.

5.15 Interpretation and conclusions of economic evidence

The economic evaluation considered patient populations that are consistent with the overall patient population defined in the decision problem, i.e. patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-lowering therapies would be considered in line with current NICE guidance. Although evolocumab provides a consistent and intensive LDL-C lowering treatment effect in all patient populations indicated and in line with current NICE guidance, the priority for use of evolocumab is in those patients who are at the highest residual risk and are most vulnerable to CV events.

In patients without existing CVD, 10-year CVD risk threshold analyses were conducted to identify the minimum 10-year risk required for evolocumab to be cost-effective at different willingness-to-pay thresholds. Although QRISK2 is the risk assessment tool recommended in NICE CG181 for patients without existing CVD, 10-year CVD risks based on the Framingham study (primary prevention) and REACH registry (recurrent events) were used in the economic evaluation for patients without existing CVD, for the reasons outlined in Section 5.3. However, to align with NICE guidance, the absolute minimum 10-year risks expressed as QRISK2 scores are proposed as criteria for initiation of treatment with evolocumab in this population. This can be considered a conservative approach, given that the Framingham study includes a narrower definition of CVD events (i.e. any given risk based on the Framingham definition of CVD will be higher than that of QRISK2 in any given patient).

To date, no other economic evaluations have specifically assessed the cost-effectiveness of lipid-lowering therapies in patients with existing CVD and at high residual risk due to the presence of additional risk factors. NICE CG181 recommends that a risk assessment tool should not be used in patients with existing CVD. Further, currently-available risk assessment tools (e.g. QRISK2 and SCORE) are not intended for use in patients with existing CVD. Therefore, threshold analyses based on 10-year CVD risk as conducted for patients without existing CVD would not be appropriate in the context of current clinical practice and guidelines. To enable the identification of patients at high residual risk due to additional risk factors, various sources of evidence were assessed, i.e. ESC/EAS 2011 guidelines for the management of dyslipidaemias, a targeted literature review of recurrent CVD risk equations and consultation with UK clinicians. Based on this assessment, patient characteristics relevant for identifying patients with existing CVD at high residual risk were identified where the clinical and cost-effectiveness of evolocumab will be optimal in accordance with recognised willingness-to-pay thresholds.

There are a number of strengths in the economic evaluation. Firstly, the clinical evidence underpinning the economic evaluation is based on robust, high-quality evidence (with low risk of bias) on the consistent and sustained effectiveness of evolocumab with respect to lowering LDL-C across various patient populations and therapeutic settings. Secondly, UK observational data (CPRD, HES, and Office of National Statistics) has been used to quantify the acute and long-term CV baseline rates for patient populations of interest and the costs of CV events of interest. These sources are supplementary to previously conducted economic evaluations in the UK. This provides certainty that the anticipated benefits and costs are relevant and reflect the decision problem for this appraisal. Thirdly, evidence for the baseline risk in the HeFH population was identified in a systematic manner (including assessment of bias) in order to estimate the rate ratio for CV event in these high-risk populations. Fourthly, the *de novo* model included additional combined CVD states in order to attenuate the memory-less attribute of a Markov model to appropriately associated CVD history for risk, costs, and utilities. This has been attempted indirectly previously in economic evaluations by associating differential utility weights based on number of CV events.

There are some weaknesses associated with the economic evaluation. Firstly, there are limited long-term data on clinical effectiveness and safety evidence for evolocumab requiring the extrapolation of LDL-C treatment effect over the lifetime horizon. However, supplementary evidence from ongoing, long-term extension studies (OSLER and OSLER-2) indicates that the reduction in LDL-C is maintained for more than 2 years and that evolocumab has a favourable safety and tolerability profile (data representing 7,235 patient-years of exposure to date). Secondly, in the absence of long-term clinical effectiveness data for CV events, we have translated changes in surrogate outcomes (LDL-C) to reductions in CV events based on established findings from the CTTC meta-analysis of 26 statin trials with 129,138 individuals. This relationship is based on evidence from observational, clinical, and genetic data. It is anticipated that the long-term efficacy of evolocumab with respect to reduction of CV events will be demonstrated in a fully-enrolled ongoing study assessing the impact of evolocumab on CV morbidity/mortality (FOURIER). In the interim, supplementary evidence from ongoing, long-term extension studies (OSLER and OSLER-2) show that the reduction in LDL-C is maintained for more than 2 years and that evolocumab is associated with a reduction in CV events of approximately 50%, which is consistent with that predicted as per the CTTC. Additionally, the external validity assessment indicates that the predictions from the model are consistent with the findings from the CTTC in terms of LDL-C reduction to CV events and the findings of OSLER/OSLER-2. Thirdly, there is a lack of direct evidence of evolocumab versus ezetimibe in patients with HeFH. In the absence of this, head-to-head evidence for the relative treatment effect from LAPLACE-2 and GAUSS-2 are used in the HeFH population since the treatment effect of evolocumab was consistent regardless of patient population and patient characteristics, evolocumab dosing regimen, and presence and type of background lipid-lowering therapy.

Further research and analyses for HRQoL data representing disabilities associated with the CVD health states used in the economic evaluation use a number of assumptions to model the changes associated with events. As for risks and costs, evidence is required for differences in short- and long-term changes in HRQoL associated with individual events and any potential difference in HRQoL associated with primary or subsequent events.

6 Assessment of factors relevant to the NHS and other parties

Eligible patient population

Without existing CVD

The number of prioritised eligible patients was estimated based on the following assumptions in Table 6-5. These have been applied to population estimates for adults in England and Wales derived from the Office of National Statistics,²⁰⁷ including population growth projections from 2014 to 2019. There are an estimated 12,000 eligible patients without existing CVD and high risk under the care of a specialist in England and Wales (Table 6-2). This estimate is based on patients with diabetes mellitus without existing CVD as an indicator for the high-risk patient population.

Table 6-1 Without existing CVD eligible patient population – assumptions

Assumption	Value	Rationale
Prevalence of high-risk patients without CVD	0.13%	Estimated prevalence based on patients with diabetes mellitus without history of CVD receiving lipid-lowering therapy based on the CPRD study ⁸⁹
Proportion of patients with elevated cholesterol	20%	Proportion of patients with elevated LDL-C despite lipid-lowering therapy (LDL-C >3 mmol/L) ⁸⁹
Specialist care	80%	Assumption
Eligible proportion	0.012%	Based on overall CVD prevalence, high-risk CVD, and patients under specialist care
CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; low-density lipoprotein cholesterol		

Table 6-2 Estimated eligible adult population without existing CVD in England and Wales

Assumption	2015	2016	2017	2018	2019
England and Wales population	57,874,445	58,344,152	58,817,753	59,295,282	59,776,770
High-risk patients without CVD	74,733	75,340	75,951	76,568	77,190
Adults with elevated cholesterol	14,947	15,068	15,190	15,314	15,438
High-risk patients without CVD under specialist care	11,957	12,054	12,152	12,251	12,350
CVD, cardiovascular disease					

With existing CVD

The number of prioritised eligible patients was estimated based on the following assumptions in Table 6-3. These have been applied to population estimates for adults in England and Wales derived from the Office of National Statistics,²⁰⁷ including population growth projections from 2014 to 2019. There are an estimated 62,000 eligible patients with CVD and high risk under the care of a specialist in England and Wales (Table 6-4).

Table 6-3 With existing CVD eligible patient population – assumptions

Assumption	Value	Rationale
Prevalence of CVD	11.7%	Estimated prevalence of CVD in patients aged 16 years and over ²⁰⁸
High-risk CVD	1.1%	Estimated proportion of patients with existing CVD receiving lipid-lowering therapy based on CPRD study with diabetes mellitus ⁸⁹
Specialist care	80%	Assumption
Eligible proportion	0.107%	Based on overall CVD prevalence, high-risk CVD, and patients under specialist care
CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease		

Table 6-4 Estimated eligible adult population with existing CVD in England and Wales

Assumption	2015	2016	2017	2018	2019
England and Wales population	57,874,445	58,344,152	58,817,753	59,295,282	59,776,770
Adults with CVD	6,788,672	6,843,769	6,899,322	6,955,337	7,011,815
High-risk CVD	77,563	78,193	78,827	79,467	80,113
High-risk CVD under specialist care	62,051	62,554	63,062	63,574	64,090
CVD, cardiovascular disease					

Heterozygous familial hypercholesterolaemia

The number of eligible patients was estimated based on the following assumptions in Table 6-5. These have been applied to population estimates for adults in England and Wales derived from the Office of National Statistics,²⁰⁷ including population growth projections from 2014 to 2019. This is estimated at 5,500 eligible HeFH adult patients who have been diagnosed and are under the care of a specialist in England and Wales (Table 6-6).

Table 6-5 HeFH eligible patient population – assumptions

Assumption	Value	Rationale
Prevalence of HeFH	0.2%	Estimated prevalence of 1 per 500 population ²⁰⁹
Diagnosed population	15%	Patients currently diagnosed ²¹⁰
Specialist care	40%	Estimated 30% and 10% under the care of specialist and cardiologist, respectively. It is anticipated that evolocumab will be initiated in this setting ²⁰⁹
Eligible proportion	0.012%	Based on prevalence, diagnosis and patients under specialist care
HeFH, heterozygous familial hypercholesterolaemia		

Table 6-6 Estimated eligible adult population with HeFH in England and Wales

Assumption	2015	2016	2017	2018	2019
England and Wales population	57,874,445	58,344,152	58,817,753	59,295,282	59,776,770
Adult population (+18 years)	115,749	116,688	117,636	118,591	119,554
Adults with HeFH	17,362	17,503	17,645	17,789	17,933
Diagnosed HeFH	13,653	13,764	13,876	13,989	14,102
HeFH under specialist care	5,461	5,506	5,550	5,595	5,641
HeFH, heterozygous familial hypercholesterolaemia					

Current treatment options and market share

The current treatment option in the relevant populations is ezetimibe (NICE TA132) for those in whom LDL-C is not adequately controlled with statin therapy, or for those that are intolerant to statins. It is assumed that the absolute market share for ezetimibe will remain constant over time and is estimated at 15% and 37% in patients with and without existing CVD, and patients with HeFH, respectively.²¹¹ The uptake of evolocumab was assumed to increase over time as an alternative to ezetimibe. These are summarised in Table 6-7.

Table 6-7 Absolute market share of ezetimibe and evolocumab (current and proposed) in eligible patient populations

Scenario	Population	Medicine	2015	2016	2017	2018	2019
Current	Without existing CVD	Ezetimibe	15%	15%	15%	15%	15%
	Existing CVD	Ezetimibe	15%	15%	15%	15%	15%
	HeFH	Ezetimibe	37%	37%	37%	37%	37%
Proposed	Without existing CVD	Ezetimibe	■	■	■	■	■
		Evolocumab	■	■	■	■	■
	Existing CVD	Ezetimibe	■	■	■	■	■
		Evolocumab	■	■	■	■	■
	HeFH	Ezetimibe	■	■	■	■	■
		Evolocumab	■	■	■	■	■

CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia

Additional treatment costs

The costs of monitoring and training have been included in addition to drug acquisition costs.

Unit costs

The following unit costs have been considered for the budget impact analysis.

- Drug acquisition costs for evolocumab and ezetimibe were based on the respective dosing regimens, cost per pack, and total doses per year (Table 5-21). The cost of ezetimibe was based on the NHS Drug Tariff.²⁰⁴
- Monitoring costs for evolocumab and ezetimibe were based on healthcare resource use from NICE CG181 and unit costs from NHS Reference Costs 2013/2014²⁰⁶ and PSSRU (Table 5-22).^{202,205}

Resource savings

Between 2014 and 2020, the estimated direct cost of CVD is expected to rise from approximately £10 billion per year to approximately £12 billion per year, underlying the importance of making available new therapeutic options to reduce the incidence and long-term costs of CVD (Section 3). The costs associated with acute and long-term management of CV events are based on those described in Table 5-23. The introduction of evolocumab is anticipated to result in a significantly greater reduction of CV events due to substantially greater magnitude of LDL-C reduction relative to ezetimibe. These were based on a CPRD study for healthcare resource use and unit costs from NHS Reference Costs 2013/2014²⁰⁶ and PSSRU Unit Costs of Health and Social Care 2013.²⁰⁵

Estimated annual budget impact

The annual budget impact for the years 2015 to 2019 is provided in Table 6-8 to

Table 6-10 for high-risk patients with and without existing CVD, and patients with HeFH, respectively. The budget impact estimation includes the costs associated with drug acquisition and monitoring and management of CV events. Evolocumab is anticipated to be used at the fixed 140mg Q2W dose which provides certainty associated with drug acquisition costs given no requirement for dose adjustment. The introduction of evolocumab is anticipated to have an incremental budget impact of:

- £[REDACTED] in 2015 and £[REDACTED] in 2019 in high-risk patients without existing CVD
- £[REDACTED] in 2015 and £[REDACTED] in 2019 in high-risk patients with existing CVD
- £[REDACTED] in 2015 and £[REDACTED] in 2019 in patients with HeFH.

Table 6-8 England and Wales budget impact – without existing CVD

Scenario	Costs	Year				
		2015	2016	2017	2018	2019
Current	Drug	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Monitoring	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	CV events	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Total	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Future	Drug	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Monitoring	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	CV events	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Total	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net budget impact		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CV, cardiovascular; CVD, cardiovascular disease						

Table 6-9 England and Wales budget impact – existing CVD

Scenario	Costs	Year				
		2015	2016	2017	2018	2019
Current	Drug	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Monitoring	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	CV events	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Total	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Future	Drug	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Monitoring	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	CV events	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Total	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net budget impact		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CV, cardiovascular; CVD, cardiovascular disease						

Table 6-10 England and Wales budget impact – HeFH

Scenario	Costs	Year				
		2015	2016	2017	2018	2019
Current	Drug	██████	██████	██████	██████	██████
	Monitoring	██████	██████	██████	██████	██████
	CV events	██████	██████	██████	██████	██████
	Total	██████	██████	██████	██████	██████
Future	Drug	██████	██████	██████	██████	██████
	Monitoring	██████	██████	██████	██████	██████
	CV events	██████	██████	██████	██████	██████
	Total	██████	██████	██████	██████	██████
Net budget impact		██████	██████	██████	██████	██████
CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia						

7 References

1. Abifadel M, Rabes JP, Devillers M *et al.* Mutations and polymorphisms in the proprotein convertase subtilisin kexin 9 (PCSK9) gene in cholesterol metabolism and disease. *Hum Mutat* 2009;30:520-9.
2. Reiner Z, Catapano AL, De Backer G *et al.* ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011;32:1769-818.
3. World Health Organisation in collaboration with the World Heart Federation and the World Stroke Organization. Global atlas on cardiovascular disease prevention and control. 2011. editors: Shanthi Mendis, Pekka Puska and Bo Norrving. Available from: http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf (Accessed May 2015).
4. Roger VL, Go AS, Lloyd-Jones DM *et al.* Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 2012;125:e2-e220.
5. Longo DL, Fauci AS, Kasper DL *et al.* Harrison's Online. Harrison's Principles of Internal Medicine, 18th edition - volume 1, 2012. Available from: <http://accessmedicine.mhmedical.com/book.aspx?bookId=331> (Accessed June 2015).
6. Fuster V, Walsh RA, Harrington RA. Hurst's The Heart, 13th edition - volume 1, 2011. Available from: <http://accessmedicine.mhmedical.com/book.aspx?bookID=376> (Accessed June 2015).
7. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. *JAMA* 1987;257:2176-80.
8. Assmann G, Schulte H, Cullen P. New and classical risk factors--the Munster heart study (PROCAM). *Eur J Med Res* 1997;2:237-42.
9. Grundy SM, Cleeman JI, Merz CN *et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.
10. Sharrett AR, Ballantyne CM, Coady SA *et al.* Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2001;104:1108-13.
11. Wilson PW, D'Agostino RB, Levy D *et al.* Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-47.
12. Goldberg AC, Hopkins PN, Toth PP *et al.* Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol* 2011;5:S1-8.
13. Hopkins PN. Encouraging appropriate treatment for familial hypercholesterolemia. *Clinical Lipidology* 2010;5:339-354.
14. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* 1991;303:893-6.

15. Versmissen J, Oosterveer DM, Yazdanpanah M *et al*. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008;337:a2423.
16. Raal FJ, Pilcher GJ, Panz VR *et al*. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. *Circulation* 2011;124:2202-7.
17. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *J Clin Endocrinol Metab* 2012;97:3956-64.
18. Genest J, Hegele RA, Bergeron J *et al*. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. *Can J Cardiol* 2014;30:1471-81.
19. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol* 2011;5:S9-17.
20. Nordestgaard BG, Chapman MJ, Humphries SE *et al*. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013;34:3478-90a.
21. Robinson JG. Management of familial hypercholesterolemia: a review of the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Manag Care Pharm* 2013;19:139-49.
22. Civeira F. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2004;173:55-68.
23. Neil HA, Hammond T, Huxley R, Matthews DR, Humphries SE. Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. *BMJ* 2000;321:148.
24. Office for National Statistics (ONS). 2011 census, population and household estimates for England and Wales. 16 July 2012. Available from: <http://www.ons.gov.uk/ons/rel/census/2011-census/population-and-household-estimates-for-england-and-wales/index.html> (Accessed 24 February 2015).
25. Bhatt DL, Eagle KA, Ohman EM *et al*. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010;304:1350-7.
26. Wilson PW, D'Agostino R, Sr., Bhatt DL *et al*. An international model to predict recurrent cardiovascular disease. *Am J Med* 2012;125:695-703 e1.
27. Health and Social Care Information Centre. National Diabetes Audit 2012–2013 report 2: complications and mortality. 2015. Findings about the quality of care for people with diabetes in England and Wales. Report for the audit period 2012–2013. Available from: <http://www.hscic.gov.uk/catalogue/PUB16496/nati-diab-audi-12-13-rep2.pdf> (Accessed May 2015).
28. National Institute for Health and Care Excellence. NICE CG182. Chronic kidney disease, early identification and management of chronic kidney

disease in adults in primary and secondary care. Issued: July 2014 last modified: March 2015. Available from:

<https://www.nice.org.uk/guidance/cg182/resources/guidance-chronic-kidney-disease-pdf> (Accessed May 2015).

29. Boekholdt SM, Arsenault BJ, Mora S *et al*. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA* 2012;307:1302-9.
30. Criqui MH, Golomb BA. Epidemiologic aspects of lipid abnormalities. *Am J Med* 1998;105:48S-57S.
31. Kastelein JJ, van der Steeg WA, Holme I *et al*. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation* 2008;117:3002-9.
32. Mora S, Otvos JD, Rifai N *et al*. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation* 2009;119:931-9.
33. Mora S, Wenger NK, Demicco DA *et al*. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. *Circulation* 2012;125:1979-87.
34. Nordestgaard BG, Chapman MJ, Ray K *et al*. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J* 2010;31:2844-53.
35. Department of Health. Cardiovascular Disease Outcomes Strategy: Improving outcomes for people with or at risk of cardiovascular disease. Available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/217118/9387-2900853-CVD-Outcomes_web1.pdf. 2013.
36. Office for National Statistics (ONS). Mortality in the United Kingdom, 1983–2013. 11 December 2014. Available from: http://www.ons.gov.uk/ons/dcp171776_387854.pdf (Accessed May 2015).
37. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Supplementary Information. *Lancet* 2015;385:117-71.
38. Department of Health. The NHS outcomes framework 2015/16. Available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf. 2015.
39. Department of Health. Improving outcomes and supporting transparency. Part 1A: A public health outcomes framework for England, 2013-2016. Available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/263658/2901502_PHOF_Improving_Outcomes_PT1A_v1_1.pdf. 2013.
40. Levine DA, Davydow DS, Hough CL *et al*. Functional disability and cognitive impairment after hospitalization for myocardial infarction and stroke. *Circ Cardiovasc Qual Outcomes* 2014;7:863-71.
41. De Smedt D, Clays E, Annemans L *et al*. Health related quality of life in coronary patients and its association with their cardiovascular risk profile: results from the EUROASPIRE III survey. *Int J Cardiol* 2013;168:898-903.

42. McCullagh E, Brigstocke G, Donaldson N, Kalra L. Determinants of caregiving burden and quality of life in caregivers of stroke patients. *Stroke* 2005;36:2181-6.
43. Leal J, Luengo-Fernandez R, Gray A. European Cardiovascular Disease Statistics, 2012 edition. Available from: http://www.escardio.org/static_file/Escardio/Press-media/press-releases/2013/EU-cardiovascular-disease-statistics-2012.pdf (Accessed June 2015).
44. Danese M, Gleeson M, Kutikova L *et al.* Data on file. Costs of cardiovascular (CV) events in the United Kingdom (UK) using real-world data. Abstract submitted to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 18th Annual European Congress, 7–11 November 2015, Milan, Italy.
45. Centre for Economics and Business Research (CEBR). The economic cost of cardiovascular disease from 2014-2020 in six European economies. Research paper prepared for AstraZeneca. August 2014. Available from: <http://www.cebr.com/wp-content/uploads/2014/08/Short-Report-18.08.14.pdf> (Accessed May 2015).
46. Abifadel M, Varret M, Rabes JP *et al.* Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet* 2003;34:154-6.
47. Baigent C, Blackwell L, Emberson J *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-81.
48. Baigent C, Keech A, Kearney PM *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78.
49. Cohen JC, Boerwinkle E, Mosley TH, Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;354:1264-72.
50. LaRosa JC, Grundy SM, Waters DD *et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-35.
51. LaRosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H. Safety and efficacy of Atorvastatin-induced very low-density lipoprotein cholesterol levels in Patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). *Am J Cardiol* 2007;100:747-52.
52. Perk J, De Backer G, Gohlke H *et al.* European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33:1635-701.
53. Wiviott SD, Cannon CP, Morrow DA *et al.* Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. *J Am Coll Cardiol* 2005;46:1411-6.
54. Cannon CP, Braunwald E, McCabe CH *et al.* Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.

55. Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *J Am Coll Cardiol* 2011;57:1666-75.
56. Leeper NJ, Ardehali R, deGoma EM, Heidenreich PA. Statin use in patients with extremely low low-density lipoprotein levels is associated with improved survival. *Circulation* 2007;116:613-8.
57. Boekholdt SM, Hovingh GK, Mora S *et al*. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol* 2014;64:485-94.
58. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
59. Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. *J Lipid Res* 2009;50 Suppl:S172-7.
60. Cullen P, Funke H, Schulte H, Assmann G. Lipoproteins and cardiovascular risk--from genetics to CHD prevention. *Eur Heart J* 1998;19 Suppl C:C5-11.
61. Grundy SM. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia. *J Clin Lipidol* 2013;7:561-5.
62. National Institute for Health and Care Excellence. NICE TA132. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. November 2007. Available from: <http://www.nice.org.uk/guidance/ta132> (Accessed May 2015).
63. Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J Am Coll Cardiol* 2005;46:1855-62.
64. IMPROVE-IT Investigators. IMProved Reduction of Outcomes: Vytorin Efficacy International Trial. A multicenter, double-blind, randomized study to establish the clinical benefit and safety of vytorin (ezetimibe/simvastatin tablet) vs simvastatin monotherapy in high-risk subjects presenting with acute coronary syndrome. 2014. Available from: <http://www.eas-society.org/fileArchive/IMPROVE%20IT%20-%20PRESENTATION%202014-11-17.pdf> (Accessed May 2015).
65. Grundy SM, Cleeman JI, Merz CN *et al*. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Arterioscler Thromb Vasc Biol* 2004;24:e149-61.
66. De Caterina R, Scarano M, Marfisi R *et al*. Cholesterol-lowering interventions and stroke: insights from a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2010;55:198-211.
67. Corvol JC, Bouzamondo A, Sirol M *et al*. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. *Arch Intern Med* 2003;163:669-76.
68. Mihaylova B, Emberson J, Blackwell L *et al*. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581-90.

69. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation* 1998;97:946-52.
70. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326:1423.
71. LaRosa JC, Pedersen TR, Somaratne R, Wasserman SM. Safety and effect of very low levels of low-density lipoprotein cholesterol on cardiovascular events. *Am J Cardiol* 2013;111:1221-9.
72. Sniderman A, Thanassoulis G, Couture P *et al*. Is lower and lower better and better? A re-evaluation of the evidence from the Cholesterol Treatment Trialists' Collaboration meta-analysis for low-density lipoprotein lowering. *J Clin Lipidol* 2012;6:303-9.
73. Stern RH, Yang BB, Hounslow NJ *et al*. Pharmacodynamics and pharmacokinetic-pharmacodynamic relationships of atorvastatin, an HMG-CoA reductase inhibitor. *J Clin Pharmacol* 2000;40:616-23.
74. Jones PH, Davidson MH, Stein EA *et al*. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003;92:152-60.
75. Paramsothy P, Knopp R. Management of dyslipidaemias. *Heart* 2006;92:1529-34.
76. Toth PP. Drug treatment of hyperlipidaemia: a guide to the rational use of lipid-lowering drugs. *Drugs* 2010;70:1363-79.
77. National Institute for Health and Care Excellence. NICE CG181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. July 2014. Available from: <http://www.nice.org.uk/guidance/cg181> (Accessed May 2015).
78. Mancini GB, Baker S, Bergeron J *et al*. Diagnosis, prevention, and management of statin adverse effects and intolerance: proceedings of a Canadian Working Group Consensus Conference. *Can J Cardiol* 2011;27:635-62.
79. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. *Cardiovasc Drugs Ther* 2005;19:403-14.
80. AstraZeneca UK Ltd. Crestor 5mg, 10mg, 20mg and 40mg film-coated tablets – summary of product characteristics, 2014. Available from: <https://www.medicines.org.uk/emc/medicine/11976> (Accessed 24 February 2015).
81. Pfizer Ireland Pharmaceuticals. Lipitor 10 mg film-coated tablets – summary of product characteristics, 2013. Available from: <http://www.medicines.org.uk/EMC/medicine/1424/SPC/Lipitor+10mg,+20mg,+40mg,+80mg+Tablets/> (Accessed February 2015).
82. Merck Sharpe & Dohme Ltd. Zocor 10mg, 20mg, 40mg and 80mg film-coated tablets – summary of product characteristics. Available from: <https://www.medicines.org.uk/emc/medicine/1201> (Accessed February 2015).
83. Kastelein JJ, Akdim F, Stroes ES *et al*. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;358:1431-43.

84. Bays HE, Neff D, Tomassini JE, Tershakovec AM. Ezetimibe: cholesterol lowering and beyond. *Expert Rev Cardiovasc Ther* 2008;6:447-70.
85. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Executive summary, 2001. Available from: <http://www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf> (Accessed May 2015).
86. Kolovou G, Hatzigeorgiou G, Mihas C *et al*. Changes in Lipids and Lipoproteins after Selective LDL Apheresis (7-Year Experience). *Cholesterol* 2012;2012:976578.
87. Heigl F, Hettich R, Lotz N *et al*. Indication and implementation of lipidapheresis, rheopheresis, or immunoabsorption (lessons learnt from Germany's largest apheresis center). *Atheroscler Suppl* 2009;10:137-41.
88. Schmid T, Michailov G. Data on file. Apheresis treatment in German patients with severe hypercholesterolemia - a psychodrama market research. Abstract submitted to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 18th Annual European Congress, 7–11 November 2015, Milan, Italy. 2015.
89. Amgen. Data on file. Healthcare Utilization, Costs and Treatment Patterns Associated with Cardiovascular Events in Patients with Elevated Cardiovascular Risk or Prior CV Events in the UK CPRD Database. 2015.
90. Pedersen KH, SE; Roughton, M; Besford, JS. National Clinical Audit of the Management of Familial Hypercholesterolaemia 2010: Full Report. Clinical Standards Department, Royal College of Physicians. Available at <https://www.rcplondon.ac.uk/sites/default/files/fh-full-audit-report-2011.pdf>. 2010.
91. National Institute for Health and Care Excellence. NICE CG71. Identification and management of familial hypercholesterolaemia. August 2008. Available from: <http://www.nice.org.uk/guidance/cg71> (Accessed May 2015).
92. National Institute for Health and Care Excellence. NICE CG181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Full Guideline. July 2014. Available from: <http://www.nice.org.uk/guidance/cg181/evidence/cg181-lipid-modification-update-full-guideline3> (Accessed May 2015).
93. D'Agostino RB, Russell MW, Huse DM *et al*. Primary and subsequent coronary risk appraisal: new results from the Framingham study. *Am Heart J* 2000;139:272-81.
94. Kannel WB, D'Agostino RB, Silbershatz H *et al*. Profile for estimating risk of heart failure. *Arch Intern Med* 1999;159:1197-204.
95. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke* 1994;25:40-3.
96. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation* 2008;117:176-84.

97. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;301:2331-9.
98. British Heart Foundation. Cardiovascular Disease Statistics 2014. Published: 18 December 2014. Available from: https://www.bhf.org.uk/~media/files/publications/research/bhf_cvd-statistics-2014_web_2.pdf (Accessed May 2015).
99. Go AS, Mozaffarian D, Roger VL *et al.* Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation* 2014;129:e28-e292.
100. Robinson JG, Nedergaard BS, Rogers WJ *et al.* Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* 2014;311:1870-82.
101. Amgen. Data on file. LAPLACE-2 CSR. 2014.
102. Raal FJ, Stein EA, Dufour R *et al.* PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;385:331-40.
103. Amgen. Data on file. RUTHERFORD-2 CSR. 2014.
104. Stroes E, Colquhoun D, Sullivan D *et al.* Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* 2014;63:2541-8.
105. Amgen. Data on file. GAUSS-2 CSR 2014.
106. Blom DJ, Hala T, Bolognese M *et al.* A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med* 2014;370:1809-19.
107. Amgen. Data on file. DESCARTES CSR. 2014.
108. Robinson JG, Rogers WJ, Nedergaard BS *et al.* Rationale and design of LAPLACE-2: a phase 3, randomized, double-blind, placebo- and ezetimibe-controlled trial evaluating the efficacy and safety of evolocumab in subjects with hypercholesterolemia on background statin therapy. *Clin Cardiol* 2014;37:195-203.
109. Amgen. Data on file. LAPLACE-2 study protocol. 2012.
110. Amgen. Data on file. RUTHERFORD-2 study protocol. 2012.
111. Cho L, Rocco M, Colquhoun D *et al.* Design and rationale of the GAUSS-2 study trial: a double-blind, ezetimibe-controlled phase 3 study of the efficacy and tolerability of evolocumab (AMG 145) in subjects with hypercholesterolemia who are intolerant of statin therapy. *Clin Cardiol* 2014;37:131-9.
112. Amgen. Data on file. GAUSS-2 study protocol. 2012.
113. Amgen. Data on file. DESCARTES study protocol. 2013.
114. Robinson JG, Farnier M, Krempf M *et al.* Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1489-99.
115. Centre for Reviews and Dissemination (CRD). Systematic Reviews: CRD's Guidance for Undertaking Reviews in Healthcare. Available from: http://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed June 2015. 2009.
116. Amgen. Data on file. LAPLACE-2 – supplementary data tables
117. Amgen. Data on file. DESCARTES – supplementary data tables

118. Amgen. Data on file. DESCARTES – supplementary figures.
119. Amgen. Data on file. OSLER CSR. Data cut-off, 1st April 2014
120. Amgen. Data on file. OSLER-2 CSR. Data cut-off, 1st April 2014
121. Sabatine MS, Giugliano RP, Wiviott SD *et al.* Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1500-9.
122. Amgen. Data on file. Supplemental statistical analysis plan
123. Amgen. Data on file. TAUSSIG interim CSR. Data cut-off, 1st July 2014
124. Bruckert E, Blaha V, Stein E *et al.* Trial Assessing Long-Term Use of PCSK9 Inhibition in Patients with Genetic LDL Disorders (TAUSSIG): Efficacy and Safety in Patients with Familial Hypercholesterolemia Receiving Lipid Apheresis. Poster presented at the AHA (American Heart Association) Scientific Sessions, 15–19 November 2014, Chicago, USA.
125. Amgen. Data on file. Evolocumab FDA 120-day update. 2014.
126. Amgen. Data on file. Evolocumab Summary of Clinical Safety.
127. Toth PP, Sattar N, Genest J *et al.* A comprehensive safety analysis of 6026 patients from phase 2 and 3 short- and long-term clinical trials with evolocumab (AMG 145). Poster presented at the Annual meeting of the American College of Cardiology, 14–16 March 2015, San Diego, CA.
128. Navarese EP, Kolodziejczak M, Schulze V *et al.* Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. *Ann Intern Med* 2015.
129. Amgen. Data on file. Identification and management of statin intolerance in clinical practice. Results of a web-based clinician survey in the UK. 2015.
130. University of York. Systematic Reviews: CRD's guidance for undertaking reviews in health care. 2009. Available from <http://www.york.ac.uk/crd/> (Accessed June 2015).
131. National Institute for Health and Care Excellence. NICE CG181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Appendices. July 2014. Available from: <http://www.nice.org.uk/guidance/cg181/evidence> (Accessed May 2015).
132. Ara R, Rafia R, Ward SE *et al.* Are intensive lipid-lowering regimens an optimal economic strategy in patients with ACS? An acute and chronic perspective. *Expert Rev Pharmacoecon Outcomes Res* 2009;9:423-33.
133. Ara R, Pandor A, Stevens J *et al.* Prescribing high-dose lipid-lowering therapy early to avoid subsequent cardiovascular events: is this a cost-effective strategy? *Eur J Prev Cardiol* 2012;19:474-83.
134. Ara R, Pandor A, Tumur I *et al.* Cost effectiveness of ezetimibe in patients with cardiovascular disease and statin intolerance or contraindications: a Markov model. *Am J Cardiovasc Drugs* 2008;8:419-27.
135. Ara R, Pandor A, Tumur I *et al.* Estimating the health benefits and costs associated with ezetimibe coadministered with statin therapy compared with higher dose statin monotherapy in patients with established cardiovascular disease: results of a Markov model for UK costs using data registries. *Clin Ther* 2008;30:1508-23.

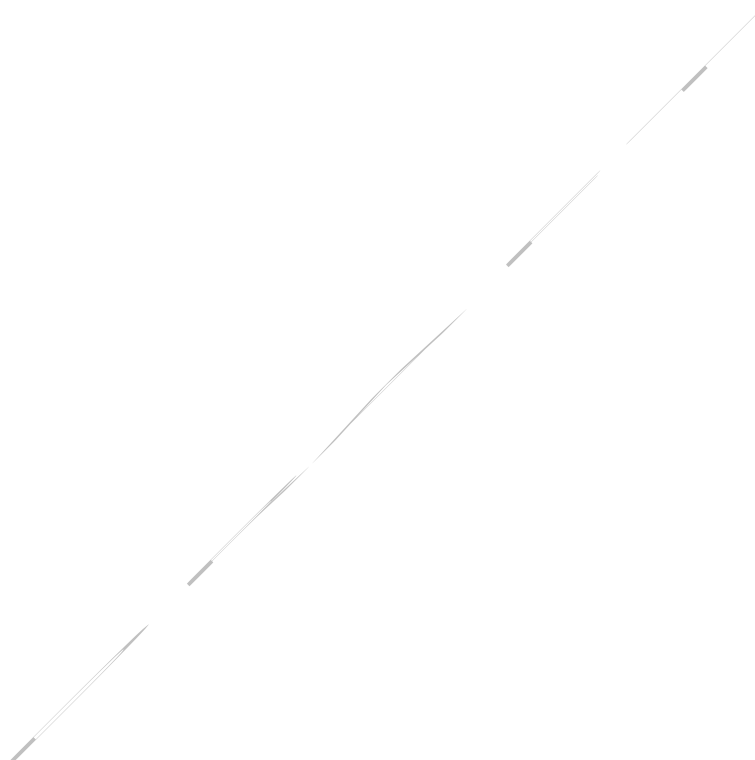
136. Ara R, Tumur I, Pandor A *et al.* Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. *Health Technol Assess* 2008;12:iii, xi-xiii, 1-212.
137. AWMMSG Secretariat Assessment Report. Rosuvastatin (Crestor®) for the prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors. 2011.
138. Mihaylova B, Briggs A, Armitage J *et al.* Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. *BMJ* 2006;333:1145.
139. Nherera L, Calvert NW, Demott K *et al.* Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolaemia. *Curr Med Res Opin* 2010;26:529-36.
140. Reckless J, Davies G, Tunceli K, Hu XH, Brudi P. Projected cost-effectiveness of ezetimibe/simvastatin compared with doubling the statin dose in the United Kingdom: findings from the INFORCE study. *Value Health* 2010;13:726-34.
141. Scottish Medicines Consortium. Rosuvastatin, 5mg, 10mg, 20mg, film-coated tablets (Crestor®) SMC No. (725/11). 2011.
142. Ward S, Lloyd Jones M, Pandor A *et al.* A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007;11:1-160, iii-iv.
143. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;313:275-83.
144. Erickson KF, Japa S, Owens DK *et al.* Cost-effectiveness of statins for primary cardiovascular prevention in chronic kidney disease. *J Am Coll Cardiol* 2013;61:1250-8.
145. Greving JP, Visseren FL, de Wit GA, Algra A. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. *BMJ* 2011;342:d1672.
146. Mould-Quevedo J, Gutiérrez-Ardila M, Eduardo Ordóñez Molina J, Pinsky B, Vargas Zea N. Cost-effectiveness analysis of atorvastatin versus rosuvastatin in primary and secondary cardiovascular prevention populations in Brazil and Columbia. *Value in Health* 2014:48-57.
147. Taylor DC, Pandya A, Thompson D *et al.* Cost-effectiveness of intensive atorvastatin therapy in secondary cardiovascular prevention in the United Kingdom, Spain, and Germany, based on the Treating to New Targets study. *Eur J Health Econ* 2009;10:255-65.
148. Wagner M, Goetghebuer M, Merikle E *et al.* Cost-effectiveness of intensive lipid lowering therapy with 80 mg of atorvastatin, versus 10 mg of atorvastatin, for secondary prevention of cardiovascular disease in Canada. *Can J Clin Pharmacol* 2009;16:e331-45.
149. Barton P, Andronis L, Briggs A, McPherson K, Capewell S. Effectiveness and cost effectiveness of cardiovascular disease prevention in whole populations: modelling study. *BMJ* 2011;343:d4044.

150. National Institute for Health and Care Excellence. NICE TA335: Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome.
151. Bagust A, Boland A, Blundell M *et al*. Ticagrelor for the treatment of acute coronary syndromes. . 2011.
152. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;13:509-18.
153. Ara R, Basarir H, Ward SE. Principles of health economic evaluations of lipid-lowering strategies. *Curr Opin Lipidol* 2012;23:271-81.
154. (ONS) OfNS. 1019 - Office for National Statistics. Death tables 2012: table 5.9. 2013. Available from: <http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Causes+of+Death#tab-data-tables> [Last accessed: June 2015] (1019).
155. (ONS) OfNS. 1020 - Office for National Statistics. Interim Life Tables 2010-12. 2013. Available from: <http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables#tab-data-tables> [Last accessed: June 2015].
156. Kongnakorn T, Ward A, Roberts CS *et al*. Economic evaluation of atorvastatin for prevention of recurrent stroke based on the SPARCL trial. *Value Health* 2009;12:880-7.
157. Lindgren P, Graff J, Olsson AG, Pedersen TJ, Jonsson B. Cost-effectiveness of high-dose atorvastatin compared with regular dose simvastatin. *Eur Heart J* 2007;28:1448-53.
158. van Nooten F, Davies GM, Jukema JW *et al*. Economic evaluation of ezetimibe combined with simvastatin for the treatment of primary hypercholesterolaemia. *Neth Heart J* 2011;19:61-7.
159. Soini EJ, Davies G, Martikainen JA *et al*. Population-based health-economic evaluation of the secondary prevention of coronary heart disease in Finland. *Curr Med Res Opin* 2010;26:25-36.
160. Conly J, Clement F, Tonelli M *et al*. Cost-effectiveness of the use of low- and high-potency statins in people at low cardiovascular risk. *CMAJ* 2011;183:E1180-8.
161. de Vries FM, Denig P, Visser ST, Hak E, Postma MJ. Cost-effectiveness of statins for primary prevention in patients newly diagnosed with type 2 diabetes in the Netherlands. *Value Health* 2014;17:223-30.
162. Fragoulakis V, Kourlaba G, Maniadakis N. Economic evaluation of statins in high-risk patients treated for primary and secondary prevention of cardiovascular disease in Greece. *Clinicoecon Outcomes Res* 2012;4:135-43.
163. National Institute for Health and Care Excellence. NICE: Guide to the methods of technology appraisal 2013 - Process and methods guides. 04 April 2013. 2013.
164. Lothgren M, Danese M, Taylor B, Villa G. Data on file. Avoiding overestimation in annualization of event risk from risk functions for use in economic modeling. Abstract submitted to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 18th Annual European Congress, 7–11 November 2015, Milan, Italy. 2015.
165. D'Agostino RB, Sr., Vasan RS, Pencina MJ *et al*. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743-53.

166. Wong B, Kruse G, Kutikova L *et al.* Data on file. Cardiovascular disease risk associated with familial hypercholesterolemia a literature review. Abstract submitted to American Heart Association (AHA), 7-11 November 2015 Orlando, Florida.
167. Ward S, Lloyd Jones M, Pandor A *et al.* Statins for the Prevention of Coronary Events. Technology assessment report commissioned by the HTA Programme on behalf of The National Institute for Clinical Excellence. . 2005.
168. National Collaborating Centre for Primary Care. A model to estimate the cost-effectiveness of higher versus lower intensity statins in the treatment of coronary heart disease. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE Clinical Guideline 67 Appendix C. 2008.
169. Brown N, Young T, Gray D, Skene AM, Hampton JR. Inpatient deaths from acute myocardial infarction, 1982-92: analysis of data in the Nottingham heart attack register. *BMJ* 1997;315:159-64.
170. Wolfe CD, Rudd AG, Howard R *et al.* Incidence and case fatality rates of stroke subtypes in a multiethnic population: the South London Stroke Register. *J Neurol Neurosurg Psychiatry* 2002;72:211-6.
171. Juul-Moller S, Edvardsson N, Jahnmatz B *et al.* Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. *Lancet* 1992;340:1421-5.
172. Caro J, Migliaccio-Walle K, Ishak KJ, Proskorovsky I. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. *BMC Cardiovasc Disord* 2005;5:14.
173. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;325:293-302.
174. Yusuf S, Zhao F, Mehta SR *et al.* Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
175. Chamnan P, Simmons RK, Hori H *et al.* A simple risk score using routine data for predicting cardiovascular disease in primary care. *Br J Gen Pract* 2010;60:e327-34.
176. Briffa TG, Hobbs MS, Tonkin A *et al.* Population trends of recurrent coronary heart disease event rates remain high. *Circ Cardiovasc Qual Outcomes* 2011;4:107-13.
177. Chun S, Tu JV, Wijeyesundera HC *et al.* Lifetime analysis of hospitalizations and survival of patients newly admitted with heart failure. *Circ Heart Fail* 2012;5:414-21.
178. Ezekowitz JA, Kaul P, Bakal JA *et al.* Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. *J Am Coll Cardiol* 2009;53:13-20.
179. Wells GS, B; O'Connell, D; Peterson, J; Welch, V; Losos, M; Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Accessed June 2015).
180. Amgen. Data on file. GAUSS-2 – supplementary data tables

181. Matza LS, Stewart KD, Gandra SR *et al.* Acute and chronic impact of cardiovascular events on health state utilities. *BMC Health Serv Res* 2015;15:173.
182. Dolan P, Gudex C, Kind P, Williams A. The time trade-off method: results from a general population study. *Health Econ* 1996;5:141-54.
183. Ali K, Warusevitane A, Lally F *et al.* The stroke oxygen pilot study: a randomized controlled trial of the effects of routine oxygen supplementation early after acute stroke--effect on key outcomes at six months. *PLoS One* 2014;8:e59274.
184. Alva M, Gray A, Mihaylova B, Clarke P. The effect of diabetes complications on health-related quality of life: the importance of longitudinal data to address patient heterogeneity. *Health Econ* 2014;23:487-500.
185. Bowen A, Hesketh A, Patchick E *et al.* Clinical effectiveness, cost-effectiveness and service users' perceptions of early, well-resourced communication therapy following a stroke: a randomised controlled trial (the ACT NoW Study). *Health Technol Assess* 2012;16:1-160.
186. Calvert M, Duffy H, Freemantle N *et al.* Population health status of South Asian and African-Caribbean communities in the United Kingdom. *BMC Health Serv Res* 2012;12:101.
187. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). *Med Decis Making* 2002;22:340-9.
188. Dennis M. Effect of intermittent pneumatic compression on disability, living circumstances, quality of life, and hospital costs after stroke: secondary analyses from CLOTS 3, a randomised trial. *Lancet Neurol* 2014;13:1186-92.
189. Kim J, Henderson RA, Pocock SJ *et al.* Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation myocardial infarction: one-year results of the third Randomized Intervention Trial of unstable Angina (RITA-3). *J Am Coll Cardiol* 2005;45:221-8.
190. Logan PA, Armstrong S, Avery TJ *et al.* Rehabilitation aimed at improving outdoor mobility for people after stroke: a multicentre randomised controlled study (the Getting out of the House Study). *Health Technol Assess* 2014;18:vii-viii, 1-113.
191. Longworth L, Buxton MJ, Sculpher M, Smith DH. Estimating utility data from clinical indicators for patients with stable angina. *Eur J Health Econ* 2005;6:347-53.
192. Luengo-Fernandez R, Gray AM, Bull L *et al.* Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. *Neurology* 2013;81:1588-95.
193. Peters M, Crocker H, Jenkinson C, Doll H, Fitzpatrick R. The routine collection of patient-reported outcome measures (PROMs) for long-term conditions in primary care: a cohort survey. *BMJ Open* 2014;4:e003968.
194. Rivero-Arias O, Ouellet M, Gray A *et al.* Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. *Med Decis Making* 2010;30:341-54.
195. Ryan T, Enderby P, Rigby AS. A randomized controlled trial to evaluate intensity of community-based rehabilitation provision following stroke or hip fracture in old age. *Clin Rehabil* 2006;20:123-31.

196. Stafford M, Soljak M, Pledge V, Mindell J. Socio-economic differences in the health-related quality of life impact of cardiovascular conditions. *Eur J Public Health* 2012;22:301-5.
197. Whynes DK, Sprigg N, Selby J, Berge E, Bath PM. Testing for differential item functioning within the EQ-5D. *Med Decis Making* 2013;33:252-60.
198. Whynes DK. Does the correspondence between EQ-5D health state description and VAS score vary by medical condition? *Health Qual Life Outcomes* 2013;11:155.
199. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;316:736-41.
200. Ara R, Pandor A, Stevens J, Rees A, Rafia R. Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation. *Health Technol Assess* 2009;13:1-74, 75-118.
201. McConnachie A, Walker A, Robertson M *et al*. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. *Eur Heart J* 2014;35:290-8.
202. National Institute for Health and Care Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. . 2014.
203. Roze S, Ferrieres J, Bruckert E *et al*. Cost-effectiveness of raising HDL cholesterol by adding prolonged-release nicotinic acid to statin therapy in the secondary prevention setting: a French perspective. *Int J Clin Pract* 2007;61:1805-11.
204. NHS. NHS Electronic Drug Tariff. 2015. Available at [http://www.drugtariff.nhsbsa.nhs.uk/#/00175224-FA/FA00175149/Part VIII](http://www.drugtariff.nhsbsa.nhs.uk/#/00175224-FA/FA00175149/Part%20VIII) products (Accessed May 2015).
205. Curtis L. Unit costs of health & social care 2013. . 2013.
206. Department of Health. NHS Reference Costs 2013 to 2014. Available from: <https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014> (Accessed June 2015).
207. Office for National Statistics (ONS). Office of National Statistics. Annual Mid-year Population Estimates 2014. 2015. Available from: http://ons.gov.uk/ons/dcp171778_406922.pdf (Accessed June 2015).
208. National Institute for Health and Care Excellence. Services for the prevention of cardiovascular disease – commissioning guide 45. 2012. Available at: <https://www.nice.org.uk/guidance/cmg45/chapter/Executive-summary>. (Accessed June 2015).
209. National Institute for Health and Care Excellence. Familial hypercholesterolaemia Costing Template. 2009. Available from: <http://www.nice.org.uk/guidance/cg71/resources/familial-hypercholesterolaemia-costing-template2> (Accessed June 2015).
210. Seed M, Roughton M, Pedersen K *et al*. Current statin treatment, DNA testing and cascade testing of UK patients with familial hypercholesterolaemia *PCCJ* 2012.
211. Amgen. Data on file. Cegedim Secondary Care Lipid Analysis Report. 2014.



**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL
EXCELLENCE**

Single Technology Appraisal (STA)

**Evolocumab for treating primary hypercholesterolaemia
(heterozygous familial and non-familial) and mixed
dyslipidaemia**

**Appendix to the manufacturer/sponsor submission of
evidence**

Amgen Limited

Date: July 2015

Appendix IV: Additional clinical efficacy results

1	Rationale for selection of relevant RCT clinical efficacy evidence to be presented in the main submission and submission appendices.....	6
2	Additional clinical efficacy data for the relevant RCTs.....	9
2.1	Additional LDL-C outcome data.....	9
2.2	Other lipid parameters.....	44
3	Additional clinical efficacy data for the supplementary ongoing long-term extension studies	52
3.1	OSLER	52
3.2	OSLER-2.....	56
4	References.....	57

List of tables

Table 1-1	Details of clinical efficacy results from the relevant RCTs presented in detail in the main submission	6
Table 1-2	Details of clinical efficacy results from the relevant RCTs presented in detail in the submission appendices.....	7
Table 2-1	Mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS) ^a	10
Table 2-2	Treatment difference in mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and week 12 in LAPLACE-2 (FAS) ^a	12
Table 2-3	Absolute (mmol/L) change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS).....	13
Table 2-4	Treatment difference in absolute (mmol/L) change in calculated LDL-C from baseline at the mean of weeks 10/12 and week 12 in LAPLACE-2 (FAS)	15
Table 2-5	Absolute (mmol/L) change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS) ^a	17
Table 2-6	Treatment difference in absolute (mmol/L) change in reflexive LDL-C from baseline at the mean of weeks 10/12 and week 12 in LAPLACE-2 (FAS) ^a	19
Table 2-7	Proportion of subjects achieving calculated LDL-C < 1.8 mmol/L at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS).....	21
Table 2-8	Treatment difference in proportion of subjects achieving calculated LDL-C < 1.8 mmol/L at the mean of weeks 10/12 and at week 12 in LAPLACE-2	23
Table 2-9	Proportion of subjects achieving reflexive LDL-C < 1.8 mmol/L at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS) ^a	25
Table 2-10	Treatment difference in proportion of subjects achieving reflexive LDL-C < 1.8 mmol/L at the mean of weeks 10/12 and at week 12 in LAPLACE-2 ^a	27
Table 2-11	Mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 in RUTHERFORD-2 (FAS) ^a	30
Table 2-12	Absolute change in LDL-C (calculated and reflexive) in mmol/L from baseline at the mean of weeks 10/12 and at week 12 in RUTHERFORD-2 (FAS).....	31
Table 2-13	Proportion of patients achieving LDL-C <1.8 mmol/L (calculated and reflexive) at the mean of weeks 10/12 and at week 12 in RUTHERFORD-2 (FAS).....	33
Table 2-14	Mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 in GAUSS-2 (FAS) ^a	35
Table 2-15	Absolute change in LDL-C (calculated and reflexive) in mmol/L from baseline at the mean of weeks 10/12 and at week 12 in GAUSS-2 (FAS).....	36
Table 2-16	Proportion of patients achieving LDL-C <1.8 mmol/L (calculated and reflexive) at the mean of weeks 10/12 and at week 12 in GAUSS-2 (FAS).....	38
Table 2-17	Mean percent change in ultracentrifugation LDL-C from baseline at week 12 and week 52 in DESCARTES (FAS)	40
Table 2-18	Absolute change (mmol/L) in calculated and ultracentrifugation LDL-C from baseline at week 52 in DESCARTES (FAS).....	41
Table 2-19	Proportion of patients achieving LDL-C <1.8 mmol/L (calculated and ultracentrifugation) at week 52 in DESCARTES (FAS).....	42
Table 2-20	Analysis of percent change from baseline in ultracentrifugation LDL-C between week 12 and week 52 in DESCARTES (FAS).....	43

Table 2-21	Treatment difference (% , 95% CI) ^a of evolocumab compared with placebo and ezetimibe in prespecified cosecondary and teritiary additional lipid endpoints at the mean of weeks 10/12 in LAPLACE-2 (FAS).....	45
Table 2-22	Treatment difference (% , 95% CI) ^a of evolocumab compared with placebo and ezetimibe in prespecified cosecondary and teritiary additional lipid endpoints at week 12 in LAPLACE-2 (FAS).....	47
Table 2-23	Treatment difference (% , 95% CI) ^a of evolocumab compared with placebo in prespecified secondary and teritiary additional lipid endpoints at the mean of weeks 10/12 and week 12 in RUTHERFORD-2 (FAS).....	49
Table 2-24	Treatment difference (% , 95% CI) ^a of evolocumab compared with ezetimibe in prespecified secondary and teritiary additional lipid endpoints at the mean of weeks 10/12 and week 12 in GAUSS-2 (FAS).....	50
Table 2-25	Treatment difference (% , 95% CI) ^a of evolocumab compared with placebo in prespecified secondary and teritiary non-LDL-C endpoints at week 12 and 52 in DESCARTES (FAS).....	51
Table 3-1	Summary of mean percent change from parent study baseline in calculated LDL-C by scheduled visit in year 1 (OSLER, ICOAS).....	53
Table 3-2	Summary of mean percent change from parent study baseline in calculated LDL-C by scheduled visit in year 2+ (OSLER, IAAS).....	54
Table 3-3	Summary of mean percent change from parent study baseline in calculated LDL-C by scheduled visit in year 1 (OSLER-2, ICOAS).....	56

List of figures

Figure 3-1	Plot of mean percent change from baseline in calculated LDL-C by scheduled visit and treatment group (OSLER, ICOAS and IAAS).....	55

1 Rationale for selection of relevant RCT clinical efficacy evidence to be presented in the main submission and submission appendices

All prespecified primary, secondary and tertiary efficacy outcomes from each of the relevant RCTs are presented in the main submission and in this appendix.

A rationale for selection of clinical efficacy evidence from the relevant RCTs presented in the main submission is provided in Table 1-1.

Table 1-1 Details of clinical efficacy results from the relevant RCTs presented in detail in the main submission

Study	Outcomes presented in main submission	Rationale for inclusion in main submission
20110115 (LAPLACE-2)	Co-primary endpoints at the mean of weeks 10/12 and at week 12:	• Co-primary endpoints • Percent change in LDL-C is the key efficacy driver of the economic evaluation
20110117 (RUTHERFORD-2)	• LDL-C (calculated) – mean percent change from baseline and treatment differences • LDL-C (calculated) – mean percent change from baseline and treatment differences in a pooled analysis across all statin cohorts and in a pooled analysis across atorvastatin cohorts (LAPLACE-2 only)	• Calculated LDL-C assessment is the method of LDL-C assessment primarily utilised in clinical practice • Alignment with the draft SmPC which presents calculated LDL-C results • Pooled statin and atorvastatin analysis presented for LAPLACE-2 as analyses included in the draft SmPC
20110116 (GAUSS-2)		
20110109 (DESCARTES)	Primary endpoint: • LDL-C (calculated) – mean percent change from baseline at week 52 and treatment differences	• Primary endpoint (LDL-C mean percent change from baseline at week 52) • Percent change in LDL-C is the key efficacy driver of the economic evaluation
	Secondary endpoint: • LDL-C (calculated) – mean percent change from baseline at week 12 and treatment differences	• Calculated LDL-C assessment is the method of LDL-C assessment primarily utilised in clinical practice • Alignment with the draft SmPC which presents calculated LDL-C results
LDL-C, low-density lipoprotein cholesterol; SmPC, summary of product characteristics		

In addition to brevity (given the large volume of clinical data presented in the main submission), a rationale for inclusion of clinical efficacy evidence from the relevant RCTs in this appendix instead of the main submission is provided in Table 1-2

Table 1-2 Details of clinical efficacy results from the relevant RCTs presented in detail in the submission appendices

Study	Outcomes presented	Rationale for inclusion in appendices instead of main submission
20110115 (LAPLACE-2)	Co-primary endpoints at the mean of weeks 10/12 and at week 12: • LDL-C (reflexive) – mean percent change from baseline and treatment differences	• Ultracentrifugation (utilised in the reflexive approach to LDL-C assessment) is not routinely utilised in UK clinical practice
20110116 (GAUSS-2)	Co-secondary endpoints at the mean of weeks 10/12 and at week 12: • LDL-C (calculated and reflexive) - absolute (mmol/L) mean change from baseline and treatment differences • LDL-C (calculated and reflexive) -proportion of subjects achieving LDL-C < 1.8 mmol/L and treatment differences (calculated and reflexive) • Mean percent change from baseline in non-HDL-C, ApoB, TC/HDL-C, ApoB/ApoA1 ratio, Lp(a) , triglycerides, VLDL-C, and HDL-C (summary of treatment differences only)	• Ultracentrifugation (utilised in the reflexive approach to LDL-C assessment) is not routinely utilised in UK clinical practice • Endpoints do not feed into the economic evaluation • Relevant NICE guidelines do not discuss endpoints (apart from non-HDL-C) as being relevant for clinical decision-making • Summary of treatment differences for lipid outcomes other than LDL-C only presented for brevity
20110117 (RUTHERFORD-2)	Tertiary endpoints at the mean of weeks 10/12 and at week 12: • Mean percent change from baseline in ApoA1 (summary of treatment differences only)	
20110109 (DESCARTES)	Primary endpoint: • LDL-C (ultracentrifugation) - mean percent change from baseline at week 52	• Ultracentrifugation is not routinely utilised in UK clinical practice

Study	Outcomes presented	Rationale for inclusion in appendices instead of main submission
	Secondary endpoints: • LDL-C (ultracentrifugation) - mean percent change from baseline at week 12 • LDL-C (calculated and ultracentrifugation) - absolute (mmol/L) mean change from baseline and treatment differences at week 52 • LDL-C (calculated and ultracentrifugation) - proportion of subjects achieving LDL-C < 1.8 mmol/L and treatment differences at week 52 • Mean percent change from baseline in TC, non-HDL-C, ApoB, TC/HDL-C ratio, ApoB/ApoA1, Lp(a), TG, HDL-C, and VLDL-C at week 52 (summary of treatment differences only) • Mean percent change from baseline in TC at week 12 (summary of treatment differences only) • LDL-C (ultracentrifugation) - mean percent change from week 12 in LDL-C at week 52 Tertiary endpoint: • Mean percent change from baseline in ApoA1 at week 52 (summary of treatment differences only)	• Endpoints do not feed into the economic evaluation • Ultracentrifugation is not routinely utilised in UK clinical practice • Relevant NICE guidelines do not discuss endpoints (apart from non-HDL-C) as being relevant for clinical decision-making • Summary of treatment differences for lipid outcomes other than LDL-C only presented for brevity LDL-C - mean percent change from week 12 in LDL-C at week 52 is an estimation endpoint (not hypothesis testing)
ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); SmPC, summary of product characteristics; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol		

2 Additional clinical efficacy data for the relevant RCTs

2.1 Additional LDL-C outcome data

LAPLACE-2

The following additional LDL-C clinical efficacy results for LAPLACE-2 are provided below:

- Summary of mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 (Table 2-1 and Table 2-2)
- Summary of absolute change in LDL-C in mmol/L from baseline at the mean of weeks 10/12 and at week 12
 - Calculated LDL-C (Table 2-3 and Table 2-4)
 - Reflexive LDL-C (Table 2-5 and Table 2-6)
- Summary of the proportion (%) of patients achieving LDL-C < 1.8 mmol/L at the mean of weeks 10/12 and at week 12 (Table 2-13)
 - Calculated LDL-C (Table 2-7 and Table 2-8)
 - Reflexive LDL-C (Table 2-9 and Table 2-10)

Table 2-1 Mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS) ^a

	Atorvastatin 10 mg cohort					
	Placebo Q2W + Ezetimibe 10 mg QD (N=56)	Placebo Q2W + Placebo QD (N=56)	EvoMab 140 mg Q2W + Placebo QD (N=110)	Placebo QM + Ezetimibe 10 mg QD (N=55)	Placebo QM + Placebo QD (N=55)	EvoMab 420 mg QM + Placebo QD (N=110)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^b	-23.9 (-28.5, -19.3)	8.5 (4.1, 13.0)	-61.4 (-64.6, -58.2)	-19.0 (-24.0, -13.9)	0.4 (-4.8, 5.5)	-62.5 (-66.1, -58.9)
Week 12 mean percent change from baseline (95% CI) ^b	-22.0 (-27.1, -16.8)	9.9 (4.9, 14.9)	-61.6 (-65.1, -58.0)	-17.1 (-22.6, -11.6)	1.0 (-4.6, 6.5)	-58.2 (-62.1, -54.3)
	Atorvastatin 80 mg cohort					
	Placebo Q2W + Ezetimibe 10 mg QD (N=56)	Placebo Q2W + Placebo QD (N=55)	EvoMab 140 mg Q2W + Placebo QD (N=109)	Placebo QM + Ezetimibe 10 mg QD (N=54)	Placebo QM + Placebo QD (N=55)	EvoMab 420 mg QM + Placebo QD (N=110)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^b	-16.9 (-24.5, -9.2)	13.1 (5.3, 21.0)	-61.8 (-67.3, -56.3)	-21.3 (-28.0, -14.5)	9.8 (3.1, 16.5)	-65.1 (-69.8, -60.3)
Week 12 mean percent change from baseline (95% CI) ^b	-14.6 (-23.1, -6.2)	14.5 (5.8, 23.2)	-61.8 (-67.8, -55.8)	-19.8 (-27.4, -12.2)	11.8 (4.2, 19.4)	-58.7 (-64.1, -53.3)

	Rosuvastatin 5 mg cohort				Rosuvastatin 40 mg cohort				Simvastatin 40 mg cohort			
	Placebo Q2W (N=58)	EvoMab 140 mg Q2W (N=113)	Placebo QM (N=57)	EvoMab 420 mg QM (N=115)	Placebo Q2W (N=56)	EvoMab 140 mg Q2W (N=111)	Placebo QM (N=55)	EvoMab 420 mg QM (N=112)	Placebo Q2W (N=56)	EvoMab 140 mg Q2W (N=112)	Placebo QM (N=55)	EvoMab 420 mg QM (N=115)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^b	7.6 (2.8, 12.3)	-59.3 (-62.8,-55.9)	2.8 (-2.1, 7.7)	-63.8 (-67.3,-60.3)	6.6 (0.4, 12.7)	-59.1 (-63.5,54.7)	0.0 (-7.0, 6.9)	-62.9 (-67.8,58.1)	3.3 (-3.4, 10.0)	-66.2 (-72.0,60.4)	6.0 (-3.5, 15.5)	-62.5 (-70.0,54.9)
Week 12 mean percent change from baseline (95% CI) ^b	8.1 (2.8, 13.4)	-60.1 (-63.9,-56.3)	5.1 (-0.1, 10.3)	-59.4 (-63.1,-55.7)	9.4 (2.3, 16.5)	-58.9 (-64.0,53.8)	2.6 (-5.9, 11.1)	-52.4 (-58.3,46.5)	4.7 (-2.4, 11.8)	-65.9 (-71.9,59.9)	3.4 (-6.3, 13.1)	-57.0 (-64.8,49.3)
References: LAPLACE-2 primary study publication ¹ and CSR ² Tables 14-4.1.1, 14-4.1.2, 14-4.1.3, 14-4.1.4 and 14-4.1.5												
Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Three patients did not receive investigational product as randomised (one in the evolocumab Q2W + oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis ^a For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available; ^b Values are least squares means, which are from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates												
CI, confidence interval; EvoMab, evolocumab; FAS, full analysis set; LDL-C, low-density lipoprotein cholesterol; N, number of subjects randomised and dosed in the full analysis set; Q2W, every 2 weeks; QD, daily; QM, monthly.												

Table 2-2 Treatment difference in mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and week 12 in LAPLACE-2 (FAS) ^a

Mean of weeks 10/12		Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg QD or Placebo Q2W					Evolocumab 420 mg QM vs. Ezetimibe 10 mg QD or Placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^{b, c}	-70.0 (-75.4, -64.5) p < 0.001 ^d	-74.9 (-84.5, -65.4) p < 0.001 ^d	-66.9 (-72.7, -61.1) p < 0.001 ^d	-65.7 (-73.2, -58.1) p < 0.001 ^d	-69.4 (-74.9, -64.0) p < 0.001 ^d	-62.8 (-69.1, -56.6) p < 0.001 ^d	-74.8 (-83.0, -66.6) p < 0.001 ^d	-66.6 (-72.6, -60.6) p < 0.001 ^d	-62.9 (-71.4, -54.5) p < 0.001 ^d	-68.5 (-76.7, -60.2) p < 0.001 ^d
	Treatment difference vs. ezetimibe (95% CI) ^{b, c}	-37.5 (-43.0, -32.0) p < 0.001 ^d	-45.0 (-54.3, -35.6) p < 0.001 ^d	-	-	-	-43.5 (-49.7, -37.3) p < 0.001 ^d	-43.8 (-52.1, -35.6) p < 0.001 ^d	-	-	-
Week 12		Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg QD or Placebo Q2W					Evolocumab 420 mg QM vs. Ezetimibe 10 mg QD or Placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^{b, c}	-71.4 (-77.6, -65.3) p < 0.001 ^d	-76.3 (-86.9, -65.7) p < 0.001 ^d	-68.2 (-74.7, -61.7) p < 0.001 ^d	-68.3 (-77.0, -59.6) p < 0.001 ^d	-70.6 (-76.7, -64.4) p < 0.001 ^d	-59.2 (-65.9, -52.4) p < 0.001 ^d	-70.5 (-79.8, -61.2) p < 0.001 ^d	-64.5 (-70.8, -58.1) p < 0.001 ^d	-55.0 (-65.3, -44.7) p < 0.001 ^d	-60.4 (-69.1, -51.7) p < 0.001 ^d
	Treatment difference vs. ezetimibe (95% CI) ^{b, c}	-39.6 (-45.8, -33.4) p < 0.001 ^d	-47.2 (-57.5, -36.9) p < 0.001 ^d	-	-	-	-41.1 (-47.8, -34.4) p < 0.001 ^d	-38.9 (-48.2, -29.6) p < 0.001 ^d	-	-	-

References: LAPLACE-2 primary study publication¹ and CSR² Tables 10-3, Tables 14-4.1.1, 14-4.1.2, 14-4.1.3, 14-4.1.4 and 14-4.1.5

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Three patients did not receive investigational product as randomised (one in the evolocumab Q2W + oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis ^a For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available; ^b Values are least squares means, which are from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates; ^c Treatment differences were within each dose frequency group using oral placebo + subcutaneous placebo or ezetimibe + subcutaneous placebo as the reference; ^d Nominal p-value and adjusted p-value. Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, and the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance.

CI, confidence interval; N, number of subjects randomised and dosed in the full analysis set; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly.

Table 2-3 Absolute (mmol/L) change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS)

	Atorvastatin 10 mg cohort					
	Placebo Q2W + Ezetimibe 10 mg QD (N=56)	Placebo Q2W + Placebo QD (N=56)	EvoMab 140 mg Q2W + Placebo QD (N=110)	Placebo QM + Ezetimibe 10 mg QD (N=55)	Placebo QM + Placebo QD (N=55)	EvoMab 420 mg QM + Placebo QD (N=110)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^a	-0.8 (-1.0, -0.6)	0.2 (-0.0, 0.4)	-2.1 (-2.2, -1.9)	-0.6 (-0.9, -0.4)	0.0 (-0.2, 0.2)	-2.1 (-2.3, -2.0)
Week 12 mean percent change from baseline (95% CI) ^a	-0.7 (-1.0, -0.5)	0.2 (0.0, 0.4)	-2.1 (-2.2, -1.9)	-0.6 (-0.8, -0.4)	0.0 (-0.2, 0.3)	-2.0 (-2.2, -1.8)
	Atorvastatin 80 mg cohort					
	Placebo Q2W + Ezetimibe 10 mg QD (N=56)	Placebo Q2W + Placebo QD (N=55)	EvoMab 140 mg Q2W + Placebo QD (N=109)	Placebo QM + Ezetimibe 10 mg QD (N=54)	Placebo QM + Placebo QD (N=55)	EvoMab 420 mg QM + Placebo QD (N=110)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^a	-0.3 (-0.6, -0.1)	0.3 (0.0, 0.5)	-1.6 (-1.8, -1.4)	-0.6 (-0.8, -0.4)	0.1 (-0.0, 0.3)	-1.6 (-1.8, -1.5)
Week 12 mean percent change from baseline (95% CI) ^a	-0.3 (-0.5, -0.0)	0.3 (0.1, 0.6)	-1.6 (-1.8, -1.4)	-0.5 (-0.7, -0.3)	0.2 (-0.0, 0.4)	-1.5 (-1.6, -1.3)

	Rosuvastatin 5 mg cohort				Rosuvastatin 40 mg cohort				Simvastatin 40 mg cohort			
	Placebo Q2W (N=58)	EvoMab 140 mg Q2W (N=113)	Placebo QM (N=57)	EvoMab 420 mg QM (N=115)	Placebo Q2W (N=56)	EvoMab 140 mg Q2W (N=111)	Placebo QM (N=55)	EvoMab 420 mg QM (N=112)	Placebo Q2W (N=56)	EvoMab 140 mg Q2W (N=112)	Placebo QM (N=55)	EvoMab 420 mg QM (N=115)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^a	0.2 (-0.0, 0.4)	-1.8 (-2.0, -1.7)	0.0 (-0.2, 0.2)	-2.1 (-2.2, -1.9)	0.1 (-0.1, 0.3)	-1.4 (-1.5, -1.3)	-0.1 (-0.3, 0.1)	-1.5 (-1.7, -1.4)	-0.1 (-0.4, 0.1)	-2.3 (-2.5, -2.0)	0.0 (-0.4, 0.4)	-2.1 (-2.4, -1.8)
Week 12 mean percent change from baseline (95% CI) ^a	0.2 (0.0, 0.4)	-1.9 (-2.0, -1.7)	0.1 (-0.2, 0.3)	-1.9 (-2.1, -1.8)	0.1 (0.0, 0.3)	-1.4 (-1.5, -1.3)	-0.0 (-0.3, 0.2)	-1.3 (-1.4, -1.1)	-0.1 (-0.4, 0.2)	-2.3 (-2.5, -2.0)	-0.1 (-0.4, 0.3)	-1.9 (-2.2, -1.6)
References: LAPLACE-2 CSR ² Tables 14-4.27.16, 14-4.27.17, 14-4.27.18, 14-4.27.19, and 14-4.27.20												
Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Three patients did not receive investigational product as randomised (one in the evolocumab Q2W + oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis ^a Values are least squares means, which are from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates												
CI, confidence interval; EvoMab, evolocumab; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; Q2W, every 2 weeks; QD, daily; QM, monthly.												

Table 2-4 Treatment difference in absolute (mmol/L) change in calculated LDL-C from baseline at the mean of weeks 10/12 and week 12 in LAPLACE-2 (FAS)

Mean of weeks 10/12		Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg QD or Placebo Q2W					Evolocumab 420 mg QM vs. Ezetimibe 10 mg QD or Placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^{a,b}	-2.2 (-2.5, -2.0) p < 0.001 ^c	-1.9 (-2.2, -1.6) p < 0.001 ^c	-2.0 (-2.2, -1.8) p < 0.001 ^c	-1.5 (-1.7, -1.3) p < 0.001 ^c	-2.1 (-2.3, -1.9) p < 0.001 ^c	-2.1 (-2.4, -1.8) p < 0.001 ^c	-1.8 (-2.0, -1.5) p < 0.001 ^c	-2.0 (-2.3, -1.8) p < 0.001 ^c	-1.4 (-1.7, -1.1) p < 0.001 ^c	-2.1 (-2.4, -1.8) p < 0.001 ^c
	Treatment difference vs. ezetimibe (95% CI) ^{a,b}	-1.2 (-1.5, -1.0) p < 0.001 ^c	-1.3 (-1.6, -1.0) p < 0.001 ^c	-	-	-	-1.5 (-1.8, -1.2) p < 0.001 ^c	-1.1 (-1.3, -0.8) p < 0.001 ^c	-	-	-
Week 12		Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg QD or Placebo Q2W					Evolocumab 420 mg QM vs. Ezetimibe 10 mg QD or Placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^{a,b}	-2.3 (-2.6, -2.0) p < 0.001 ^c	-1.9 (-2.3, -1.6) p < 0.001 ^c	-2.1 (-2.3, -1.8) p < 0.001 ^c	-1.5 (-1.8, -1.3) p < 0.001 ^c	-2.1 (-2.4, -1.9) p < 0.001 ^c	-2.0 (-2.3, -1.7) p < 0.001 ^c	-1.7 (-1.9, -1.4) p < 0.001 ^c	-2.0 (-2.2, -1.7) p < 0.001 ^c	-1.2 (-1.5, -0.9) p < 0.001 ^c	-1.9 (-2.2, -1.5) p < 0.001 ^c
	Treatment difference vs. ezetimibe (95% CI) ^{a,b}	-1.3 (-1.6, -1.1) p < 0.001 ^c	-1.3 (-1.7, -1.0) p < 0.001 ^c	-	-	-	-1.4 (-1.7, -1.1) p < 0.001 ^c	-1.0 (-1.2, -0.7) p < 0.001 ^c	-	-	-

References: LAPLACE-2 CSR² Tables 14-4.27.16, 14-4.27.17, 14-4.27.18, 14-4.27.19, and 14-4.27.20

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Three patients did not receive investigational product as randomised (one in the evolocumab Q2W + oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis

^a Values are least squares means, which are from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates

^b Treatment differences were within each dose frequency group using oral placebo + subcutaneous placebo or ezetimibe + subcutaneous placebo as the reference

^c Nominal p-value. No multiplicity adjustment was carried for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy, though the least significant p-value across the co-primary endpoints is < 0.001

CI, confidence interval; N, number of subjects randomised and dosed in the full analysis set; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly.

Table 2-5 Absolute (mmol/L) change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS) ^a

	Atorvastatin 10 mg cohort					
	Placebo Q2W + Ezetimibe 10 mg QD (N=56)	Placebo Q2W + Placebo QD (N=56)	EvoMab 140 mg Q2W + Placebo QD (N=110)	Placebo QM + Ezetimibe 10 mg QD (N=55)	Placebo QM + Placebo QD (N=55)	EvoMab 420 mg QM + Placebo QD (N=110)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^b	-0.8 (-1.0, -0.6)	0.2 (-0.0, 0.4)	-2.0 (-2.1, -1.9)	-0.7 (-0.9, -0.4)	0.0 (-0.2, 0.2)	-2.1 (-2.2, -1.9)
Week 12 mean percent change from baseline (95% CI) ^b	-0.8 (-1.0, -0.6)	0.2 (0.0, 0.4)	-2.0 (-2.1, -1.8)	-0.6 (-0.8, -0.4)	0.0 (-0.2, 0.3)	-1.9 (-2.1, -1.8)
	Atorvastatin 80 mg cohort					
	Placebo Q2W + Ezetimibe 10 mg QD (N=56)	Placebo Q2W + Placebo QD (N=55)	EvoMab 140 mg Q2W + Placebo QD (N=109)	Placebo QM + Ezetimibe 10 mg QD (N=54)	Placebo QM + Placebo QD (N=55)	EvoMab 420 mg QM + Placebo QD (N=110)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^b	-0.3 (-0.6, -0.1)	0.3 (0.0, 0.5)	-1.5 (-1.7, -1.3)	-0.6 (-0.7, -0.4)	0.1 (-0.0, 0.3)	-1.6 (-1.7, -1.4)
Week 12 mean percent change from baseline (95% CI) ^b	-0.3 (-0.5, 0.0)	0.3 (0.1, 0.6)	-1.5 (-1.7, -1.3)	-0.5 (-0.7, -0.3)	0.2 (0.0, 0.4)	-1.4 (-1.6, -1.3)

	Rosuvastatin 5 mg cohort				Rosuvastatin 40 mg cohort				Simvastatin 40 mg cohort			
	Placebo Q2W (N=58)	EvoMab 140 mg Q2W (N=113)	Placebo QM (N=57)	EvoMab 420 mg QM (N=115)	Placebo Q2W (N=56)	EvoMab 140 mg Q2W (N=111)	Placebo QM (N=55)	EvoMab 420 mg QM (N=112)	Placebo Q2W (N=56)	EvoMab 140 mg Q2W (N=112)	Placebo QM (N=55)	EvoMab 420 mg QM (N=115)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^b	0.2 (-0.0, 0.3)	-1.8 (-1.9, -1.7)	0.0 (-0.2, 0.2)	-2.0 (-2.2, -1.9)	0.1 (-0.1, 0.2)	-1.4 (-1.5, -1.2)	-0.1 (-0.3, 0.1)	-1.4 (-1.6, -1.3)	-0.1 (-0.4, 0.1)	-2.2 (-2.4, -1.9)	0.0 (-0.3, 0.4)	-2.0 (-2.3, -1.8)
Week 12 mean percent change from baseline (95% CI) ^b	0.2 (0.0, 0.4)	-1.8 (-1.9, -1.7)	0.1 (-0.2, 0.3)	-1.9 (-2.1, -1.7)	0.1 (0.0, 0.3)	-1.4 (-1.5, -1.2)	-0.1 (-0.3, 0.2)	-1.2 (-1.4, -1.0)	-0.1 (-0.4, 0.2)	-2.2 (-2.4, -1.9)	0.0 (-0.4, 0.3)	-1.9 (-2.1, -1.6)
References: LAPLACE-2 primary study publication ¹ and CSR ² Tables 14-4.27.6, 14-4.27.7, 14-4.27.8, 14-4.27.9, and 14-4.27.10												
Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Three patients did not receive investigational product as randomised (one in the evolocumab Q2W + oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis												
^a For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available												
^b Values are least squares means, which are from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.												
CI, confidence interval; EvoMab, evolocumab; FAS, full analysis set; LDL-C, low-density lipoprotein cholesterol; N, number of subjects randomised and dosed in the full analysis set; Q2W, every 2 weeks; QD, daily; QM, monthly.												

Table 2-6 Treatment difference in absolute (mmol/L) change in reflexive LDL-C from baseline at the mean of weeks 10/12 and week 12 in LAPLACE-2 (FAS) ^a

Mean of weeks 10/12		Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg QD or Placebo Q2W					Evolocumab 420 mg QM vs. Ezetimibe 10 mg QD or Placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^{b, c}	-2.2 (-2.4, -1.9) p < 0.001 ^d	-1.8 (-2.1, -1.5) p < 0.001	-2.0 (-2.2, -1.7) p < 0.001	-1.4 (-1.6, -1.3) p < 0.001	-2.0 (-2.2, -1.8) p < 0.001	-2.1 (-2.3, -1.8) p < 0.001	-1.7 (-1.9, -1.5) p < 0.001	-2.0 (-2.3, -1.8) p < 0.001	-1.3 (-1.6, -1.1) p < 0.001	-2.1 (-2.4, -1.8) p < 0.001
	Treatment difference vs. ezetimibe (95% CI) ^{b, c}	-1.1 (-1.4, -0.9) p < 0.001 ^d	-1.2 (-1.5, -0.9) p < 0.001 ^d	-	-	-	-1.4 (-1.7, -1.2) p < 0.001 ^d	-1.0 (-1.2, -0.8) p < 0.001 ^d	-	-	-
Week 12		Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg QD or Placebo Q2W					Evolocumab 420 mg QM vs. Ezetimibe 10 mg QD or Placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^{b, c}	-2.2 (-2.5, -2.0) p < 0.001 ^d	-1.9 (-2.2, -1.5) p < 0.001 ^d	-2.0 (-2.2, -1.8) p < 0.001 ^d	-1.5 (-1.7, -1.3) p < 0.001 ^d	-2.0 (-2.3, -1.8) p < 0.001 ^d	-2.0 (-2.2, -1.7) p < 0.001 ^d	-1.6 (-1.9, -1.3) p < 0.001 ^d	-2.0 (-2.2, -1.7) p < 0.001 ^d	-1.2 (-1.4, -0.9) p < 0.001 ^d	-1.9 (-2.2, -1.6) p < 0.001 ^d
	Treatment difference vs. ezetimibe (95% CI) ^{b, c}	-1.2 (-1.5, -1.0) p < 0.001 ^d	-1.3 (-1.6, -0.9) p < 0.001 ^d	-	-	-	-1.3 (-1.6, -1.1) p < 0.001 ^d	-0.9 (-1.2, -0.7) p < 0.001 ^d	-	-	-

References: LAPLACE-2 primary study publication¹ and CSR² Tables 14-4.27.6, 14-4.27.7, 14-4.27.8, 14-4.27.9, and 14-4.27.10

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Three patients did not receive investigational product as randomised (one in the evolocumab Q2W + oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis.

^a For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available

^b Values are least squares means, which are from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit, and the

interaction of treatment with scheduled visit as covariates

^c Treatment differences were within each dose frequency group using oral placebo + subcutaneous placebo or ezetimibe + subcutaneous placebo as the reference

^d Nominal p-value and adjusted p-value. Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, and the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance.

CI, confidence interval; N, number of subjects randomised and dosed in the full analysis set; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly.

Table 2-7 Proportion of subjects achieving calculated LDL-C < 1.8 mmol/L at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS)

	Atorvastatin 10 mg cohort					
	Placebo Q2W + Ezetimibe 10 mg QD (N=56)	Placebo Q2W + Placebo QD (N=56)	EvoMab 140 mg Q2W + Placebo QD (N=110)	Placebo QM + Ezetimibe 10 mg QD (N=55)	Placebo QM + Placebo QD (N=55)	EvoMab 420 mg QM + Placebo QD (N=110)
Mean of weeks 10/12 number of patients (%) (95% CI) ^a	10 (20.4) (11.5, 33.6)	3 (5.7) (1.9, 15.4)	96 (88.1) (80.7, 92.9)	9 (16.7) (9.0, 28.7)	3 (5.6) (1.9, 15.1)	91 (85.8) (78.0, 91.2)
Week 12 number of patients (%) (95% CI) ^a	10 (20.8) (11.7, 34.3)	1 (2.0) (0.3, 10.3)	87 (85.3) (77.1, 90.9)	10 (20.0) (11.2, 33.0)	3 (5.9) (2.0, 15.9)	85 (84.2) (75.8, 90.0)
	Atorvastatin 80 mg cohort					
	Placebo Q2W + Ezetimibe 10 mg QD (N=56)	Placebo Q2W + Placebo QD (N=55)	EvoMab 140 mg Q2W + Placebo QD (N=109)	Placebo QM + Ezetimibe 10 mg QD (N=54)	Placebo QM + Placebo QD (N=55)	EvoMab 420 mg QM + Placebo QD (N=110)
Mean of weeks 10/12 number of patients (%) (95% CI) ^a	28 (50.9) (38.1, 63.6)	7 (13.7) (6.8, 25.7)	102 (94.4) (88.4, 97.4)	33 (62.3) (48.8, 74.1)	5 (9.3) (4.0, 19.9)	99 (92.5) (85.9, 96.2)
Week 12 number of patients (%) (95% CI) ^a	26 (52.0) (38.5, 65.2)	6 (13.0) (6.1, 25.7)	95 (93.1) (86.5, 96.6)	29 (56.9) (43.3, 69.5)	5 (9.8) (4.3, 21.0)	91 (91.0) (83.8, 95.2)

	Rosuvastatin 5 mg cohort				Rosuvastatin 40 mg cohort				Simvastatin 40 mg cohort			
	Placebo Q2W (N=58)	EvoMab 140 mg Q2W (N=113)	Placebo QM (N=57)	EvoMab 420 mg QM (N=115)	Placebo Q2W (N=56)	EvoMab 140 mg Q2W (N=111)	Placebo QM (N=55)	EvoMab 420 mg QM (N=112)	Placebo Q2W (N=56)	EvoMab 140 mg Q2W (N=112)	Placebo QM (N=55)	EvoMab 420 mg QM (N=115)
Mean of weeks 10/12 number of patients (%) (95% CI) ^a	4 (7.0) (2.8, 16.7)	94 (88.7) (81.2,93.4)	3 (5.3) (1.8, 14.4)	97 (89.8) (82.7,94.2)	21 (38.9) (27.0,52.2)	99 (93.4) (87.0,96.8)	15 (29.4) (18.7,43.0)	104 (94.5) (88.6,97.5)	1 (1.9) (0.3, 9.8)	101 (93.5) (87.2,96.8)	2 (4.1) (1.1, 13.7)	98 (88.3) (81.0,93.0)
Week 12 number of patients (%) (95% CI) ^a	4 (7.8) (3.1, 18.5)	82 (84.5) (76.0,90.4)	3 (5.6) (1.9, 15.1)	89 (86.4) (78.5,91.7)	20 (38.5) (26.5,52.0)	92 (92.0) (85.0,95.9)	14 (28.0) (17.5,41.7)	96 (92.3) (85.6,96.1)	1 (1.9) (0.3, 10.1)	101 (94.4) (88.3,97.4)	3 (6.7) (2.3, 17.9)	86 (84.3) (76.0,90.1)
References: LAPLACE-2 CSR² Tables 14-4.32.6, 14-4.32.7, 14-4.32.8, 14-4.32.9, and 14-4.32.10 Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Three patients did not receive investigational product as randomised (one in the evolocumab Q2W + oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis. Summary statistics are based on observed data with no imputation for missing values. ^a 95% CI is calculated the Wilson Score method. CI, confidence interval; EvoMab, evolocumab; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; Q2W, every 2 weeks; QD, daily; QM, monthly.												

Table 2-8 Treatment difference in proportion of subjects achieving calculated LDL-C < 1.8 mmol/L at the mean of weeks 10/12 and at week 12 in LAPLACE-2

Mean of weeks 10/12		Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg QD or Placebo Q2W					Evolocumab 420 mg QM vs. Ezetimibe 10 mg QD or Placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^a	82.4 (70.2, 88.5) p < 0.001 ^b	80.7 (67.3, 88.3) p < 0.001 ^b	81.7 (69.5, 88.0) p < 0.001 ^b	54.5 (39.7, 66.8) p < 0.001 ^b	91.7 (81.5, 95.3) p < 0.001 ^b	80.3 (67.9, 86.8) p < 0.001 ^b	83.3 (70.7, 89.6) p < 0.001 ^b	84.6 (73.0, 90.1) p < 0.001 ^b	65.1 (50.3, 76.2) p < 0.001 ^b	84.2 (72.1, 89.8) p < 0.001 ^b
	Treatment difference vs. ezetimibe (95% CI) ^a	67.7 (52.5, 77.8) p < 0.001 ^b	43.5 (29.5, 56.7) p < 0.001 ^b	-	-	-	69.2 (54.8, 78.5) p < 0.001 ^b	30.3 (16.7, 44.2) p < 0.001 ^b	-	-	-
Week 12		Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg QD or Placebo Q2W					Evolocumab 420 mg QM vs. Ezetimibe 10 mg QD or Placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^a	83.3 (71.7, 89.1) p < 0.001 ^b	80.1 (65.8, 87.9) p < 0.001 ^b	76.7 (63.1, 84.2) p < 0.001 ^b	53.5 (38.3, 66.1) p < 0.001 ^b	92.5 (82.3, 95.9) p < 0.001 ^b	78.3 (65.2, 85.3) p < 0.001 ^b	81.2 (67.9, 88.1) p < 0.001 ^b	80.9 (68.4, 87.3) p < 0.001 ^b	64.3 (49.1, 75.5) p < 0.001 ^b	77.6 (63.7, 84.9) p < 0.001 ^b
	Treatment difference vs. ezetimibe (95% CI) ^a	64.5 (48.8, 75.1) p < 0.001 ^b	41.1 (26.4, 55.1) p < 0.001 ^b	-	-	-	64.2 (48.7, 74.7) p < 0.001 ^b	34.1 (19.6, 48.4) p < 0.001 ^b	-	-	-

References: LAPLACE-2 CSR² Tables 14-4.32.6, 14-4.32.7, 14-4.32.8, 14-4.32.9, and 14-4.32.10

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Three patients did not receive investigational product as randomised (one in the evolocumab Q2W + oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis. Treatment difference estimates are based on observed data with no imputation for missing values.

^a Treatment differences are within each dose frequency group using either subcutaneous placebo + oral placebo or subcutaneous placebo + ezetimibe as the reference.

^b Nominal p-value based on CMH test stratified by the stratification factor, with non-achievement imputed for subjects with a missing value. No multiplicity adjustment was carried for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy.

CI, confidence interval; N, number of subjects randomised and dosed in the full analysis set; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly.

Table 2-9 Proportion of subjects achieving reflexive LDL-C < 1.8 mmol/L at the mean of weeks 10/12 and at week 12 in LAPLACE-2 (FAS) ^a

	Atorvastatin 10 mg cohort					
	Placebo Q2W + Ezetimibe 10 mg QD (N=56)	Placebo Q2W + Placebo QD (N=56)	EvoMab 140 mg Q2W + Placebo QD (N=110)	Placebo QM + Ezetimibe 10 mg QD (N=55)	Placebo QM + Placebo QD (N=55)	EvoMab 420 mg QM + Placebo QD (N=110)
Mean of weeks 10/12 number of patients (%) (95% CI) ^b	10 (20.0) (11.2, 33.0)	3 (5.7) (1.9, 15.4)	96 (88.1) (80.7, 92.9)	9 (16.7) (9.0, 28.7)	3 (5.6) (1.9, 15.1)	91 (85.8) (78.0, 91.2)
Week 12 number of patients (%) (95% CI) ^b	11 (22.4) (13.0, 35.9)	1 (2.0) (0.3, 10.3)	88 (85.4) (77.4, 91.0)	10 (19.2) (10.8, 31.9)	3 (5.9) (2.0, 15.9)	85 (84.2) (75.8, 90.0)
	Atorvastatin 80 mg cohort					
	Placebo Q2W + Ezetimibe 10 mg QD (N=56)	Placebo Q2W + Placebo QD (N=55)	EvoMab 140 mg Q2W + Placebo QD (N=109)	Placebo QM + Ezetimibe 10 mg QD (N=54)	Placebo QM + Placebo QD (N=55)	EvoMab 420 mg QM + Placebo QD (N=110)
Mean of weeks 10/12 number of patients (%) (95% CI) ^b	28 (50.9) (38.1, 63.6)	7 (13.7) (6.8, 25.7)	102 (94.4) (88.4, 97.4)	33 (62.3) (48.8, 74.1)	5 (9.3) (4.0, 19.9)	99 (92.5) (85.9, 96.2)
Week 12 number of patients (%) (95% CI) ^b	26 (52.0) (38.5, 65.2)	6 (13.0) (6.1, 25.7)	95 (93.1) (86.5, 96.6)	29 (55.8) (42.3, 68.4)	5 (9.8) (4.3, 21.0)	91 (91.0) (83.8, 95.2)

	Rosuvastatin 5 mg cohort				Rosuvastatin 40 mg cohort				Simvastatin 40 mg cohort			
	Placebo Q2W (N=58)	EvoMab 140 mg Q2W (N=113)	Placebo QM (N=57)	EvoMab 420 mg QM (N=115)	Placebo Q2W (N=56)	EvoMab 140 mg Q2W (N=111)	Placebo QM (N=55)	EvoMab 420 mg QM (N=112)	Placebo Q2W (N=56)	EvoMab 140 mg Q2W (N=112)	Placebo QM (N=55)	EvoMab 420 mg QM (N=115)
Mean of weeks 10/12 number of patients (%) (95% CI) ^b	4 (7.0) (2.8, 16.7)	94 (88.7) (81.2, 93.4)	3 (5.3) (1.8, 14.4)	98 (89.9) (82.8, 94.3)	21 (38.9) (27.0, 52.2)	100 (93.5) (87.1, 96.8)	15 (28.8) (18.3, 42.3)	104 (94.5) (88.6, 97.5)	1 (1.9) (0.3, 9.8)	102 (93.6) (87.3, 96.9)	2 (3.9) (1.1, 13.2)	100 (88.5) (81.3, 93.2)
Week 12 number of patients (%) (95% CI) ^b	4 (7.7) (3.0, 18.2)	85 (85.0) (76.7, 90.7)	3 (5.5) (1.9, 14.9)	90 (86.5) (78.7, 91.8)	21 (39.6) (27.6, 53.1)	96 (92.3) (85.6, 96.1)	14 (28.0) (17.5, 41.7)	96 (92.3) (85.6, 96.1)	1 (1.9) (0.3, 10.1)	102 (94.4) (88.4, 97.4)	3 (6.4) (2.2, 17.2)	89 (84.8) (76.7, 90.4)
References: LAPLACE-2 primary study publication ¹ and CSR ² Tables 14-4.32.1, 14-4.32.2, 14-4.32.3, 14-4.32.4, 14-4.32.5												
Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Three patients did not receive investigational product as randomised (one in the evolocumab Q2W + oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis. Summary statistics are based on observed data with no imputation for missing values.												
^a For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available												
^b 95% CI is calculated the Wilson Score method.												
CI, confidence interval; EvoMab, evolocumab; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; Q2W, every 2 weeks; QD, daily; QM, monthly.												

Table 2-10 Treatment difference in proportion of subjects achieving reflexive LDL-C < 1.8 mmol/L at the mean of weeks 10/12 and at week 12 in LAPLACE-2 ^a

Mean of weeks 10/12		Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg QD or Placebo Q2W					Evolocumab 420 mg QM vs. Ezetimibe 10 mg QD or Placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^b	82.4 (70.2, 88.5) p < 0.001 ^c	80.7 (67.3, 88.3) p < 0.001 ^c	81.7 (69.5, 88.0) p < 0.001 ^c	54.6 (39.8, 66.9) p < 0.001 ^c	91.7 (81.6, 95.3) p < 0.001 ^c	80.3 (67.9, 86.8) p < 0.001 ^c	83.3 (70.7, 89.6) p < 0.001 ^c	84.6 (73.1, 90.2) p < 0.001 ^c	65.7 (51.0, 76.6) p < 0.001 ^c	84.6 (72.8, 90.0) p < 0.001 ^c
	Treatment difference vs. ezetimibe (95% CI) ^b	68.1 (53.1, 78.1) p < 0.001 ^c	43.5 (29.5, 56.7) p < 0.001 ^c	-	-	-	69.2 (54.8, 78.5) p < 0.001 ^c	30.3 (16.7, 44.2) p < 0.001 ^c	-	-	-
Week 12		Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg QD or Placebo Q2W					Evolocumab 420 mg QM vs. Ezetimibe 10 mg QD or Placebo QM				
		Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Rosuvastatin 5 mg cohort	Rosuvastatin 40 mg cohort	Simvastatin 40 mg cohort
	Treatment difference vs. placebo (95% CI) ^b	83.5 (71.9, 89.2) p < 0.001 ^c	80.1 (65.8, 87.9) p < 0.001 ^c	77.3 (63.9, 84.7) p < 0.001 ^c	52.7 (37.6, 65.3) p < 0.001 ^c	92.5 (82.3, 95.9) p < 0.001 ^c	78.3 (65.2, 85.3) p < 0.001 ^c	81.2 (67.9, 88.1) p < 0.001 ^c	81.1 (68.8, 87.5) p < 0.001 ^c	64.3 (49.1, 75.5) p < 0.001 ^c	78.4 (64.9, 85.4) p < 0.001 ^c
	Treatment difference vs. ezetimibe (95% CI) ^b	63.0 (47.3, 73.9) p < 0.001 ^c	41.1 (26.4, 55.1) p < 0.001 ^c	-	-	-	64.9 (49.8, 75.2) p < 0.001 ^c	35.2 (20.7, 49.3) p < 0.001 ^c	-	-	-

References: LAPLACE-2 primary study publication appendix¹ and CSR² Tables 14-4.32.1, 14-4.32.2, 14-4.32.3, 14-4.32.4, 14-4.32.5

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Three patients did not receive investigational product as randomised (one in the evolocumab Q2W + oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS and this analysis. Treatment difference estimates are based on observed data with no imputation for missing values.

^a For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available

^b Treatment differences are within each dose frequency group using either subcutaneous placebo + oral placebo or subcutaneous placebo + ezetimibe as the reference

^c Nominal p-value and adjusted p-value. Nominal p-value based on CMH test stratified by the stratification factor with non-achievement imputed for subjects with a missing value. Adjusted p-value based on a combination of sequential testing, the Hochberg procedure, and the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance.

CI, confidence interval; N, number of subjects randomised and dosed in the full analysis set; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly.

RUTHERFORD-2

The following additional LDL-C clinical efficacy results for RUTHERFORD-2 are provided below:

- Summary of mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 (Table 2-11)
- Summary of absolute change in LDL-C (calculated and reflexive) in mmol/L from baseline at the mean of weeks 10/12 and at week 12 (Table 2-12)
- Summary of the proportion (%) of patients achieving LDL-C <1.8 mmol/L (calculated and reflexive) at the mean of weeks 10/12 and at week 12 (Table 2-13)

Table 2-11 Mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 in RUTHERFORD-2 (FAS) ^a

	Evolocumab Q2W vs. placebo Q2W		Evolocumab QM vs. placebo QM	
	Placebo Q2W (N=54)	Evolocumab 140 mg Q2W (N=110)	Placebo QM (N=55)	Evolocumab 420 mg QM (N=110)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^b	-1.1 (-5.8, 3.7)	-61.2 (-64.6, -57.8)	2.3 (-2.5, 7.1)	-63.3 (-66.6, -59.9)
Mean of weeks 10/12 treatment difference (95% CI) ^c	-	-60.1 (-65.8, -54.5) p < 0.001 ^d	-	-65.5 (-71.3, -59.8) p < 0.001 ^d
Week 12 mean percent change from baseline (95% CI) ^b	-2.0 (-6.9, 2.9)	-61.3 (-64.7, -57.8)	5.5 (-0.9, 12.0)	-55.7 (-60.2, -51.3)
Week 12 treatment difference (95% CI) ^c	-	-59.2 (-65.1, -53.4) p < 0.001 ^d	-	-61.3 (-69.0, -53.4) p < 0.001 ^d
References: RUTHERFORD-2 primary study publication⁹ and CSR⁴ Tables 10-3 and 14-4.1.1 Note: The RUTHERFORD-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Two patients did not receive investigational product as randomised (one in the placebo Q2W group and one in the evolocumab Q2W group) and were excluded from the FAS and this analysis. ^a For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available; ^b Values are least squares means, which is from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates; ^c Treatment differences were within each dose frequency group using placebo in same group as the reference; ^d Nominal and adjusted p-value. Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary endpoints. CI, confidence interval; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; non-HDL-C, non-high-density lipoprotein cholesterol; Q2W, every other week; QM, monthly				

Table 2-12 Absolute change in LDL-C (calculated and reflexive) in mmol/L from baseline at the mean of weeks 10/12 and at week 12 in RUTHERFORD-2 (FAS)

	Evolocumab Q2W vs. placebo Q2W		Evolocumab QM vs. placebo QM	
	Placebo Q2W (N=54)	Evolocumab 140 mg Q2W (N=110)	Placebo QM (N=55)	Evolocumab 420 mg QM (N=110)
Calculated LDL-C assessment				
Mean of weeks 10/12 mean change from baseline (95% CI) ^a	-0.2 (-0.4, 0.0)	-2.7 (-2.8, -2.5)	-0.1 (-0.3, 0.1)	-2.6 (-2.8, -2.5)
Mean of weeks 10/12 treatment difference (95% CI) ^b	-	-2.5 (-2.7, -2.2) p <0.001 ^c	-	-2.6 (-2.8, -2.3) p <0.001 ^c
Week 12 mean change from baseline (95% CI) ^a	-0.2 (-0.5, -0.0)	-2.7 (-2.8, -2.5)	0.1 (-0.2, 0.3)	-2.3 (-2.4, -2.1)
Week 12 treatment difference (95% CI) ^b	-	-2.4 (-2.7, -2.1) p <0.001 ^c	-	-2.3 (-2.7, -2.0) p <0.001 ^c
Reflexive LDL-C assessment ^a				
Mean of weeks 10/12 mean change from baseline (95% CI) ^a	-0.2 (-0.4, 0.0)	-2.6 (-2.8, -2.5)	0.0 (-0.2, 0.2)	-2.6 (-2.7, -2.4)
Mean of weeks 10/12 treatment difference (95% CI) ^b	-	-2.5 (-2.7, -2.2) p <0.001 ^e	-	-2.5 (-2.8, -2.3) p <0.001 ^e
Week 12 mean change from baseline (95% CI) ^a	-0.2 (-0.4, 0.0)	-2.6 (-2.8, -2.5)	0.1 (-0.2, 0.4)	-2.3 (-2.4, -2.1)
Week 12 treatment difference (95% CI) ^b	-	-2.4 (-2.7, -2.1) p <0.001 ^e	-	-2.4 (-2.7, -2.0) p <0.001 ^e
References: RUTHERFORD-2 primary study publication ³ and CSR ⁴ Tables 14-4.7.2 and 14-4.7.4				
Note: The RUTHERFORD-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Two patients did not receive investigational product as randomised (one in the placebo Q2W group and one in the evolocumab Q2W group) and were excluded from the FAS and this analysis.				
^a Values are least squares means, which is from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates; ^b Treatment differences were within each dose frequency group using placebo in same group as the reference; ^c Nominal p-value. No multiplicity adjustment was carried for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy; ^d For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available; ^e Nominal p-value and adjusted p-value. Adjusted p-value is based on a combination of sequential testing, the				

	Evolocumab Q2W vs. placebo Q2W		Evolocumab QM vs. placebo QM	
	Placebo Q2W (N=54)	Evolocumab 140 mg Q2W (N=110)	Placebo QM (N=55)	Evolocumab 420 mg QM (N=110)
Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary endpoints.				
CI, confidence interval; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; non-HDL-C, non-high-density lipoprotein cholesterol; Q2W, every other week; QM, monthly				

Table 2-13 Proportion of patients achieving LDL-C <1.8 mmol/L (calculated and reflexive) at the mean of weeks 10/12 and at week 12 in RUTHERFORD-2 (FAS)

	Evolocumab Q2W vs. placebo Q2W		Evolocumab QM vs. placebo QM	
	Placebo Q2W (N=54)	Evolocumab 140 mg Q2W (N=110)	Placebo QM (N=55)	Evolocumab 420 mg QM (N=110)
Calculated LDL-C assessment				
Mean of weeks 10/12 n (%) (95% CI) ^a	1 (1.9) (0.3, 9.9)	73 (67.6) (58.3, 75.7)	1 (1.9) (0.3, 9.8)	90 (84.1) (76.0, 89.8)
Mean of weeks 10/12 treatment difference (95% CI) ^b	-	65.7 (53.4, 73.9) p < 0.001 ^c	-	82.3 (70.9, 88.2) p < 0.001 ^c
Week 12 n (%) (95% CI) ^a	1 (2.0) (0.4, 10.5)	70 (68.6) (59.1, 76.8)	1 (2.2) (0.4, 11.6)	65 (63.1) (53.5, 71.8)
Week 12 treatment difference (95% CI) ^b	-	66.6 (53.9, 75.0) p < 0.001 ^c	-	60.9 (47.5, 69.8) p < 0.001 ^c
Reflexive LDL-C assessment ^d				
Mean of weeks 10/12 n (%) (95% CI) ^a	1 (1.9) (0.3, 9.9)	73 (67.0) (57.7, 75.1)	1 (1.9) (0.3, 9.8)	86 (80.4) (71.9, 86.8)
Mean of weeks 10/12 treatment difference (95% CI) ^b	-	65.1 (52.8, 73.4) p < 0.001 ^e	-	78.5 (66.9, 85.1) p < 0.001 ^e
Week 12 n (%) (95% CI) ^a	1 (2.0) (0.3, 10.3)	71 (68.3) (58.8, 76.4)	1 (2.2) (0.4, 11.3)	65 (63.1) (53.5, 71.8)
Week 12 treatment difference (95% CI) ^b	-	66.3 (53.7, 74.6) p < 0.001 ^e	-	60.9 (47.6, 69.8) p < 0.001 ^e
References: RUTHERFORD-2 CSR ⁴ Tables 10-4, 14-4.8.1 and 14-4.8.2				
Note: The RUTHERFORD-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Two patients did not receive investigational product as randomised (one in the placebo Q2W group and one in the evolocumab Q2W group) and were excluded from the FAS and this analysis. Summary statistics and treatment differences are based on observed data with no imputation for missing values ^a Values are least squares means, which is from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates; ^b Treatment differences were within each dose frequency group using placebo in same group as the reference ^c Nominal p-value based on CMH test stratified by the stratification factors. For testing, non-achievement was imputed for subjects with a missing value. No multiplicity adjustment was carried for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy ^d For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L,				

	Evolocumab Q2W vs. placebo Q2W		Evolocumab QM vs. placebo QM	
	Placebo Q2W (N=54)	Evolocumab 140 mg Q2W (N=110)	Placebo QM (N=55)	Evolocumab 420 mg QM (N=110)
calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available;^e Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary endpoints. CI, confidence interval; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; non-HDL-C, non-high-density lipoprotein cholesterol; Q2W, every other week; QM, monthly				

GAUSS-2

The following additional LDL-C clinical efficacy results for GAUSS-2 are provided below:

- Summary of mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 (Table 2-14)
- Summary of absolute change in LDL-C (calculated and reflexive) in mmol/L from baseline at the mean of weeks 10/12 and at week 12 (Table 2-15)
- Summary of proportion (%) of patients achieving LDL-C <1.8 mmol/L (calculated and reflexive) at the mean of weeks 10/12 and at week 12 (Table 2-16)

Table 2-14 Mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 and at week 12 in GAUSS-2 (FAS) ^a

	Evolocumab 140mg Q2W vs. Ezetimibe		Evolocumab 420 mg QM vs. Ezetimibe	
	Placebo Q2W + Ezetimibe 10 mg QD (N=51)	Evolocumab Q2W + Placebo QD (N=103)	Placebo Q2W + Ezetimibe 10 mg QD (N=51)	Evolocumab QM + Placebo QD (N=102)
Mean of weeks 10/12 mean percent change from baseline (95% CI) ^b	-19.2 (-23.9, -14.5)	-56.1 (-59.7, -52.5)	-16.6 (-20.6, -12.6)	-55.3 (-58.3, -52.3)
Mean of weeks 10/12 treatment difference (95% CI) ^c	-	-36.9 (-42.3, -31.6) p < 0.001 ^d	-	-38.7 (-43.1, -34.3) p < 0.001 ^d
Week 12 mean percent change from baseline (95% CI) ^b	-18.1 (-23.1, -13.1)	-56.1 (-59.9, -52.4)	15.1 (-19.3, -10.9)	-52.6 (-55.7, -49.5)
Week 12 treatment difference (95% CI) ^c	-	-38.1 (-43.7, -32.4) p < 0.001 ^d	-	-37.6 (-42.2, -32.9) p < 0.001 ^d
References: GAUSS-2 primary study publication ⁵ and CSR ⁶ Table 10-1				
Note: The GAUSS-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. All patients received investigational product as randomised and were included in the FAS and this analysis.				
^a For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available				
^b Values are least squares means, which is from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates				
^c Treatment differences were within each dose frequency group using placebo + ezetimibe in the same group as the reference				
^d Nominal p-value and adjusted p-value. Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance.				
CI, confidence interval; FAS, full analysis set; LDL-C, low-density lipoprotein cholesterol; N, number of subjects randomised and dosed in the full analysis set; Q2W, every 2 weeks; QD, daily; QM, monthly				

Table 2-15 Absolute change in LDL-C (calculated and reflexive) in mmol/L from baseline at the mean of weeks 10/12 and at week 12 in GAUSS-2 (FAS)

	Evolocumab 140mg Q2W vs. Ezetimibe		Evolocumab 420 mg QM vs. Ezetimibe	
	Placebo Q2W + Ezetimibe 10 mg QD (N=51)	Evolocumab Q2W + Placebo QD (N=103)	Placebo QM + Ezetimibe 10 mg QD (N=51)	Evolocumab QM + Placebo QD (N=102)
Calculated LDL-C assessment				
Mean of weeks 10/12 mean change from baseline (95% CI) ^a	-1.0 (-1.3, -0.7)	-2.8 (-3.0, -2.6)	-0.8 (-1.1, -0.6)	-2.7 (-2.9, -2.5)
Mean of weeks 10/12 treatment difference (95% CI) ^b	-	-1.8 (-2.1, -1.5) p < 0.001 ^c	-	-1.9 (-2.1, -1.6) p < 0.001 ^c
Week 12 mean change from baseline (95% CI) ^a	-0.9 (-1.2, -0.7)	-2.8 (-3.0, -2.6)	-0.8 (-1.0, -0.5)	-2.6 (-2.8, -2.4)
Week 12 treatment difference (95% CI) ^b	-	-1.9 (-2.2, -1.5) p < 0.001 ^c	-	-1.8 (-2.1, -1.5) p < 0.001 ^c
Reflexive LDL-C assessment ^d				
Mean of weeks 10/12 mean change from baseline (95% CI) ^a	-1.0 (-1.3, -0.8)	-2.7 (-2.9, -2.5)	-0.9 (-1.1, -0.6)	-2.7 (-2.9, -2.5)
Mean of weeks 10/12 treatment difference (95% CI) ^b	-	-1.7 (-2.0, -1.4) p < 0.001 ^e	-	-1.8 (-2.1, -1.6) p < 0.001 ^e
Week 12 mean change from baseline (95% CI) ^a	-0.9 (-1.2, -0.7)	-2.7 (-3.0, -2.5)	-0.8 (-1.0, -0.5)	-2.6 (-2.7, -2.4)
Week 12 treatment difference (95% CI) ^b	-	-1.8 (-2.1, -1.5) p < 0.001 ^e	-	-1.8 (-2.1, -1.5) p < 0.001 ^e
References: GAUSS-2 primary study publication ⁵ and CSR ⁶ Tables 14-4.7.2 and 14-4.7.6				
Note: The GAUSS-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. All patients received investigational product as randomised and were included in the FAS and this analysis.				
^a Values are least squares means, which is from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates				
^b Treatment differences were within each dose frequency group using placebo in same group as the reference				
^c Nominal p-value. No multiplicity adjustment was carried for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy				

	Evolocumab 140mg Q2W vs. Ezetimibe		Evolocumab 420 mg QM vs. Ezetimibe	
	Placebo Q2W + Ezetimibe 10 mg QD (N=51)	Evolocumab Q2W + Placebo QD (N=103)	Placebo QM + Ezetimibe 10 mg QD (N=51)	Evolocumab QM + Placebo QD (N=102)
^d For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available ^e Nominal p-value and adjusted p-value. Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance. CI, confidence interval; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; non-HDL-C, non-high-density lipoprotein cholesterol; Q2W, every other week; QM, monthly				

Table 2-16 Proportion of patients achieving LDL-C <1.8 mmol/L (calculated and reflexive) at the mean of weeks 10/12 and at week 12 in GAUSS-2 (FAS)

	Evolocumab 140mg Q2W vs. Ezetimibe		Evolocumab 420 mg QM vs. Ezetimibe	
	Placebo Q2W + Ezetimibe 10 mg QD (N=51)	Evolocumab Q2W + Placebo QD (N=103)	Placebo QM + Ezetimibe 10 mg QD (N=51)	Evolocumab QM + Placebo QD (N=102)
Calculated LDL-C assessment				
Mean of weeks 10/12 n (%) (95% CI) ^a	1 (2.0) (0.4, 10.5)	46 (46.0) (36.6, 55.7)	0 (0.0) (0.0, 7.6)	41 (41.0) (31.9, 50.8)
Mean of weeks 10/12 treatment difference (95% CI) ^b	-	44.0% (31.3, 53.9) p < 0.001 ^c	-	41.0% (29.1, 50.8) p < 0.001 ^c
Week 12 n (%) (95% CI) ^a	1 (2.0) (0.4, 10.7)	48 (50.5) (40.6, 60.4)	0 (0.0) (0.0, 8.4)	36 (37.5) (28.5, 47.5)
Week 12 treatment difference (95% CI) ^b	-	48.5% (35.4, 58.5) p < 0.001 ^c	-	37.5% (25.2, 47.5) p < 0.001 ^c
Reflexive LDL-C assessment ^d				
Mean of weeks 10/12 n (%) (95% CI) ^a	1 (2.0) (0.4, 10.5)	46 (45.5) (36.2, 55.2)	0 (0.0) (0.0, 7.3)	42 (42.0) (32.8, 51.8)
Mean of weeks 10/12 treatment difference (95% CI) ^b	-	43.5% (30.9, 53.4) p < 0.001 ^e	-	42.0% (30.3, 51.8) p < 0.001 ^e
Week 12 n (%) (95% CI) ^a	1 (2.0) (0.4, 10.7)	49 (50.0) (40.3, 59.7)	0 (0.0) (0.0, 7.9)	36 (37.5) (28.5, 47.5)
Week 12 treatment difference (95% CI) ^b	-	48.0% (35.0, 57.8) p < 0.001 ^e	-	37.5% (25.5, 47.5) p < 0.001 ^e
References: GAUSS-2 primary study publication ⁵ and CSR ⁶ Tables 14-4.8.1 and 14-4.8.3				
Note: The GAUSS-2 efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. All patients received investigational product as randomised and were included in the FAS and this analysis. Summary statistics and treatment difference estimates are based on observed data with no imputation for missing values				
^a 95% Confidence interval is calculated using the Wilson Score method				
^b Treatment differences were within each dose frequency group using placebo + ezetimibe in same group as the reference				
^c Nominal p-value based on CMH test stratified by the stratification factors. For testing, non-achievement was imputed for subjects with a missing value. No multiplicity adjustment was carried for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy				

	Evolocumab 140mg Q2W vs. Ezetimibe		Evolocumab 420 mg QM vs. Ezetimibe	
	Placebo Q2W + Ezetimibe 10 mg QD (N=51)	Evolocumab Q2W + Placebo QD (N=103)	Placebo QM + Ezetimibe 10 mg QD (N=51)	Evolocumab QM + Placebo QD (N=102)
^d For reflexive LDL-C assessment, when the calculated LDL-C is < 1 mmol/L or triglycerides are > 4.5 mmol/L, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available; ^e Nominal p-value and adjusted p-value. Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, and the fallback procedure to control the overall significance level for all primary and secondary endpoints CI, confidence interval; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; non-HDL-C, non-high-density lipoprotein cholesterol; Q2W, every other week; QM, monthly				

DESCARTES

The following additional LDL-C clinical efficacy results for DESCARTES are provided below:

- Summary of mean percent change in ultracentrifugation LDL-C from baseline at week 12 and week 52 (Table 2-17)
- Summary of absolute change in mmol/L in calculated and ultracentrifugation LDL-C from baseline at week 52 (Table 2-18)
- Summary of proportion (%) of patients achieving LDL-C <1.8 mmol/L (calculated and ultracentrifugation) at week 52 (Table 2-19)
- Analysis of percent change from baseline in ultracentrifugation LDL-C between week 12 and week 52 (Table 2-20)

Table 2-17 Mean percent change in ultracentrifugation LDL-C from baseline at week 12 and week 52 in DESCARTES (FAS)

	Placebo QM (N=302)	Evolocumab QM (N=599)
Week 12 mean percent change from baseline (95% CI) ^a	3.2 (0.6, 5.7)	-54.4 (-56.2, -52.5)
Week 12 treatment difference (95% CI) ^b	-	-57.5 (-60.6, -54.5) p < 0.001 ^c
Week 52 mean percent change from baseline (95% CI) ^a	6.8 (3.4, 10.3)	-50.1 (-52.6, -47.7)
Week 52 treatment difference (95% CI) ^b	-	-57.0 (-61.1, -52.9) p < 0.001 ^c
References: DESCARTES primary study publication⁷ and CSR⁸ Tables 10-1, 10-2, 10-3, 14-4.1.1, 14-4.11.2 Note: The DESCARTES efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Four subjects (three in the evolocumab group and one in the placebo group) did not receive investigational product as randomised and were excluded from the FAS and this analysis ^a Values are least squares means, which is from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates ^b Treatment differences using placebo as the reference ^c Nominal and adjusted p-value. Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance CI, confidence interval; FAS, full analysis set; LDL-C, low-density lipoprotein cholesterol; N, number of subjects randomised and dosed in the full analysis set; QM, monthly		

Table 2-18 Absolute change (mmol/L) in calculated and ultracentrifugation LDL-C from baseline at week 52 in DESCARTES (FAS)

	Placebo QM (N=302)	Evolocumab QM (N=599)
Calculated LDL-C		
Week 52 mean change from baseline (95% CI) ^a	0.2 (0.1, 0.3)	-1.3 (-1.4, -1.3)
Week 52 treatment difference (95% CI) ^b	-	-1.5 (-1.6, -1.4) p < 0.001 ^c
Ultracentrifugation LDL-C		
Week 52 mean change from baseline (95% CI) ^a	0.1 (0.0, 0.2)	-1.4 (-1.4, -1.3)
Week 52 treatment difference (95% CI) ^b	-	-1.5 (-1.6, -1.4) p < 0.001 ^d
References: DESCARTES primary study publication⁷ and CSR⁸ Tables 14-4.9.3 , 14-4.9.6, and 14-4.24.1 Note: The DESCARTES efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Four subjects (three in the evolocumab group and one in the placebo group) did not receive investigational product as randomised and were excluded from the FAS and this analysis ^a Values are least squares means, which is from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates ^b Treatment differences using placebo as the reference ^c Nominal p-value. No multiplicity adjustment was carried for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy ^d Nominal and adjusted p-value. Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value is compared to 0.05 to determine statistical significance (Note, adjusted p-value missing from Table 14-4.9.3, sourced from Table 14-4.9.1 where data presented in conventional units i.e. mg/dL). CI, confidence interval; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; LDL-C, low-density lipoprotein cholesterol; QM, monthly		

Table 2-19 Proportion of patients achieving LDL-C <1.8 mmol/L (calculated and ultracentrifugation) at week 52 in DESCARTES (FAS)

	Placebo QM (N=302)	Evolocumab QM (N=599)
Calculated LDL-C		
Week 52 n (%) (95% CI) ^a	18 (7.0) (4.5, 10.8)	431 (84.7) (81.3, 87.5)
Week 52 treatment difference (95% CI) ^b	-	77.7% (72.6, 81.5) p < 0.001 ^c
Ultracentrifugation LDL-C		
Week 52 n (%) (95% CI) ^a	17 (6.4) (4.1, 10.1)	446 (82.3) (78.8, 85.3)
Week 52 treatment difference (95% CI) ^b	-	75.8% (70.8, 79.7) p < 0.001 ^d
References: DESCARTES primary study publication⁷ and CSR⁸ Tables 14-4.10.1, 14-4.10.3, and 14-4.24.1 Note: The DESCARTES efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Four subjects (three in the evolocumab group and one in the placebo group) did not receive investigational product as randomised and were excluded from the FAS and this analysis. Summary statistics and treatment differences are based on observed data with no imputation for missing values. ^a 95% confidence interval is calculated using the Wilson Score method ^b Treatment differences using placebo as the reference ^c Nominal p-value based on CMH test stratified by the stratification factors. For testing, non-achievement was imputed for subjects with a missing value. No multiplicity adjustment was carried for this analysis as LDL-C measured using the calculated approach to LDL-C assessment was not in the pre-specified multiplicity adjustment hierarchy ^d Nominal p-value and adjusted p-value. Adjusted p-value is based on a combination of sequential testing, the Hochberg procedure, and the fallback procedure to control the overall significance level for all primary and secondary endpoints CI, confidence interval; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; LDL-C, low-density lipoprotein cholesterol; QM, monthly		

Table 2-20 Analysis of percent change from baseline in ultracentrifugation LDL-C between week 12 and week 52 in DESCARTES (FAS)

	Placebo QM (N=302)	Evolocumab QM (N=599)	Treatment difference^b
Week 12 (95% CI) ^a	3.2 (0.6, 5.7)	-54.4 (-56.2, -52.5)	-57.5 (-60.6, -54.5)
Week 52 (95% CI) ^a	6.8 (3.4, 10.3)	-50.1 (-52.6, -47.7)	-57.0 (-61.1, -52.9)
Difference week 12 to week 52	3.7 (0.3, 7.0)	4.2 (1.9, 6.5)	0.5 (-3.5, 4.6)
References: DESCARTES CSR⁸ Table 10-5 Note: The DESCARTES efficacy and safety analyses employed a modified intention-to-treat approach; all subjects randomised and dosed with investigational product were included in the FAS and this analysis. Four subjects (three in the evolocumab group and one in the placebo group) did not receive investigational product as randomised and were excluded from the FAS and this analysis. No equivalent analysis utilising calculated LDL-C was conducted. ^a Values are least squares means, which is from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates ^b Treatment differences using placebo as the reference CI, confidence interval; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; LDL-C, low-density lipoprotein cholesterol; QM, monthly.			

2.2 *Other lipid parameters*

A summary of treatment differences for evolocumab vs. placebo and/or ezetimibe in secondary/co-secondary and tertiary endpoint lipid parameters (other than LDL-C) is provided below for:

- LAPLACE-2 (Table 2-21 and Table 2-22)
- RUTHERFORD-2 (Table 2-23)
- GAUSS-2 (Table 2-24)
- DESCARTES (Table 2-25)

Table 2-21 Treatment difference (%; 95% CI)^a of evolocumab compared with placebo and ezetimibe in prespecified cosecondary and tertiary additional lipid endpoints at the mean of weeks 10/12 in LAPLACE-2 (FAS)

Statin cohort	EvoMab regimen	Secondary endpoint								Tertiary endpoint
		Non-HDL-C (%)	ApoB (%)	ApoB/ ApoA1 ratio (%)	TC/HDL-C ratio (%)	Lp(a) (%)	TG (%)	VLDL-C (%)	HDL-C (%)	ApoA1 (%)
Evolocumab vs. placebo										
Atorvastatin 10 mg	140 mg Q2W	-60 ^b (-65, -55)	-58 ^b (-63, -54)	-60 ^b (-65, -55)	-46 ^b (-51, -42)	-32 ^b (-39, -25)	-12 (-22, -3)	-13 (-22, -5)	7 ^c (3, 10)	5 ^c (1, 8)
	420 mg QM	-57 ^b (-63, -52)	-52 ^b (-57, -47)	-54 ^b (-60, -49)	-45 ^b (-50, -40)	-22 ^b (-30, -14)	-23 ^c (-33, -12)	-21 ^c (-32, -11)	8 ^c (3, 13)	4 (^{<} 1, 8)
Atorvastatin 80 mg	140 mg Q2W	65 ^b (-74, -57)	-59 ^b (-67, -52)	-57 ^b (-64, -50)	-44 ^b (-51, -38)	-21 ^b (-28, -13)	-15 (-25, -6)	-15 (-25, -6)	4 (^{<} 1, 8)	1 (-3, 5)
	420 mg QM	-65 ^b (-72, -57)	-59 ^b (-66, -52)	-62 ^b (-69, -55)	-47 ^b (-52, -41)	-29 ^b (-37, -21)	-14 ^c (-25, 4)	-15 ^c (-25, -4)	9 ^b (5, 14)	8 ^b (4, 13)
Rosuvastatin 5 mg	140 mg Q2W	-60 ^b (-65, -54)	-55 ^b (-60, -50)	-55 ^b (-61, -50)	-45 ^b (-50, -40)	-36 ^b (-43, -28)	-23 ^b (-33, -13)	-25 ^b (-35, -16)	5 ^b (2, 9)	2 (-1, 6)
	420 mg QM	-59 ^b (-65, -54)	-56 ^b (-61, -52)	-59 ^b (-64, -54)	-47 ^b (-52, -42)	-27 ^b (-35, -18)	-20 ^c (-31, -8)	-20 ^c (-31, -9)	9 ^c (3, 15)	7 ^c (1, 12)
Rosuvastatin 40 mg	140 mg Q2W	-58 ^b (-65, -52)	-51 ^b (-57, -45)	-51 ^b (-57, -44)	-41 ^b (-45, -36)	-34 ^b (-41, -26)	-18 ^c (-27, -8)	-16 ^c (-25, -7)	5 ^c (2, 9)	2 (-1, 6)
	420 mg QM	-57 ^b (-64, -50)	-55 ^b (-61, -49)	-57 ^b (-64, -50)	-40 ^b (-46, -35)	-32 ^b (-41, -24)	-26 ^b (-36, -17)	-23 ^b (-32, -14)	7 ^c (2, 11)	4 ^c (1, 8)
Simvastatin 40 mg	140 mg Q2W	-60 ^b (-65, -55)	-55 ^b (-60, -51)	-58 ^b (-63, -53)	-47 ^b (-52, -42)	-28 ^b (-35, -21)	-21 ^b (-32, -10)	-23 ^b (-33, -13)	10 ^b (5, 15)	7 ^b (3, 11)
	420 mg QM	-63 ^b (-70, -55)	-57 ^b (-63, -50)	-56 ^b (-62, -50)	-49 ^b (-54, -43)	-27 ^b (-35, -20)	-30 ^b (-41, -19)	-33 ^b (-44, -22)	9 ^b (5, 13)	3 (-1, 7)

Statin cohort	EvoMab regimen	Secondary endpoint								Tertiary endpoint
		Non-HDL-C (%)	ApoB (%)	ApoB/ApoA1 ratio (%)	TC/HDL-C ratio (%)	Lp(a) (%)	TG (%)	VLDL-C (%)	HDL-C (%)	ApoA1 (%)
Evolocumab vs. ezetimibe										
Atorvastatin 10 mg	140 mg Q2W	-33 ^b (-38, -28)	-34 ^b (-38, -29)	-38 ^b (-43, -33)	-26 ^b (-30, -22)	-27 ^b (-35, -20)	-2 (-12, 7)	-2 (-10, 7)	7 ^b (3, 10)	8 ^b (4, 11)
	420 mg QM	-40 ^b (-45, -34)	-40 ^b (-45, -35)	-42 ^b (-47, -36)	-32 ^b (-37, -27)	-29 ^b (-37, -22)	-15 (-25, -4)	-14 (-24, -3)	9 ^c (4, 13)	4 ^c (^{<} 1, 8)
Atorvastatin 80 mg	140 mg Q2W	-38 ^b (-47, -30)	-35 ^b (-42, -28)	-37 ^b (-44, -30)	-28 ^b (-34, -22)	-32 ^b (-39, -25)	-1 (-11, 8)	< 1 (-10, 9)	8 ^c (4, 12)	6 ^c (2, 10)
	420 mg QM	-38 ^b (-45, -30)	-40 ^b (-47, -33)	-43 ^b (-50, -37)	-28 ^b (-34, -23)	-37 ^b (-46, -29)	-2 (-12, 9)	< 1 (-11, 10)	8 ^c (4, 13)	9 ^b (5, 13)
References: LAPLACE-2 primary study publication appendix ¹ and CSR ² Tables 10-5, 10-6, 14-4.38.1 through 14-4.38.5, 14-4.39.1 through 14-4.39.5, 14-4.40.1 through 14-4.40.5.										
^a Treatment difference reflects between-group difference in the percent change from baseline for each endpoint within each statin cohort and each dose frequency group using placebo or ezetimibe as the reference										
^b Multiplicity adjusted p < 0.001 when compared with placebo or ezetimibe										
^c Multiplicity adjusted p < 0.05 when compared with placebo or ezetimibe										
ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CI, confidence interval; EvoMab, evolocumab; FAS, full analysis set; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Q2W, every 2 weeks; QM, monthly; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol										

Table 2-22 Treatment difference (%; 95% CI)^a of evolocumab compared with placebo and ezetimibe in prespecified cosecondary and tertiary additional lipid endpoints at week 12 in LAPLACE-2 (FAS)

Statin cohort	EvoMab regimen	Secondary endpoint								Tertiary endpoint
		Non-HDL-C (%)	ApoB (%)	ApoB/ ApoA1 ratio (%)	TC/HDL-C ratio (%)	Lp(a) (%)	TG (%)	VLDL-C (%)	HDL-C (%)	ApoA1 (%)
Evolocumab vs. placebo										
Atorvastatin 10 mg	140 mg Q2W	-62 ^b (-67, -56)	-59 ^b (-64, -54)	-60 ^b (-66, -55)	-47 ^b (-52, -42)	-33 ^b (-41, -26)	-12 (-25, 0.6)	-14 (-24, -5)	7 ^c (3, 11)	5 ^c (2, 9)
	420 mg QM	-55 ^b (-61, -48)	-47 ^b (-53, -42)	-48 ^b (-54, -43)	-43 ^b (-48, -37)	-20 ^b (-28, -12)	-28 ^c (-42, -13)	-26 ^c (-41, -12)	8 ^c (3, 13)	3 (-1, 7)
Atorvastatin 80 mg	140 mg Q2W	-67 ^b (-76, -57)	-61 ^b (-69, -54)	-58 ^b (-66, -50)	-45 ^b (-52, -39)	-22 ^b (-30, -14)	-17 (-27, -6)	-16 (-27, -6)	4 (-0.4, 9)	1 (-4, 5)
	420 mg QM	-60 ^b (-68, -52)	-53 ^b (-61, -45)	-57 ^b (-65, -50)	-42 ^b (-49, -36)	-28 ^b (-37, -20)	-9 ^c (-22, 3)	-10 ^c (-22, 2)	7 ^b (2, 12)	8 ^b (3, 12)
Rosuvastatin 5 mg	140 mg Q2W	-60 ^b (-66, -54)	-57 ^b (-62, -51)	-54 ^b (-60, -49)	-43 ^b (-49, -38)	-37 ^b (-45, -28)	-18 ^b (-32, -4)	-22 ^b (-34, -10)	3 ^b (-1, 8)	0.2 (-4, 4)
	420 mg QM	-57 ^b (-63, -52)	-53 ^b (-58, -48)	-56 ^b (-62, -51)	-45 ^b (-51, -40)	-25 ^b (-34, -16)	-20 ^c (-33, -7)	-19 ^c (-32, -6)	7 ^c (1, 14)	6 ^c (0.4, 11)
Rosuvastatin 40 mg	140 mg Q2W	-60 ^b (-67, -52)	-51 ^b (-57, -44)	-49 ^b (-56, -43)	-41 ^b (-47, -36)	-36 ^b (-44, -29)	-17 ^c (-28, -5)	-16 ^c (-27, -5)	5 ^c (1, 10)	1 (-3, 4)
	420 mg QM	-50 ^b (-58, -41)	-47 ^b (-54, -39)	-49 ^b (-57, -40)	-35 ^b (-42, -28)	-32 ^b (-43, -22)	-21 ^b (-31, -10)	-19 ^b (-29, -8)	5 ^c (0.1, 10)	3 (-1, 8)
Simvastatin 40 mg	140 mg Q2W	-61 ^b (-67, -55)	-56 ^b (-61, -51)	-58 ^b (-63, -53)	-47 ^b (-52, -42)	-31 ^b (-38, -24)	-22 ^b (-33, -11)	-22 ^b (-33, -12)	10 ^b (4, 16)	7 ^c (2, 11)
	420 mg QM	-57 ^b (-65, -49)	-53 ^b (-59, -46)	-52 ^b (-58, -46)	-45 ^b (-51, -39)	-28 ^b (-37, -20)	-31 ^b (-44, -19)	-37 ^b (-49, -25)	9 ^b (4, 14)	3 (-2, 7)

Statin cohort	EvoMab regimen	Secondary endpoint								Tertiary endpoint
		Non-HDL-C (%)	ApoB (%)	ApoB/ApoA1 ratio (%)	TC/HDL-C ratio (%)	Lp(a) (%)	TG (%)	VLDL-C (%)	HDL-C (%)	ApoA1 (%)
Evolocumab vs. ezetimibe										
Atorvastatin 10 mg	140 mg Q2W	-35 ^b (-41, -29)	-35 ^b (-40, -30)	-40 ^b (-45, -34)	-29 ^b (-34, -24)	-29 ^b (-37, -21)	-3 (-16, 9)	-2 (-11, 8)	9 ^c (5, 13)	9 ^b (5, 12)
	420 mg QM	-38 ^b (-44, -31)	-36 ^b (-42, -30)	37 ^b (-43, -32)	-30 ^b (-36, -25)	-27 ^b (-36, -19)	-18 (-32, -4)	-15 (-29, -1)	8 ^c (3, 13)	4 (-.3, 8)
Atorvastatin 80 mg	140 mg Q2W	-41 ^b (-50, -31)	-37 ^b (-45, -30)	-40 ^b (-48, -32)	-30 ^b (-37, -24)	-33 ^b (-40, -25)	-3 (-13, 8)	-2 (-12, 9)	8 ^c (4, 13)	7 ^c (2, 11)
	420 mg QM	-33 ^b (-41, -24)	-34 ^b (-42, -26)	-39 ^b (-46, -31)	-25 ^b (-32, -19)	-35 ^b (-44, -26)	2 (-11, 15)	5 (-7, 17)	7 ^c (2, 12)	9 ^b (4, 13)
References: LAPLACE-2 primary study publication appendix ¹ and CSR ² Tables 10-5, 10-6, 14-4.38.1 to 14-4.38.5, and 14-4.39.1 to 14-4.39.5.										
^a Treatment difference reflects between-group difference in the percent change from baseline for each endpoint within each statin cohort and each dose frequency group using placebo or ezetimibe as the reference										
^b Multiplicity adjusted p < 0.001 when compared with placebo or ezetimibe										
^c Multiplicity adjusted p < 0.05 when compared with placebo or ezetimibe										
ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CI, confidence interval; EvoMab, evolocumab; FAS, full analysis set; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Q2W, every 2 weeks; QM, monthly; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.										

Table 2-23 Treatment difference (%; 95% CI)^a of evolocumab compared with placebo in prespecified secondary and tertiary additional lipid endpoints at the mean of weeks 10/12 and week 12 in RUTHERFORD-2 (FAS)

EvoMab regimen	Secondary endpoint								Tertiary endpoint
	Non-HDL-C (%)	ApoB (%)	ApoB/ApoA1 Ratio (%)	TC/HDL-C ratio (%)	Lp(a) (%)	TG (%)	VLDL-C (%)	HDL-C (%)	ApoA1 (%)
Mean of weeks 10/12									
140 mg Q2W	-56 ^b (-61, -51)	-49 ^b (-54, -44)	-53 (-58, -48)	-47 ^b (-51, -42)	-31 ^b (-38, -24)	-22 ^b (-29, -15)	-23 ^b (-29, -16)	8 ^b (4, 12)	7 ^c (3, 12)
420 mg QM	-60 ^b (-65, -55)	-55 ^b (-60, -50)	-56 ^b (-61, -50)	-49 ^b (-54, -44)	-31 ^b (-38, -24)	-17 ^b (-24, -9)	-16 ^b (-23, -8)	9 ^b (5, 14)	5 ^c (1, 9)
Week 12									
140 mg Q2W	-55 ^b (-60, -49)	-49 ^b (-55, -44)	-54 ^b (-60, -48)	-46 ^b (-51, -41)	-32 ^b (-39, -24)	-20 ^b (-28, -11)	-21 ^b (-29, -13)	9 ^b (5, 14)	9 ^b (4, 13)
420 mg QM	-55 ^b (-62, -48)	-49 ^b (-56, -43)	-50 ^b (-58, -41)	-45 ^b (-53, -38)	-28 ^b (-36, -21)	-12 ^b (-21, -2)	-9 ^b (-19, 1)	9 ^b (3, 15)	4 (-2, 9)
References: RUTHERFORD-2 primary study publication³ and CSR⁴ Tables 10-3, 10-4, 10-5, 14-4.1.2, 14-4.17.1, 14-4.18.1, and 14-4.19. ^a Treatment difference reflects between-group difference in the percent change from baseline for each endpoint within each dose frequency group using placebo as the reference ^b Multiplicity adjusted p < 0.001 when compared with placebo or ezetimibe ^c Multiplicity adjusted p < 0.05 when compared with placebo or ezetimibe ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CI, confidence interval; EvoMab, evolocumab; FAS, full analysis set; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Q2W, every 2 weeks; QM, monthly; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.									

Table 2-24 Treatment difference (% , 95% CI)^a of evolocumab compared with ezetimibe in prespecified secondary and tertiary additional lipid endpoints at the mean of weeks 10/12 and week 12 in GAUSS-2 (FAS)

EvoMab regimen	Secondary endpoint								Tertiary endpoint
	Non-HDL-C (%)	ApoB (%)	ApoB/ApoA1 Ratio (%)	TC/HDL-C ratio (%)	Lp(a) (%)	TG (%)	VLDL-C (%)	HDL-C (%)	ApoA1 (%)
Mean of weeks 10/12									
140 mg Q2W	-32 ^b (-36, -27)	-32 ^b (-37, -27)	-35 ^b (-40, -30)	-27 ^b (-32, -23)	-24 ^b (-31, -17)	-3 (-11, 6)	-2 (-10, 7)	5 (1, 10)	5 ^c (2, 9)
420 mg QM	-35 ^b (-39, -31)	-35 ^b (-40, -30)	-36 ^b (-42, -31)	-30 ^b (-35, -25)	-25 ^b (-34, -17)	-6 (-17, 4)	-4 (-13, 6)	6 (1, 10)	3 (-1, 7)
Week 12									
140 mg Q2W	-32 ^b (-37, -27)	-33 ^b (-38, -28)	-35 ^b (-40, -29)	-26 ^b (-31, -21)	-25 ^b (-33, -17)	2 (-8, 11)	-1 (-10, 9)	4 (-1, 9)	4 ^c (0.1, 8)
420 mg QM	-33 ^b (-37, -29)	-33 ^b (-38, -28)	-34 ^b (-40, -28)	-29 ^b (-34, -23)	-28 ^b (-39, -17)	-5 (-17, 8)	0.1 (-11, 11)	5 (-0.2, 10)	2 (-2, 7)
References: GAUSS-2 primary study publication ⁵ and CSR ⁶ Tables 10-6, 10-7, 14-4.17.1, 14-4.18.1, and 14-4.19.1									
^a Treatment difference reflects between-group difference in the percent change from baseline for each endpoint within each dose frequency group using placebo + ezetimibe as the reference									
^b Multiplicity adjusted p < 0.001 when compared with ezetimibe									
^c Multiplicity adjusted p < 0.05 when compared with ezetimibe									
ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CI, confidence interval; EvoMab, evolocumab; FAS, full analysis set; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Q2W, every 2 weeks; QM, monthly; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.									

Table 2-25 Treatment difference (% , 95% CI)^a of evolocumab compared with placebo in prespecified secondary and tertiary non-LDL-C endpoints at week 12 and 52 in DESCARTES (FAS)

Week 12 ^b	Week 52 ^b									
TC (%)	Non-HDL-C (%)	ApoB (%)	ApoB/ApoA1 Ratio (%)	TC/HDL-C Ratio (%)	TC (%)	Lp(a) (%)	TG (%)	VLDL-C (%)	HDL-C (%)	ApoA1 (%)
-35 ^c (-37,-33)	-50 ^c (-54,-46)	-44 ^c (-48,-41)	-46 ^c (-50,-43)	-37 ^c (-40,-34)	-33 ^c (-36,-31)	-22 ^c (-26,-19)	-12 ^c (-17,-6)	-29 ^c (-40,-8)	5 ^c (3, 8)	3 ^c (1, 5)
References: Descartes primary study publication appendix ⁷ and CSR ⁸ Tables 10-2, 10-3, 14-4.1.3, 14-4.12.1, 14-4.13.1, 14-4.14.1, 14-4.15.1, 14-4.16.1, 14-4.17.1, 14-4.18.1, 14-4.19.1, 14-4.20.1, 14-4.21.1, 14-4.22.1, 14-4.24.1										
^a Treatment difference reflects between-group difference in the percent change from baseline for each endpoint using placebo as the reference.										
^b All prespecified secondary endpoints apart from ApoA1 at week 52 (tertiary endpoint)										
^c Multiplicity adjusted p < 0.001 when compared with placebo										
ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CI, confidence interval; FAS, full analysis set; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol										

3 Additional clinical efficacy data for the supplementary ongoing long-term extension studies

3.1 *OSLER*

The following additional clinical efficacy results for OSLER (data cut-off date 01 April 2014) is provided below:

- Summary of mean percent change from parent study baseline in calculated LDL-C by scheduled visit in year 1 (Table 3-1)
- Summary of mean percent change from parent study baseline in calculated LDL-C by scheduled visit in year 2+ (Table 3-2)
- Plot of mean percent change from baseline in calculated LDL-C by scheduled visit and treatment group (Figure 3-1)

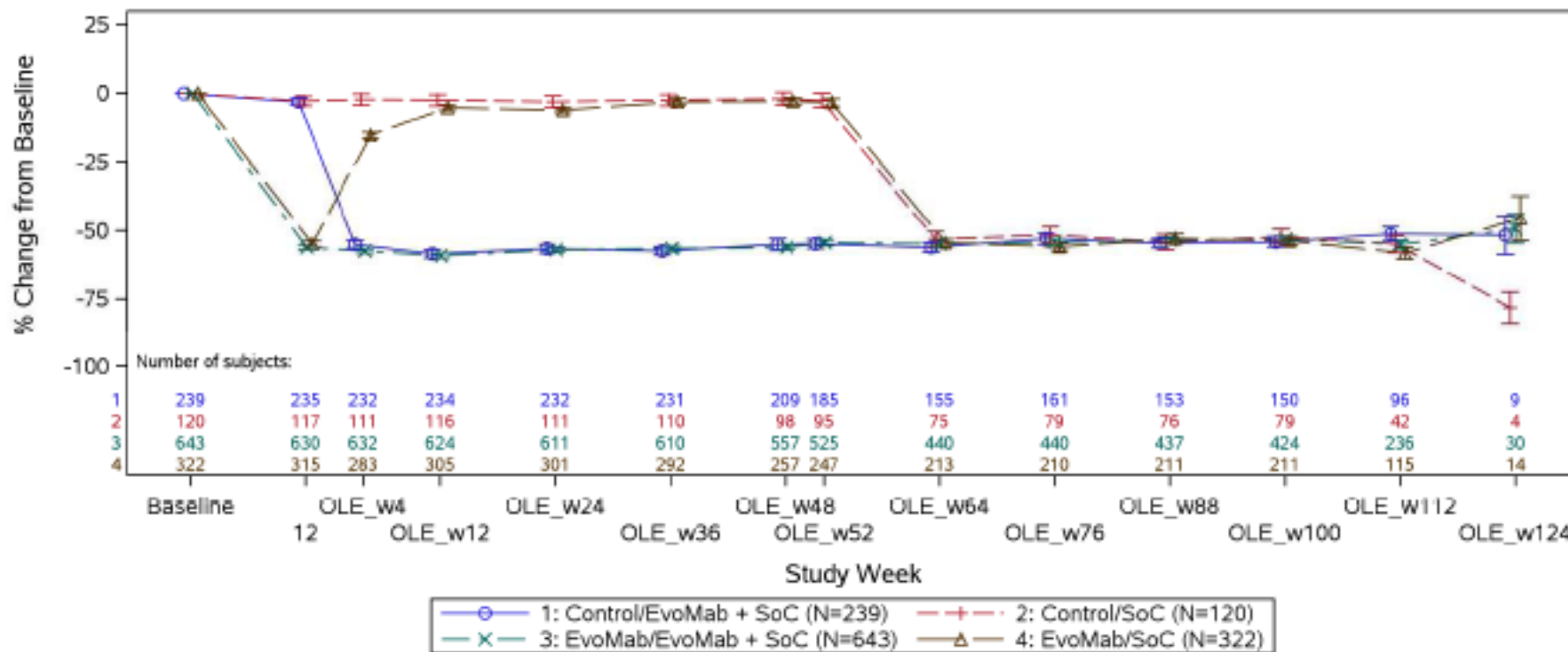
Table 3-1 Summary of mean percent change from parent study baseline in calculated LDL-C by scheduled visit in year 1 (OSLER, ICOAS)

	Control in parent study		Evolocumab in parent study	
	Control in OSLER ^a	Evolocumab in OSLER ^b	Control in OSLER ^a	Evolocumab in OSLER ^b
Percent change from baseline at parent study end of study				
n	117	235	315	630
Mean (SE)	-2.8 (1.7)	-3.0 (1.2)	-54.9 (1.1)	-56.3 (0.7)
Percent change from baseline at OSLER week 12				
n	116	234	305	624
Mean (SE)	-2.5 (2.0)	-58.5 (1.4)	-5.1 (1.0)	-59.1 (0.8)
Percent change from baseline at OSLER week 24				
N	111	232	301	611
Mean (SE)	-3.1 (2.1)	-56.7 (1.6)	-6.0 (1.1)	-57.0 (0.9)
Percent change from baseline at OSLER week 36				
n	110	231	292	610
Mean (SE)	-2.5 (2.1)	-57.4 (1.5)	-3.0 (1.3)	-56.7 (0.9)
Percent change from baseline at OSLER week 48				
n	98	209	257	557
Mean (SE)	-2.1 (2.4)	-55.1 (2.1)	-2.9 (1.2)	-56.1 (1.0)
Percent change from baseline at week 52				
n	95	185	247	525
Mean (SE)	-2.6 (2.5)	-54.9 (1.8)	-3.3 (1.4)	-54.4 (1.0)
References: OSLER Interim CSR ⁹ Table 14-4.23.1				
Note: Data cut-off 01 April 2014. The OSLER efficacy and safety analyses employed an intention-to-treat approach during the SoC-controlled period; all subjects randomised and on-study and dosed with IP were included in the ICOAS. Summary is based on observed data and no imputation is made for missing values. Baseline is defined as the parent study baseline. ^a SoC alone ^b Evolocumab 420 mg QM + SoC ICOAS, Interim SoC-Controlled Period Analysis Set; LDL-C, low-density lipoprotein cholesterol; SE, standard error				

Table 3-2 Summary of mean percent change from parent study baseline in calculated LDL-C by scheduled visit in year 2+ (OSLER, IAAS)

	Control in SoC-Controlled Period ^a	EvoMab in SoC-Controlled period ^b	Total (N=937)
	EvoMab + SoC ^b (N=305)	EvoMab + SoC ^b (N = 632)	
Percent change from baseline at OSLER week 64			
n	288	595	883
Mean (SE)	-54.1 (1.2)	-55.2 (0.9)	-54.9 (0.7)
Percent change from baseline at OSLER week 76			
n	289	601	890
Mean (SE)	-54.8 (1.3)	-53.9 (0.9)	-54.2 (0.7)
Percent change from baseline at OSLER week 88			
n	287	590	877
Mean (SE)	-53.4 (1.4)	-53.9 (0.9)	-53.7 (0.8)
Percent change from baseline at OSLER week 100			
n	290	574	864
Mean (SE)	-53.4 (1.3)	-53.4 (0.9)	-53.4 (0.8)
Percent change from baseline at OSLER week 112			
n	157	332	489
Mean (SE)	-57.4 (1.8)	-54.0 (1.4)	-55.1 (1.1)
Percent change from baseline at OSLER week 124			
n	18	29	57
Mean (SE)	-52.8 (7.1)	-49.9 (4.4)	-50.8 (3.7)
References: OSLER Interim CSR ⁹ Table 14-4.23.3			
Note: Data cut-off 01 April 2014. The interim OSLER efficacy and safety analyses employed an on-treatment approach during the all-IP period; all subjects randomised and on-study and dosed with IP in year 2+ were included in the IAAS. 49 subjects receiving evolocumab during year 1 and 20 subjects receiving control in year 1 did not receive IP and were excluded from the analyses. Summary is based on observed data and no imputation is made for missing values. Baseline is defined as the parent study baseline. ^a SoC alone ^b Evolocumab 420 mg QM + SoC IAAS, Interim All-IP Period Analysis Set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; SE, standard error			

Figure 3-1 Plot of mean percent change from baseline in calculated LDL-C by scheduled visit and treatment group (OSLER, ICOAS and IAAS)



References: OSLER Interim CSR⁹ Figure 14-4.23.1

Note: Data cut-off date 01 April 2014. OLE visits prior to or on OLE week 52 were under SoC-controlled period and OLE visits after OLE week 52 are under all-IP period. All subjects remained on or started receiving evolocumab + SoC during the all-IP period. Baseline is defined as the parent study baseline. Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.

IAAS, Interim All-IP Period Analysis; ICOAS, Interim SoC-Controlled Period Analysis Set; IP, investigational product; OLE, open label extension; SoC, standard of care

3.2 OSLER-2

A summary of the mean percent change from parent study baseline in calculated LDL-C by scheduled visit in year 1 of OSLER-2 (data cut-off date 01 April 2014) is provided in Table 3-3.

Table 3-3 Summary of mean percent change from parent study baseline in calculated LDL-C by scheduled visit in year 1 (OSLER-2, ICOAS)

	Control in parent study		Evolocumab in parent study	
	Control in OSLER ^a	Evolocumab in OSLER ^b	Control in OSLER ^a	Evolocumab in OSLER ^b
Percent change from baseline at parent study end of study				
n	318	666	587	1195
Mean (SE)	-2.7 (1.5)	-3.0 (1.0)	-60.8 (0.9)	-60.5 (0.6)
Percent change from baseline at OSLER week 12				
n	314	670	581	1184
Mean (SE)	14.9 (2.4)	-53.5 (1.3)	8.0 (1.5)	-54.4 (0.8)
Percent change from baseline at OSLER week 24				
n	229	469	382	792
Mean (SE)	9.7 (2.8)	-50.7 (1.6)	6.7 (1.7)	-52.5 (1.1)
References: OSLER-2 Interim CSR ¹⁰ Table14-4.22.9				
Note: Data cut-off 01 April 2014. The interim OSLER-2 efficacy and safety analyses employed a modified intention-to-treat approach during the SOC-controlled period; all subjects randomised in the study who had at least 12 weeks of potential follow up were included in the ICOAS and the interim efficacy and safety analyses. The restriction on potential follow-up was implemented to prevent operational bias that may occur by differences in visit schedules during the first 12 weeks of the study. Summary is based on observed data and no imputation is made for missing values. Baseline is defined as the parent study baseline. ^a SoC alone ^b Evolocumab 140 mg Q2W + SoC or 420 mg QM + SoC IAAS, Interim All-IP Period Analysis Set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; SE, standard error; SoC, standard of care				

4 References

1. Robinson JG, Nedergaard BS, Rogers WJ *et al.* Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* 2014;311:1870-82.
2. Amgen. Data on file. LAPLACE-2 CSR. 2014.
3. Raal FJ, Stein EA, Dufour R *et al.* PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;385:331-40.
4. Amgen. Data on file. RUTHERFORD-2 CSR. 2014.
5. Strokes E, Colquhoun D, Sullivan D *et al.* Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* 2014;63:2541-8.
6. Amgen. Data on file. GAUSS-2 CSR 2014.
7. Blom DJ, Hala T, Bolognese M *et al.* A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med* 2014;370:1809-19.
8. Amgen. Data on file. DESCARTES CSR. 2014.
9. Amgen. Data on file. OSLER CSR. Data cut-off, 1st April 2014
10. Amgen. Data on file. OSLER-2 CSR. Data cut-off, 1st April 2014

Single Technology Appraisal (STA)

**Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia
ID765**

Dear [REDACTED]

The Evidence Review Group, the School of Health and Related Research (SchARR) at the University of Sheffield, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 22nd of July 2015 by Amgen. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm, Tuesday 25 August**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under '**commercial in confidence**' in turquoise, and all information submitted under '**academic in confidence**' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals.

If you have any further queries on the technical issues raised in this letter then please contact Ahmed Elsada, Technical Lead (ahmed.elsada@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION.** Appendix III, Section 2, pages 5–26. The ERG notes that the clinical effectiveness searches do not include terms for dyslipidaemia/mixed dyslipidaemia. Please clarify the reasons for this.

A2. Appendix III Section 2.1, page 7. An RCT filter has been applied to the results of the clinical effectiveness Medline search. The ERG notes that this filter has been modified from the version published by Lefebvre et al. Please explain why the filter has been modified and the basis for the changes made.

A3. **PRIORITY QUESTION.** Section 4.11, page 130. Please clarify what search was performed to identify relevant non-RCT evidence, and which inclusion/exclusion criteria were applied. Please also provide details of the identified non-RCT studies that were excluded and the reasons for their exclusion.

A4. Section 5.1 and Appendix IX, Tables IX-1 and IX-2. The cost-effectiveness searches on Medline and EMBASE use a filter to identify economic evaluations. However, this contains some errors (for example, pharmaco?economic* – the “?” character cannot be used to find hyphens or spaces in Ovid). Please explain why a validated filter, such as those developed by SIGN (<http://sign.ac.uk/methodology/filters.html#econ>), has not been used.

A5. Section 5.4 pages 206–207. The submission states that bibliography checking has been used to identify records for the systematic literature review of health-related quality of life. Please clarify whether this method has also been used to identify studies for the clinical effectiveness and cost-effectiveness reviews, and whether the process involved citation searching to locate references forwards as well as backwards.

A6. **PRIORITY QUESTION.** Section 4.2, page 67. The population described in the decision problem relates to people with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidemia, whose low-density lipoprotein cholesterol (LDL-C) is not controlled by statins or cannot have statins (contraindicated or not tolerated), and who would therefore currently receive ezetimibe (with or without a statin). Relevant subgroups are people with heterozygous familial hypercholesterolaemia (HeFH), presence or risk of cardiovascular disease (CVD), and severity of hypercholesterolaemia. Please clarify how the

populations in the trials LAPLACE-2, GAUSS-2 and DESCARTES correspond to the population defined in the final scope, including details of any deviations. Please also clarify whether HeFH patients were eligible for inclusion in these trials.

A7. Section 4.2, page 67. RUTHERFORD-2 considers a specific subgroup of interest (HeFH). Please clarify whether the population in this trial had uncontrolled LDL-C levels on statins or were intolerant to statins.

A8. **PRIORITY QUESTION.** Section 4.1 and Table 4-1. RUTHERFORD-2 considers a specific subgroup of interest (HeFH), but is a placebo-controlled trial. This does not accord with the decision problem and its criteria relating to comparators, as specified under Section 4.1 (and Table 4-1) of the company's submission, which requires trials of evolocumab compared with ezetimibe. Section 4.13 explains that subgroup analyses relating to exposure to ezetimibe could not be performed. Please clarify and explain the inclusion of this trial in the systematic review of clinical effectiveness.

A9. Regarding the methods and processes of systematic review:

- Section 4-1, page 62. Please clarify the number of reviewers who conducted the study screening process and the procedures followed to minimise potential errors in study selection.
- Section 4.2. Please clarify the number of reviewers who conducted data extraction and the procedures followed to minimise potential errors.
- Section 4.6, page 100. Please clarify the number of reviewers who conducted the critical appraisal of the included trials and what procedures were followed to minimise potential errors or differences of interpretation.

A10. Figure 4-1, page 66. The numbers in the figure do not add up ($666-399=267$ not 196). Please clarify which citations are missing.

A11. Sections 4.1, 4.10, 4.11 and 4.12 apply different inclusion criteria. Sections 4.1 and 4.10 explicitly source included studies from the same search. Please clarify the exact criteria applied in Sections 4.1 and 4.10 at the process stages to reduce the numbers of citations from 666 to 196 and from 196 to 82.

A12. Section 4.12. Please assess and report the quality of the studies presenting safety data that were not assessed in Section 4.6.

A13. Section 4.7, Table 4-17, page 117 and subsequent results; executive summary; Section 1.3 and Table 1-3. Please clarify whether the provided pooled estimates across all treatment groups in the DESCARTES trial include a subgroup of patients treated with ezetimibe 10mg/day. In Section 4.13 (page 152), relevant subgroup comparisons are stated, including “(i) *evolocumab plus statin plus ezetimibe plus diet versus statin plus ezetimibe plus diet (relevant intervention and relevant comparator)*.” Please provide estimates of treatment effect for this subgroup.

A14. Section 4.10, pages 129–130. A network meta-analysis was considered for the HeFH population but was deemed unfeasible. Please clarify whether an NMA of the relevant evidence for patients with primary hypercholesterolaemia and mixed dyslipidaemia was considered.

Section B: Clarification on cost-effectiveness data

B1. Section 5.1, Figure 5-1, page 165. Please clarify why the PRISMA flowchart does not include all 108 relevant citations identified by the searching.

B2. Section 5.1, page 166. Please clarify how data were extracted from existing economic evaluation studies, including the number of reviewers who extracted the data, and the procedures followed to minimise bias.

B3. Section 5.1, page 166. Please clarify the criteria applied that reduced the number of UK studies from 28 to the 14 studies given in Table 5-2.

B4. **PRIORITY QUESTION.** Section 4.7, Table 4-13, page 111. For the (i) LAPLACE-2 primary prevention population and (ii) LAPLACE-2 secondary prevention population, as represented in the model (that is, the subgroup of patients with LDL-C>2.5, n=744 for primary prevention, n=330 for secondary prevention), please replicate the information presented in Table 4-13.

B5. PRIORITY QUESTION. Section 4.13, page 155. The current evidence base discussed in the submission does not include any evidence relating to the effect of evolocumab on CVD events. Please provide the study protocol of the FOURIER study, and further details including any interim results that are currently available.

B6. PRIORITY QUESTION. Executive summary and Section 5.4, pages 27, 28, and 279–282. The submission presents tables reporting ICERs for patients with 1 or 2 additional risk factors. The accompanying text states *“The grey cells denote patient profiles where the incremental cost per QALY gained is less than £30,000.”* However, none of the values presented in the tables are below £30,000 per QALY gained. Please clarify whether the text or tables are incorrect.

B7. PRIORITY QUESTION. Section 5, page 160. The text states *“The incremental cost per QALY gained is approximately £15,119 to £18,200 for evolocumab versus ezetimibe in patients with HeFH when assessed across the four treatment scenarios.”* These ICERs are not mentioned elsewhere in the submission and appear considerably lower than the ICERs presented in Tables 5-27, 5-42, 5-47, 5-62 and 5-63. Please clarify this discrepancy.

B8. Section 5.7, page 240. Please clarify why a threshold of >2.5 mmol/L has been selected to define “high risk” population in the LAPLACE-2 analyses. Please also clarify whether patients in the LAPLACE-2 trial were stratified according to LDL-C at baseline (LDL-C ≤ 2.5 mmol/L and LDL-C > 2.5 mmol/L). Also, please provide baseline characteristics for those with LDL-C > 2.5 mmol/L by treatment group (with p values).

B9. Section 5.5, page 229. The model includes only the costs of atorvastatin 20mg/80mg. Please justify why other statins were not included in the model. Please also provide details on how this assumption corresponds to the experience in the evolocumab trials and the high-risk LAPLACE-2 population included in the model.

B10. Section 5.3, page 196. Please clarify why LDL-C was the only surrogate used for CVD risk. Please clarify whether other markers were considered.

B11. PRIORITY QUESTION. Section 5.2, pages 174–181. Please comment on the advantages of using combined health states compared with the approach used in the NICE

clinical guideline 181, particularly with respect to the number of assumptions required and the availability of data to inform the outcomes associated with these health states. Please also comment on whether the approach taken, whereby the highest transition probability, lowest utility and highest cost is selected for combined health states, had been used in any of the previous economic analyses identified in the cost-effectiveness review presented in Section 5.1.

B12. Section 5.3, page 184. Please provide further details on why the Framingham equation was used instead of the QRISK2 equation. Were data on the additional risk factors required by QRISK2 available in the LAPLACE-2, GAUSS-2 and RUTHERFORD-2 trials? Please also justify how the threshold analysis, which assumes that CV risk is calculated with QRISK, fits in with the model in which CV risk is based on Framingham.

B13. **PRIORITY QUESTION.** Please clarify why the UKPDS risk engine was not used to assess CV risk in the diabetic population. Please also discuss the limitations of using the Framingham equations in the diabetic population in the CPRD dataset.

B14. **PRIORITY QUESTION.** Section 5.3, page 184. The company's submission suggests that calibration is necessary irrespective of whether the QRISK2 or Framingham equation is used. If the QRISK2 risk equation was used, why would this require calibration?

B15. Section 5.13, page 275–282. Please clarify why for the subgroup analysis, all patients from LAPLACE-2 included in the model were assumed to have diabetes, LDL>3, LDL> 3.5, rather than selecting the smaller subgroup of patients who actually have these particular characteristics?

B16. Section 5.14, page 283. Please provide details of the number and positions of clinical advisors who informed the development of the model.

B17. **PRIORITY QUESTION.** Company's model. Please explain the following values in the "population" sheet of the model:

- cells V43:59 are multiplied by a hard-coded value of 8.15
- cells W43:59 are multiplied by a hard-coded value of 6.95
- cells X43:59 are multiplied by a hard-coded value of 6.35

- cells Y43:59 are multiplied by a hard-coded value of 8.55
- cells Z43:59 are multiplied by a hard-coded value of 7.3
- cells AA43:59 are multiplied by a hard-coded value of 6.5

Please clarify the source of these values. Please clarify whether these multipliers were applied to the probability or the rate of each event. Please also clarify whether D'Agostino and the REACH risk equations produce rates or probabilities.

B18. Section 5.3, page 192. Please explain where the data contained in Table 5-9 are applied in the model.

B19. **PRIORITY QUESTION.** Table 5-10, page 193. The treatment effects used for the combination with statin therapy (from LAPLACE-2) relate to the treatment difference compared with background statin therapy. The treatment effects for monotherapy (from GAUSS-2) relate to the mean percentage change from baseline, which does not account for the change in LDL-C on placebo treatment. Please clarify the evidence for assuming that there will be no change in response in the placebo group, or alternatively, how this issue has been addressed in the cost-effectiveness model?

B20. Table 5-10, page 193. Please clarify the method for the “post hoc pooled analysis” that was used to provide the pooled treatment effects for ezetimibe 10mg.

B21. **PRIORITY QUESTION.** Section 5.3, Figure 5-7 and Table 5-11. Please clarify how the effect of the combination treatment is generated? For example, for scenario 4, treatment effects from LAPLACE-2 are used. For ezetimibe there was a treatment effect of -27% mean change from baseline. For evolocumab there was a treatment effect of -72 % mean change from placebo, or -64 % mean change from baseline. Assuming a baseline LDL-C of B for a given individual, would the calculated LDL-C after treatment be

- 1) $B \times (1 - 0.27) \times (1 - 0.64)$ or
- 2) $B \times (1 - 0.27 - 0.64)$

Also, was the evidence from the relevant DESCARTES subgroup (that assessed evolocumab and ezetimibe in combination) considered to inform this treatment effect?

B22. Section 5.2, pages 173–174. Please clarify why baseline characteristics from DESCARTES have not been used in the health economic analysis.

B23. Section 5.3, page 193. Please clarify why the treatment effect from RUTHERFORD-2 has not been used to inform the analyses in the HeFH population. Please comment on the differences in treatment effect for evolocumab vs. placebo (plus background statins) observed in LAPLACE-2 and RUTHERFORD-2.

B24. Section 5.3, page 193. The relative treatment effects for evolocumab in the statin-intolerant population are taken from the GAUSS-2 trial. However, the modelled risk of CVD is based on baseline characteristics from LAPLACE-2 or RUTHERFORD-2. Please clarify why patient-level data from the GAUSS-2 trial have not been used to derive the CVD risk as per the approach used for LAPLACE-2 and RUTHERFORD-2.

B25. Section 5.3, Table 5-5, page 183. The number of vascular beds (VB) and proportion of patients with atrial fibrillation (AF) are based on the mean observed in the REACH study. Please comment on the potential biases associated with this. Please also confirm that this information is not available from the LAPLACE-2, DESCARTES, RUTHERFORD-2 or GAUSS-2 trials.

B26. **PRIORITY QUESTION.** Section 5.3, page 198. Please clarify why no reduction in CV event rate associated with LDL-C levels when lower than 1.03mmol/L from baseline (equivalent to 40mg/dL) was assumed?

B27. Section 5.4, pages 219–220. Please clarify why utilities from NICE clinical guideline 181 were assumed when the company's submission includes a new systematic review of health-related quality of life literature.

B28. Section 5.5, Table 5-20, pages 227–228. Please clarify why the resource use/cost review focuses only on Markov models with lifetime horizon relating to a UK setting? Please clarify how these studies were used to inform the de novo health economic analysis.

B29. Section 5.3, Table 5-12, page 197. Please clarify why rate ratio for the “more vs less” is used for non-fatal CV events (based on 5 trials), whereas the rate ratio for all lipid agents (n=26 trials) is used for fatal CV events. Please also clarify why only ischaemic stroke (rather than other forms of stroke) is included in the model.

B30. Section 5.3, pages 196–198. The company’s model focuses on patients deemed to be at high risk of CV events (according to baseline LDL, presence of diabetes etc.). The company uses data from the CTTC meta-analysis for all patients irrespective of baseline LDL, risk factors or history of cardiac event. Please comment on the availability of data on CV risk by baseline risk factors.

B31. Company’s model. Please clarify why the 10-year risk was calculated for the overall population in the RUTHERFORD-2 trial in the HeFH population; that is, why was the Framingham risk equation applied to patients who have a history of CVD? Why were the primary and secondary prevention populations not evaluated separately?

B32. Company’s model. Please provide further explanation on how the 10-year risk was adjusted for age in the model, including any assumptions used. In particular, please explain what the calculations in worksheet “Rates & non-CVD Utilities” columns C and E are intended to do.

B33. **PRIORITY QUESTION.** Section 5.3, pages 187–192. The company attempted to calibrate the 10-year risk estimated from the Framingham algorithm using data from the CPRD (20 months from REACH using the HES data).

- Please comment on whether calibration factors are already available in the literature and if so, how these compare with the calibration factors estimated from the CPRD/HES dataset?
- Please clarify why only patients with diabetes were included in the CPRD dataset for primary prevention. Please comment on the potential biases associated with this approach.
- The submission states that about half the patients from the CPRD dataset could not be linked (or did not have information). Please comment on the potential biases resulting from this (for example, selection bias). Please also comment on any

differences between patients included and excluded (or those who could not be linked).

- How does this calibration approach compare with the methods used in NICE clinical guideline 181?
- Please explain why the event rates from the CPRD analysis were not used to directly estimate CV risk (as opposed to using Framingham as per the company's model)?

B34. Section 6, Table 6-7, page 289. Values for evolocumab are presented as 0% throughout. Please also check figures on page 290 and in Tables 6-8 and 6-9.

Section C: Data request

C1. Please provide an Excel worksheet including patient-level data for all patients from LAPLACE-2, in the same form as the "LAPLACE-2 (PP)" worksheet in the model, but also including variables for (1) primary/secondary prevention, (2) statin product and dose at baseline, and (3) randomised treatment group.

**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL
EXCELLENCE**

Single Technology Appraisal (STA)

**Evolocumab for treating primary hypercholesterolaemia
(heterozygous familial and non-familial) and mixed
dyslipidaemia**

Response to clarification questions

Amgen Limited

Date: August 2015

File name	Version	Contains confidential information	Date
		Yes CIC: Redacted AIC: Redacted	November 2015

Contents

A: Clarification on clinical-effectiveness data	6
B: Clarification on cost-effectiveness data	16
C: Data request	61
References	62
Appendices	65

List of tables

Table A-1	Generalisability of LAPLACE-2, DESCARTES, and GAUSS-2 to relevant populations in the decision problem	8
Table A-2	Quality assessment of studies other than the relevant RCTs included in the safety section of the submission	14
Table A-3	Subgroup analysis of mean percent change in ultracentrifugation LDL-C from baseline at week 52 in DESCARTES: diet + atorvastatin 80 mg + ezetimibe background therapy stratification factor (FAS)	16
Table B-1	Post-hoc combined statin analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2: primary prevention patients with LDL-C > 2.5 mmol/L (FAS)	18
Table B-2	Post-hoc combined statin analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2: secondary prevention patients with LDL-C > 2.5 mmol/L (FAS)	19
Table B-3	Post-hoc pooled placebo and ezetimibe analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2: primary prevention patients with LDL-C > 2.5 mmol/L (FAS)	20
Table B-4	Post-hoc pooled placebo and ezetimibe analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2: secondary prevention patients with LDL-C > 2.5 mmol/L (FAS)	21
Table B-5	LAPLACE-2: Baseline characteristics for subjects with baseline LDL-C > 2.5 mmol/L	24
Table B-6	Statin agents and acquisition costs	27
Table B-7	NHS prescription cost analysis, statins (April 2015)	28
Table B-8	NHS prescription cost analysis, high-intensity statins (April 2015)	28
Table B-9	Statin costs; base-case, lower and upper bound of sensitivity analysis	29
Table B-10	Univariate sensitivity analysis	29
Table B-11	LAPLACE-2: Summary of statin background therapy intensities and regimens at baseline for primary prevention subjects with baseline LDL-C > 2.5 mmol/L	31
Table B-12	LAPLACE-2: Summary of statin background therapy intensities and regimens at baseline for secondary prevention subjects with baseline LDL-C > 2.5 mmol/L	32
Table B-13	QRISK2 predictors and evolocumab studies	37
Table B-14	Adjusted hazard ratios (95% CI) for cardiovascular disease for QRISK2 model in derivation cohort with interactions	38
Table B-15	Predicted CV rates for patients with existing CVD based on actual and assumed diabetes mellitus	41
Table B-16	Summary of clinical and economic advisors involved in the economic model development	41
Table B-17	Mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe when used in combination with statins or as monotherapy	44
Table B-18	Predicted CV rates for patients with existing CVD based LAPLACE-2 and DESCARTES	46
Table B-19	Mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe when used in combination with statins in LAPLACE-2 and RUTHERFORD-2	47

Table B-20	Modelled LDL-C levels after treatment according to severity of hypercholesterolaemia (baseline LDL-C)	49
Table B-21	Existing CVD and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin, scenario 1) based on LDL-C threshold for CV event reduction	50
Table B-22	Heterozygous familial hypercholesterolaemia and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin, scenario 1) based on LDL-C threshold for CV event reduction	50
Table B-23	Consistency of identified HRQoL studies with NICE reference case	52
Table B-24	Cost-effectiveness results for heterozygous familial hypercholesterolaemia population (all, primary prevention and secondary prevention populations) for evolocumab and statin versus ezetimibe and statin	56
Table B-25	Diabetes: Overall event rates	58
Table B-26	Established cardiovascular disease: Overall event rates.....	58
Table B-27	Acute coronary syndrome: Overall event rates.....	58
Table B-28	Heart failure: Overall event rates.....	58
Table B-29	Ischaemic stroke: Overall event rates	59
Table B-30	CPRD Study: comparison of population characteristics with and without linked Hospital Episodes Statistics data	59
Appendix Table-1	List of unobtainable papers	89
Appendix Table-2	List of ongoing studies	90
Appendix Table-3	List of completed studies and publications with no data	96
Appendix Table-4	Inclusion and exclusion criteria for the broad clinical efficacy/safety systematic literature review	100
Appendix Table-5	GAUSS (Study 20090159) quality assessment.....	103
Appendix Table-6	YUKAWA (Study 20110231) quality assessment	103
Appendix Table-7	RUTHERFORD (Study 20090158) quality assessment.....	104
Appendix Table-8	LAPLACE-TIMI 57 (Study 20101155) quality assessment	105
Appendix Table-9	MENDEL (Study 20101154) quality assessment.....	105
Appendix Table-10	MENDEL-2 (Study 20110114) quality assessment.....	106
Appendix Table-11	OSLER (Study 20110110) quality assessment	107
Appendix Table-12	OSLER-2 (Study 20120138) quality assessment	108
Appendix Table-13	THOMAS-1 (Study 20120348) quality assessment	108
Appendix Table-14	THOMAS-2 (Study 20120356) quality assessment	109
Appendix Table-15	Summary table of economic evaluation studies from the UK.....	111

List of figures

Figure A-1	PRISMA flow diagram for the clinical efficacy/safety SLR.....	13
Figure B-1	PRISMA flow diagram for the cost-effectiveness studies SLR.....	17

A: Clarification on clinical-effectiveness data

A1 (PRIORITY QUESTION): Appendix III, Section 2, pages 5–26. The ERG notes that the clinical effectiveness searches do not include terms for dyslipidaemia/mixed dyslipidaemia. Please clarify the reasons for this.

A decision was made during development of the systematic literature review (SLR) that the use of the terms 'hypercholesterolaemia' and 'hyperlipidaemia' would be sufficient to identify all relevant studies given that all patients with mixed dyslipidaemia (i.e. hypercholesterolaemia and hypertriglyceridaemia) have hypercholesterolaemia. Dyslipidaemias other than hypercholesterolaemia and mixed dyslipidaemia are outside of the licensed indication for evolocumab.

The only studies that are relevant to the decision problem are those assessing evolocumab (either alone or in combination with statins with or without ezetimibe) or ezetimibe (either alone or in combination with statins). All clinical studies of evolocumab conducted to date are Amgen-sponsored, and all of these enrolled patients with either 'hypercholesterolaemia' or 'hypercholesterolemia or mixed dyslipidaemia', meaning they would have been identified using the original search terms alone. Ezetimibe is specifically indicated for hypercholesterolaemia (not mixed dyslipidaemia), so addition of a 'dyslipidaemia'/'mixed dyslipidaemia' search term is unlikely to have identified additional relevant studies in its licensed indication. Nevertheless, to assess the impact of excluding a 'dyslipidaemia'/'mixed dyslipidaemia' search term from the SLR search strategies on identification of relevant ezetimibe studies, targeted searches using a search term for 'dyslipidaemia' were conducted in Medline, Medline in Process, Embase, CENTRAL, CDSR, and DARE (search strategies provided in Appendix I of this document). These searches yielded no relevant ezetimibe studies in addition to those already identified in the original SLR.

A2: Appendix III Section 2.1, page 7. An RCT filter has been applied to the results of the clinical effectiveness Medline search. The ERG notes that this filter has been modified from the version published by Lefebvre et al. Please explain why the filter has been modified and the basis for the changes made.

The only amendment to the original filter was the addition of truncation to the word random\$ in line 56 of the strategy to increase the sensitivity and to pick up terms such as 'randomised' and 'randomisation'. In line with recommendations made by Lefebvre et al.,¹ the original source filter was clearly referenced with an indication that the filter had been amended (i.e. use of the phrase 'Based on').

A3 (PRIORITY QUESTION): Section 4.11, page 130. Please clarify what search was performed to identify relevant non-RCT evidence, and which inclusion/exclusion criteria were applied. Please also provide details of the identified non-RCT studies that were excluded and the reasons for their exclusion.

Given the robust evidence base derived from relevant randomised controlled trials (RCTs) which adequately addresses the decision problem, no systematic search was performed to identify non-RCT evidence.

The ongoing, Amgen-sponsored TAUSSIG study enrolls patients who completed study 20110233 (TESLA, a phase 2/3 study in patients with homozygous familial hypercholesterolaemia [HoFH]) as well as de novo patients with familial hypercholesterolaemia (FH), including either HoFH or heterozygous familial hypercholesterolaemia (HeFH).^{2,3} Data from the TAUSSIG 'Severe FH interim analysis set' (i.e. patients with HeFH) were included as supplementary information given that:

- subgroups according to severity of hypercholesterolaemia are defined as relevant subgroups in the decision problem. This study provides clinical efficacy data for evolocumab in patients with severe HeFH (mean baseline calculated low-density lipoprotein cholesterol [LDL-C] 4.9 mmol/L)
- TAUSSIG provides data on the effect of evolocumab on requirement of apheresis (a relevant outcome in the decision problem)
- TAUSSIG provides longer-term follow-up data in the HeFH population than RUTHERFORD-2.

A4: Section 5.1 and Appendix IX, Tables IX-1 and IX-2. The cost-effectiveness searches on Medline and EMBASE use a filter to identify economic evaluations. However, this contains some errors (for example, pharmaco?economic* – the “?” character cannot be used to find hyphens or spaces in Ovid). Please explain why a validated filter, such as those developed by SIGN (<http://sign.ac.uk/methodology/filters.html#econ>), has not been used.

We sought to update the previously conducted cost-effectiveness study SLR in NICE CG181 by replicating the search strategy. Thank you for identifying this error. As a result, the searches were re-run in Ovid for MEDLINE and EMBASE using validated filters as developed by SIGN, and NHS EED and Econlit. The search was run for the same period as the previous SLR (January 2000 to December 2014) and de-duplicated. Full details of the updated search strategies are provided in Appendix II. All the cost-effectiveness studies from the previous SLR were identified. The publications were screened at the first (title and abstract) level and second level (full-text) by two reviewers as per the methods outlined in the evidence submission (Section 5.1).

Of the additional 272 abstracts, two were identified for full-text screening; of these only one was identified (Fitch et al., 2009)⁴ for inclusion and selected for data extraction. Fitch et al.,⁴ was a cost-effectiveness study based on a three-year event forecast model with a US focus (refer to Appendix II for study data extraction).

A5: Section.5.4 pages 206–207. The submission states that bibliography checking has been used to identify records for the systematic literature review of health-related quality of life. Please clarify whether this method has also been used to identify studies for the clinical effectiveness and cost-effectiveness reviews, and whether the process involved citation searching to locate references forwards as well as backwards.

For the clinical efficacy and cost-effectiveness SLRs, the reference lists in retrieved articles and relevant systematic reviews were checked to identify additional studies. Forward citation searching was not part of the methods for these SLRs.

A6 (PRIORITY QUESTION): Section 4.2, page 67. The population described in the decision problem relates to people with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidemia, whose low-density lipoprotein cholesterol (LDL-C) is not controlled by statins or cannot have statins (contraindicated or not tolerated), and who would therefore currently receive ezetimibe (with or without a statin). Relevant subgroups are people with heterozygous familial hypercholesterolaemia (HeFH), presence or risk of cardiovascular disease (CVD), and severity of hypercholesterolaemia. Please clarify how the populations in the trials LAPLACE-2, GAUSS-2 and DESCARTES correspond to the population defined in the final scope, including details of any deviations. Please also clarify whether HeFH patients were eligible for inclusion in these trials.

As described in Table A-1, LAPLACE-2, GAUSS-2, and DESCARTES are generalisable to the populations described in the decision problem, though it is acknowledged there are some deviations given that these studies were global in nature and not designed specifically to meet the needs of the decision problem.

HeFH status was not assessed in LAPLACE-2, GAUSS-2, and DESCARTES, and was not an exclusion criterion in these studies.⁵⁻¹¹ Therefore, it is likely that some patients with HeFH were enrolled in these studies, which is supported by patient level data that show that some patients had substantially elevated LDL-C at baseline, indicative of FH.

Table A-1 Generalisability of LAPLACE-2, DESCARTES, and GAUSS-2 to relevant populations in the decision problem

Study	Population relevant to decision problem	Rationale and deviations
LAPLACE-2	People with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia when optimised initial statin therapy does not appropriately control LDL-C	The screening LDL-C inclusion criteria in LAPLACE-2 suggest that patients are unlikely to be controlled by statins:⁸ • Fasting LDL-C ≥ 2.1 mmol/L (taking an intensive^a statin at screening) • Fasting LDL-C ≥ 2.6 mmol/L (taking a non-intensive^b statin at screening) • Fasting LDL-C ≥ 4.5 mmol/L (not taking a statin at screening) at screening Following screening, patients discontinued any prior statin

Study	Population relevant to decision problem	Rationale and deviations
		therapy and were randomised to moderate- or high-intensity^c background statin therapy. Following statin randomisation and prior to randomisation to IP, patients underwent a 4-week lipid stabilisation period. There were no additional LDL-C inclusion criteria following lipid stabilisation as this could lead to imbalances in baseline characteristics across statin cohorts, therefore limiting ability to compare treatment effects across statin cohorts. Patients taking a non-intensive statin at screening or not taking a statin at screening may have potentially achieved adequate LDL-C control if they were subsequently randomised to an intensive statin (i.e. rosuvastatin 40 mg or atorvastatin 80 mg) based on the known effects of LDL-C reductions with specific statin therapies.¹² Although there are no absolute targets for LDL-C reduction in current NICE guidance,¹³⁻¹⁵ the overall mean baseline calculated LDL-C level (i.e. following randomisation to statin and lipid stabilisation) in the LAPLACE-2 FAS was 2.8 mmol/L.¹⁶ This baseline LDL-C level is indicative of inadequate LDL-C control in patients at high risk of CVD. Further, as described in the evidence submission, prespecified and <i>post hoc</i> subgroup analyses of LAPLACE-2 show that the LDL-C lowering treatment effect of evolocumab is independent of baseline LDL-C and presence or risk of CVD.^{8,16,17} Based on these data, it is reasonable to assume that the findings from LAPLACE-2 are generalisable to patients for whom optimised initial statin therapy does not appropriately control LDL-C. In any case, the economic evaluation only considered patient level data for risk estimation in patients with baseline LDL-C >2.5 mmol/L.
DESCARTES	People with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia when optimised initial statin therapy does not appropriately control LDL-C	DESCARTES was designed to assess efficacy and safety patients with a broad range of risk. The study enrolled patients with minimum baseline LDL-C requirements following assignment to one of four background lipid-lowering therapy regimens and subsequent lipid stabilisation:^{10,18} • Fasting LDL-C after 4-week lipid stabilisation period with one of four background lipid-lowering therapy regimens based on NCEP ATP III risk category goals ▪ LDL-C $\geq$ 2.0 mmol/L and < 2.6 mmol/L for those with CHD or CHD risk equivalents; ▪ LDL-C $\geq$ 2.0 mmol/L and < 3.4 mmol/L in patients without CHD or risk equivalent; OR ▪ for patients on maximal background lipid-lowering therapy (diet + atorvastatin 80 mg + ezetimibe), LDL-C $\geq$ 2.0 mmol/L Three of the four background therapy regimens included treatment with moderate- or high-intensity statins^c,

Study	Population relevant to decision problem	Rationale and deviations
		representing 89% of patients in the DESCARTES FAS. The remaining background therapy regimen (diet alone) is not relevant to the decision problem, though a prespecified subgroup analysis of the background therapy subgroups showed that the LDL-C lowering treatment effect of evolocumab was consistent across background therapy subgroups.¹⁸ The mean baseline calculated LDL-C level in the DESCARTES FAS was 2.6 mmol/L.¹⁸ This baseline LDL-C level is indicative of inadequate LDL-C control in patients at high risk of CVD. Further, as described in the evidence submission, prespecified and <i>post hoc</i> subgroup analyses of DESCARTES show that the LDL-C lowering treatment effect of evolocumab is independent of baseline LDL-C and presence or risk of CVD.^{16,18} Based on these data, it is reasonable to assume that the findings from DESCARTES are generalisable to patients for whom optimised initial statin therapy does not appropriately control LDL-C.
GAUSS-2	People with primary hypercholesterolaemia (heterozygous familial and non-familial) for whom statins are contraindicated or not tolerated	GAUSS-2 enrolled patients with previous intolerance to two or more statins, defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects. The use of muscle symptoms as a key identifier of statin intolerance is consistent with the definition of statin intolerance provided in NICE CG71¹³ and TA132¹⁵. As acknowledged in Section 4-13 of the evidence submission, GAUSS-2 did not include patients contraindicated to statins, though it is reasonable to assume that the findings from GAUSS-2 are generalisable to patients for whom statins are contraindicated.
ATP, Adult Treatment Panel; CG, clinical guideline; CHD, coronary heart disease; CVD, cardiovascular disease; FAS, full analysis set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; TA, technology appraisal ^aSimvastatin 80 mg OD, Atorvastatin 40 mg or greater OD, Rosuvastatin 20 mg or greater OD, any statin + ezetimibe ^bOther statin not defined as intensive ^cPer NICE CG181¹⁹ and ACC/AHA²⁰ statin intensity classification		

A7: Section 4.2, page 67. RUTHERFORD-2 considers a specific subgroup of interest (HeFH). Please clarify whether the population in this trial had uncontrolled LDL-C levels on statins or were intolerant to statins.

All patients in RUTHERFORD-2 had uncontrolled LDL-C levels (≥ 2.6 mmol/L) despite treatment with stable doses of statins $\pm$ other lipid-lowering therapies, as specified in the inclusion criteria column of Table 4-4 in the evidence submission ('Summary of eligibility criteria in the relevant RCTs').^{5,6}

- On a stable dose of an approved statin ± other allowed lipid-lowering therapy (e.g. ezetimibe, resins, stanols, or niacin) for ≥ 4 weeks before screening and, in the opinion of the investigator, not requiring uptitration
- Fasting LDL-C ≥ 2.6 mmol/L at screening.

In the RUTHERFORD-2 full analysis set (FAS), 76% of patients were receiving stable doses of high-intensity statins and 22% were receiving stable doses of moderate-intensity statins (per American College of Cardiology/American Heart Association statin intensity definition, which is generally consistent with NICE CG181) for ≥ 4 weeks before screening.^{16,19,20} It is therefore reasonable to assume that these patients were not statin intolerant, though no information on history of intolerance to statins was collected in the study.

A8 (PRIORITY QUESTION): Section 4.1 and Table 4-1. RUTHERFORD-2 considers a specific subgroup of interest (HeFH), but is a placebo-controlled trial. This does not accord with the decision problem and its criteria relating to comparators, as specified under Section 4.1 (and Table 4-1) of the company's submission, which requires trials of evolocumab compared with ezetimibe. Section 4.13 explains that subgroup analyses relating to exposure to ezetimibe could not be performed. Please clarify and explain the inclusion of this trial in the systematic review of clinical effectiveness.

Section 4.13 of the evidence submission does not state that subgroup analyses relating to exposure to ezetimibe could not be performed:

'Using the pre-specified ezetimibe use (yes/no) stratification factor subgroups, it is possible to make a comparison between: (i) evolocumab plus statin plus ezetimibe versus statin plus ezetimibe (relevant intervention and comparator); and (ii) evolocumab plus statin versus statin (relevant intervention, but not relevant comparator). However, due to the design of the trial, it is not possible to make a comparison between evolocumab plus statin versus ezetimibe plus statin (a relevant intervention and comparator in the decision problem).'

RUTHERFORD-2 meets the inclusion criteria of the clinical-effectiveness SLR by providing data for a relevant intervention (evolocumab plus statin plus ezetimibe) versus a relevant comparator (statin plus ezetimibe) defined in the decision problem, though it is acknowledged in the submission that this study does not provide data for another relevant intervention (evolocumab plus statin) versus the same comparator. Many patients with HeFH unable to control LDL-C with statins alone may already be receiving additional lipid-lowering therapies such as ezetimibe (62% of patients in the RUTHERFORD-2 FAS were receiving ezetimibe at baseline),⁶ and it would not have been ethical to discontinue ezetimibe use for washout prior to randomisation to IP in RUTHERFORD-2 in these high-risk patients. Further, given the uncertainty of the treatment effect of evolocumab, it would not have been ethical to enrol patients with HeFH who had not already been offered optimal treatment with currently available therapies e.g. ezetimibe.

Further, RUTHERFORD-2 is the only phase 3 RCT that assessed evolocumab specifically in the HeFH population. Exclusion of this study would therefore not allow for evaluation of evolocumab in accordance with its full marketing authorisation (primary hypercholesterolaemia [heterozygous familial] or non-familial] or mixed dyslipidaemia).

A9: Regarding the methods and processes of systematic review:

- Section 4-1, page 62. Please clarify the number of reviewers who conducted the study screening process and the procedures followed to minimise potential errors in study selection.
- Section 4.2. Please clarify the number of reviewers who conducted data extraction and the procedures followed to minimise potential errors.
- Section 4.6, page 100. Please clarify the number of reviewers who conducted the critical appraisal of the included trials and what procedures were followed to minimise potential errors or differences of interpretation.

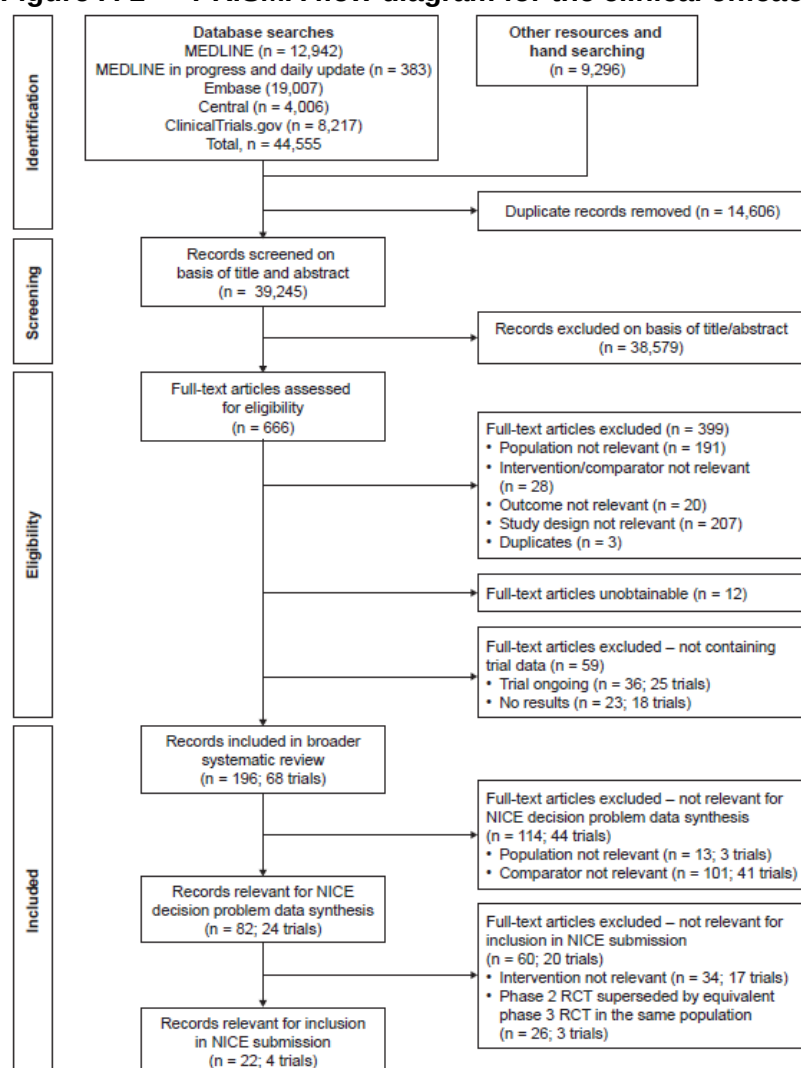
During the screening process, trials were independently selected for inclusion by two reviewers. Any discrepancies between reviewers were resolved through discussion or the intervention of a third reviewer.

Data extraction and quality assessment were performed by one reviewer and independently checked for errors against the original trial report by a second reviewer. Any discrepancies were resolved through discussion or through the intervention of a third reviewer.

A10: Figure 4-1, page 66. The numbers in the figure do not add up (666-399=267 not 196). Please clarify which citations are missing.

Thank you for identifying this error. The PRISMA flow diagram has been corrected with the addition of details of studies with unobtainable papers (n = 12 papers), and exclusion of ongoing studies (n = 36 papers) and studies with no results (n = 23 papers) (Figure A-1).

Figure A-1 PRISMA flow diagram for the clinical efficacy/safety SLR



Full details of the unobtainable papers, and the excluded ongoing studies and studies with no results are provided in Appendix III of this document.

A11: Sections 4.1, 4.10, 4.11 and 4.12 apply different inclusion criteria. Sections 4.1 and 4.10 explicitly source included studies from the same search. Please clarify the exact criteria applied in Sections 4.1 and 4.10 at the process stages to reduce the numbers of citations from 666 to 196 and from 196 to 82.

The reduction in number of citations from 666 to 196 was at assessment of eligibility of full text articles for the broad SLR. The inclusion and exclusion criteria for the broad SLR are detailed in Table 4-1 of the evidence submission and are provided again in Appendix IV of this document.

As described in Section 4-1 of the evidence submission, additional exclusion criteria were applied in a second stage of screening to further align the SLR with the decision problem, and to identify all relevant RCTs that could potentially be used for data synthesis in the absence of sufficient head-to-head data to address the information needs of the decision

problem. This second stage of screening reduced the number of citations from 196 to 82. The additional exclusion criteria were:

- study not in a population relevant to the decision problem (e.g. HoFH, Japanese population)
- study assessed neither relevant intervention nor relevant comparator defined in the decision problem
 - evolocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe
 - ezetimibe in combination with a statin (when optimised statin therapy does not appropriately control LDL-C) or ezetimibe alone (when statins are contraindicated or not tolerated)
- study did not include outcome defined in the decision problem
 - plasma lipid and lipoprotein levels, including LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), and lipoprotein (a) (Lp[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 (HRQoL).

A12: Section 4.12. Please assess and report the quality of the studies presenting safety data that were not assessed in Section 4.6.

A summary of quality assessment of studies for which safety data are presented in the submission (as part of an integrated analysis of safety), in addition to the relevant RCTs, is provided in Table A-2. A more detailed description is provided in Appendix V of this document. This quality assessment showed that these studies were of high quality (low risk of bias).

Table A-2 Quality assessment of studies other than the relevant RCTs included in the safety section of the submission

[illegible]

	MENDEL	MENDEL-2	OSLER	OSLER-2	THOMAS	THOMAS-2	GAUSS	YUKAWA	YUKAWA-2	RUTHERFORD	LAPLACE-TIMI 57
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	No	No	No	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No	No	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

A13: Section 4.7, Table 4-17, page 117 and subsequent results; executive summary; Section 1.3 and Table 1-3. Please clarify whether the provided pooled estimates across all treatment groups in the DESCARTES trial include a subgroup of patients treated with ezetimibe 10mg/day. In Section 4.13 (page 152), relevant subgroup comparisons are stated, including “(i) *evolocumab plus statin plus ezetimibe plus diet versus statin plus ezetimibe plus diet (relevant intervention and relevant comparator).*” Please provide estimates of treatment effect for this subgroup.

The four assigned background lipid-lowering therapy regimens in DESCARTES (stratification factor subgroups) were:^{10,11}

- Diet alone
- Diet + atorvastatin 10 mg
- Diet + atorvastatin 80 mg
- Diet + atorvastatin 80 mg + ezetimibe

The study level treatment effects provided in Section 1.3 and Section 4.7 of the evidence submission include patients in all of these background therapy stratification factor subgroups.

A prespecified subgroup analysis of the diet + atorvastatin 80 mg + ezetimibe stratification factor subgroup is provided in the CSR and shows a treatment difference in mean percent change from baseline in LDL-C at week 52 of -49.3% (p < 0.001) for evolocumab versus placebo (Table A-3).¹⁸ Results were consistent across background therapy subgroups (interaction p=0.089).

Table A-3 Subgroup analysis of mean percent change in ultracentrifugation LDL-C from baseline at week 52 in DESCARTES: diet + atorvastatin 80 mg + ezetimibe background therapy stratification factor (FAS)

	Placebo QM (N = 302)	Evolocumab QM (N = 599)
n	55	115
Week 52 mean percent change from baseline (95% CI) ^a	2.3 (-6.1, 10.6)	-47.1 (-52.9, -41.3)
Week 52 treatment difference (95% CI) ^{a,b}	-	-49.3 (-59.5, -39.1) p < 0.001 ^c
References: DESCARTES CSR ¹⁸ Table 14-4.7.1		
^aWithin each subgroup the least squares mean is from the repeated measures model which includes treatment group, scheduled visit, and the interaction of treatment with scheduled visit as covariates. ^bTreatment differences using placebo as the reference. ^cNominal p value. No multiplicity adjustment was carried out for subgroup analyses. CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in the FAS; n, number of subjects in the FAS with a non-missing subgroup value and data at the specified time point; QM, monthly		

A14: Section 4.10, pages 129–130. A network meta-analysis was considered for the HeFH population but was deemed unfeasible. Please clarify whether an NMA of the relevant evidence for patients with primary hypercholesterolaemia and mixed dyslipidaemia was considered.

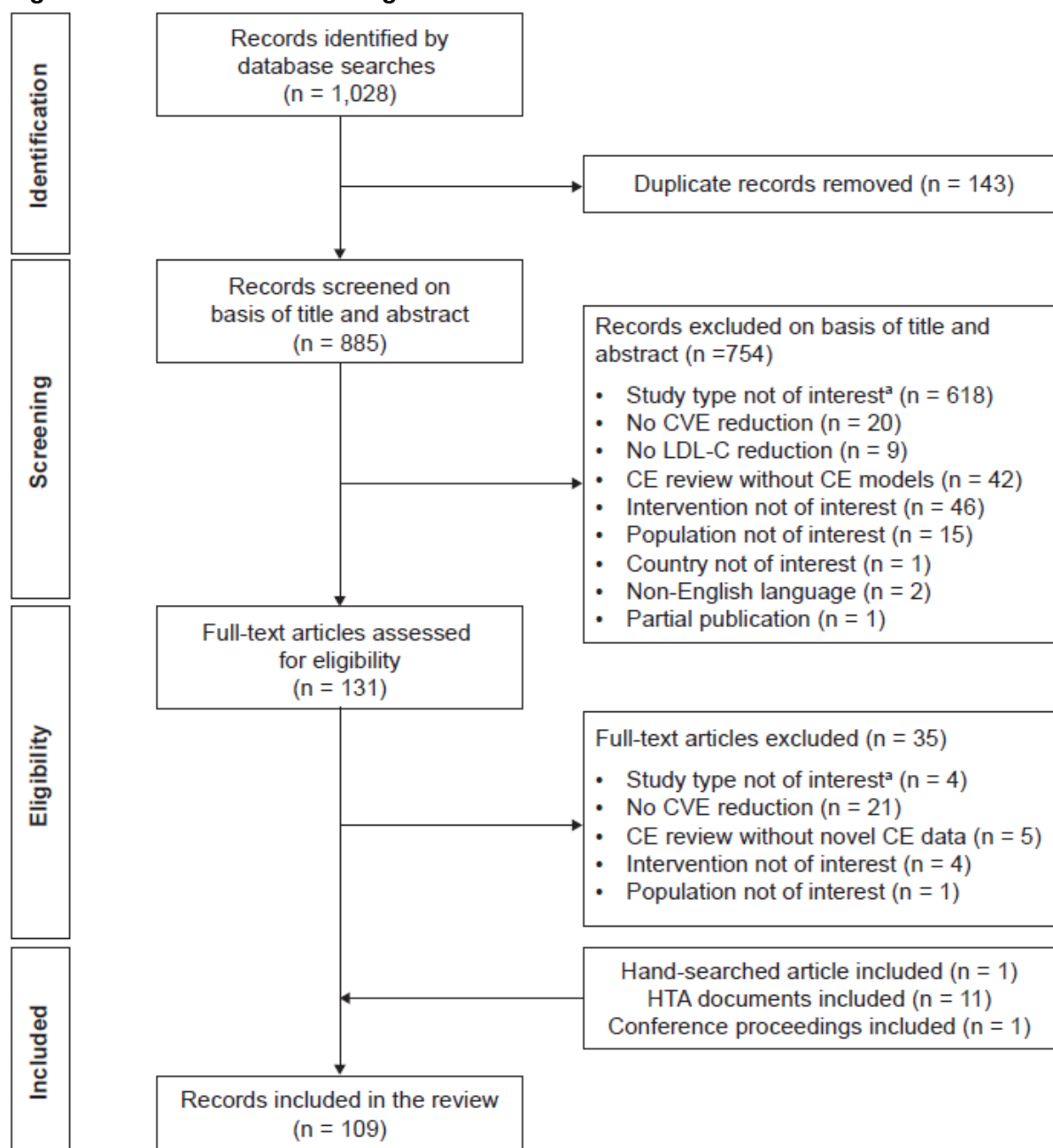
Given the availability of robust RCTs that provide head-to-head efficacy data for the intervention versus relevant comparators for patients with primary hypercholesterolaemia and mixed dyslipidaemia, a network meta-analysis was not considered to be necessary.²¹

B: Clarification on cost-effectiveness data

B1: Section 5.1, Figure 5-1, page 165. Please clarify why the PRISMA flowchart does not include all 108 relevant citations identified by the searching.

Thank you for identifying that the PRISMA flow diagram in the evidence submission did not include all 108 relevant citations. As per our response to question A4 with regards the updated cost-effectiveness studies SLR, the PRISMA flow diagram has also been updated to include HTA documents and conference proceedings (Figure B-1).

Figure B-1 PRISMA flow diagram for the cost-effectiveness studies SLR



^aStudy types not of interest include: screening, risk modeling, switching program, guidelines, non-CVD, clinical trial, and utilisation studies

B2: Section 5.1, page 166. Please clarify how data were extracted from existing economic evaluation studies, including the number of reviewers who extracted the data, and the procedures followed to minimise bias.

One reviewer conducted the data extraction and quality assessment of each study using the Drummond and Jefferson (1996) instrument.²² A second reviewer conducted a review of a sample (30%) of the abstracted studies to ensure complete extraction of relevant data and accurate quality assessments. Where key data were missing or unclear, one attempt was made to contact the primary author of that study by email to obtain complete data.

B3: Section 5.1, page 166. Please clarify the criteria applied that reduced the number of UK studies from 28 to the 14 studies given in Table 5-2.

The economic evaluations studies were further screened to identify studies that utilised Markov models and had a lifetime time horizon. Excluding studies that did not utilise Markov models or did not have a lifetime time horizon reduced the number of studies from 28 to 14. Please refer to Appendix VI of this document for details of the UK studies with respect to these two criteria.

B4 (PRIORITY QUESTION): Section 4.7, Table 4-13, page 111. For the (i) LAPLACE-2 primary prevention population and (ii) LAPLACE-2 secondary prevention population, as represented in the model (that is, the subgroup of patients with LDL-C>2.5, n=744 for primary prevention, n=330 for secondary prevention), please replicate the information presented in Table 4-13.

These data are replicated below for primary prevention and secondary prevention (Table B-1 and Table B-2, respectively). Note that the total number of patients in Table B-1 and Table B-2 are lower than specified in the question given these analyses (and Table 4-13 in the evidence submission) exclude patients randomised to ezetimibe.

Table B-1 Post-hoc combined statin analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2: primary prevention patients with LDL-C > 2.5 mmol/L (FAS)

		Placebo Q2W (N = 100)	Evolocumab 140 mg Q2W (N = 213)	Placebo QM (N = 102)	Evolocumab 420 mg QM (N = 229)
Mean of weeks 10/12	Mean percent change from baseline (95% CI) ^a	2.8 (-0.7, 6.4)	-64.6 (-67.0, -62.1)	-2.9 (-6.7, 0.8)	-65.8 (-68.4, -63.2)
	Fixed effects treatment difference (95% CI) ^{a,b}	-	-67.4 (-71.6, -63.3) p < 0.001 ^d	-	-62.9 (-67.3, -58.4) p < 0.001 ^d
	Random effects treatment difference (95% CI) ^{b,c}	-	-67.6 (-71.7, -63.4) Q = 2.3; I ² = 0.0	-	-63.5 (-68.1, -59.0) Q = 2.6; I ² = 0.0
Week 12	Mean percent change from baseline (95% CI) ^a	2.9 (-0.9, 6.6)	-64.8 (-67.4, -62.2)	-2.8 (-6.8, 1.2)	-61.8 (-64.6, -59.0)
	Fixed effects treatment difference (95% CI) ^{a,b}	-	-67.6 (-72.0, -63.2) p < 0.001 ^d	-	-59.0 (-63.7, -54.2) p < 0.001 ^d
	Random effects treatment difference (95% CI) ^{b,c}	-	-67.8 (-72.2, -63.3) Q = 1.9; I ² = 0.0	-	-59.3 (-64.1, -54.4) Q = 2.0; I ² = 0.0

Reference: Data on file.

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS. Three patients did not receive IP as randomised (one in the evolocumab Q2W plus oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS. Primary prevention subjects do not have a history of angina, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, transient ischaemic attack, vertebral artery dissection, peripheral arterial disease, heart failure, or stroke.

^aLeast-squares mean and fixed effects treatment difference are from the repeated measures model that includes the stratification factor, randomised statin dose cohort, randomised IP treatment group, visit, and randomised IP treatment group by visit. All patients in the FAS except those randomised to ezetimibe are included in the model. ^bTreatment differences were within each dose frequency group using oral placebo plus subcutaneous placebo as the reference. ^cTreatment difference estimated using DerSimonian-Laird random effect estimator. Q and I-squared statistics are provided as measures of heterogeneity. Treatment difference estimates for each statin cohort used in the random effect model are from the primary analysis model that includes all patients in the FAS in each statin cohort. ^dNominal p value. No multiplicity adjustment was carried out for this supportive analysis.

CI, confidence interval; FAS, full analysis set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly

Table B-2 Post-hoc combined statin analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2: secondary prevention patients with LDL-C > 2.5 mmol/L (FAS)

		Placebo Q2W (N = 49)	Evolocumab 140 mg Q2W (N = 97)	Placebo QM (N = 55)	Evolocumab 420 mg QM (N = 93)
Mean of weeks 10/12	Mean percent change from baseline (95% CI) ^a	3.0 (-2.2, 8.3)	-63.9 (-68.4, -59.4)	-3.8 (-12.1, 4.5)	-66.2 (-73.3, -59.0)
	Fixed effects treatment difference (95% CI) ^{a,b}	-	-66.9 (-72.7, -61.1) p < 0.001 ^d	-	-62.4 (-71.7, -53.0) p < 0.001 ^d
	Random effects treatment difference (95% CI) ^{b,c}	-	-66.6 (-73.3, -59.9) Q = 1.7; I ² = 0.0	-	-63.9 (-70.3, -57.5) Q = 2.7; I ² = 0.0
Week 12	Mean percent change from baseline (95% CI) ^a	5.1 (-0.6, 10.9)	-63.8 (-68.6, -58.9)	-1.8 (-10.3, 6.8)	-60.6 (-67.9, -53.3)
	Fixed effects treatment difference (95% CI) ^{a,b}	-	-68.9 (-75.4, -62.4) p < 0.001 ^d	-	-58.8 (-68.6, -49.0) p < 0.001 ^d
	Random effects treatment difference (95% CI) ^{b,c}	-	-68.7 (-76.2, -61.1) Q = 1.4; I ² = 0.0	-	-61.7 (-68.3, -55.0) Q = 2.4; I ² = 0.0

Reference: Data on file.

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS. Three patients did not receive IP as randomised (one in the evolocumab Q2W plus oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS. Secondary prevention subjects have a history of angina, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, transient ischaemic attack, vertebral artery dissection, peripheral arterial disease, heart failure, or stroke.

^aLeast-squares mean and fixed effects treatment difference are from the repeated measures model that includes the stratification factor, randomised statin dose cohort, randomised IP treatment group, visit, and randomised IP treatment group by visit. All patients in the FAS except those randomised to ezetimibe are included in the model. ^bTreatment differences were within each dose frequency group using oral placebo plus subcutaneous placebo as the reference. ^cTreatment difference estimated using DerSimonian-Laird random effect estimator. Q and I-squared statistics are provided as measures of heterogeneity. Treatment difference estimates for each statin cohort used in the random effect model are from the primary analysis model that includes all patients in the FAS in each statin cohort. ^dNominal p value. No multiplicity adjustment was carried out for this supportive analysis.

CI, confidence interval; FAS, full analysis set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly

In addition to the pooled statin analysis for patients from LAPLACE-2 with baseline LDL > 2.5 mmol/L in primary and secondary prevention populations (which provide treatment effects for evolocumab versus placebo) we have provided a pooled placebo and ezetimibe analysis for these same patient populations (Table B-3 and Table B-4).

Table B-3 Post-hoc pooled placebo and ezetimibe analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2: primary prevention patients with LDL-C > 2.5 mmol/L (FAS)

		Placebo (N = 202)	Ezetimibe (N = 100)
Mean of weeks 10/12	Mean percent change from baseline (95% CI) ^a	0.1 (-2.7, 2.8)	-23.4 (-27.3, -19.4)
	Treatment difference (95% CI) ^{a,b}	-	-23.4 (-28.2, -18.7) p < 0.001 ^c
Week 12	Mean percent change from baseline (95% CI) ^a	0.2 (-2.8, 3.3)	-21.4 (-25.8, -17.0)
	Treatment difference (95% CI) ^{a,b}	-	-21.6 (-26.9, -16.3) p < 0.001 ^c

Reference: Data on file.

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS. Three patients did not receive IP as randomised (one in the evolocumab Q2W plus oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W

group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS. Analysis based on pooling of all ezetimibe arms and all placebo arms in the LAPLACE-2 FAS. Primary prevention subjects do not have a history of angina, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, transient ischaemic attack, vertebral artery dissection, peripheral arterial disease, heart failure, or stroke.

^aLeast-squares mean is from the repeated measures model that includes the stratification factor, randomised statin dose cohort, randomised IP treatment group, visit, and randomised IP treatment group by visit.. ^bTreatment differences using oral placebo plus subcutaneous placebo as the reference. ^cNominal p value. No multiplicity adjustment was carried out for this supportive analysis.

CI, confidence interval; FAS, full analysis set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol

Table B-4 Post-hoc pooled placebo and ezetimibe analysis of mean percent change in calculated LDL-C from baseline at the mean of weeks 10/12 and at week 12 in LAPLACE-2: secondary prevention patients with LDL-C > 2.5 mmol/L (FAS)

		Placebo (N = 104)	Ezetimibe (N = 36)
Mean of weeks 10/12	Mean percent change from baseline (95% CI) ^a	-1.1 (-6.2, 4.1)	-19.9 (-28.3, -11.5)
	Treatment difference (95% CI) ^{a,b}	-	-18.9 (-28.3, -9.4) p < 0.001 ^c
Week 12	Mean percent change from baseline (95% CI) ^a	1.0 (-4.6, 6.5)	-16.3 (-25.5, -7.0)
	Treatment difference (95% CI) ^{a,b}	-	-17.2 (-27.6, -6.8) p < 0.001 ^c

Reference: Data on file.

Note: The LAPLACE-2 efficacy and safety analyses employed a modified intention-to-treat approach; all patients randomised and dosed with IP were included in the FAS. Three patients did not receive IP as randomised (one in the evolocumab Q2W plus oral placebo group of the atorvastatin 80 mg cohort, one in the evolocumab Q2W group of the rosuvastatin 5 mg cohort, and one in the placebo group of the rosuvastatin 40 mg cohort) and were excluded from the FAS. Analysis based on pooling of all ezetimibe arms and all placebo arms in the LAPLACE-2 FAS. Secondary prevention subjects have a history of angina, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, transient ischaemic attack, vertebral artery dissection, peripheral arterial disease, heart failure, or stroke.

^aLeast-squares mean is from the repeated measures model that includes the stratification factor, randomised statin dose cohort, randomised IP treatment group, visit, and randomised IP treatment group by visit.. ^bTreatment differences using oral placebo plus subcutaneous placebo as the reference. ^cNominal p value. No multiplicity adjustment was carried out for this supportive analysis.

CI, confidence interval; FAS, full analysis set; IP, investigational product; LDL-C, low-density lipoprotein cholesterol;

B5 (PRIORITY QUESTION): Section 4.13, page 155. The current evidence base discussed in the submission does not include any evidence relating to the effect of evolocumab on CVD events. Please provide the study protocol of the FOURIER study, and further details including any interim results that are currently available.

The FOURIER study protocol has been provided in conjunction with this document. No interim data from FOURIER are currently available.

However, the evidence base included in the submission does include some evidence relating to the effect of evolocumab on cardiovascular disease (CVD) events based on an exploratory safety analysis of data from the integrated long-term extension studies OSLER and OLSER-2 (Section 4-10 of the evidence submission). These data showed a significant 53% reduction in 1-year adjudicated cardiovascular (CV) event rates from 2.18% in the standard of care (SoC) group to 0.95% in the evolocumab plus SoC group (hazard ratio [HR] 0.47, $p = 0.003$).²³ Although it is acknowledged that these data are preliminary and the trials are not powered to detect a difference in major CV events, this is in the direction, and of the magnitude, that would be expected given the magnitude of LDL-C lowering associated with evolocumab.

B6 (PRIORITY QUESTION): Executive summary and Section 5.4, pages 27, 28, and 279–282. The submission presents tables reporting ICERs for patients with 1 or 2 additional risk factors. The accompanying text states *“The grey cells denote patient profiles where the incremental cost per QALY gained is less than £30,000.”* However, none of the values presented in the tables are below £30,000 per QALY gained. Please clarify whether the text or tables are incorrect.

We can confirm that this text is not applicable to the cost-effectiveness results presented for patients with existing CVD and one or two additional risk factors since all the values in the tables are above £30,000 per QALY gained.

B7 (PRIORITY QUESTION): Section 5, page 160. The text states *“The incremental cost per QALY gained is approximately £15,119 to £18,200 for evolocumab versus ezetimibe in patients with HeFH when assessed across the four treatment scenarios.”* These ICERs are not mentioned elsewhere in the submission and appear considerably lower than the ICERs presented in Tables 5-27, 5-42, 5-47, 5-62 and 5-63. Please clarify this discrepancy.

Thank you for identifying this discrepancy. The cost-effectiveness results summarised in Section 5, page 160 of the evidence submission, should indeed reflect the incremental cost-effectiveness ratios (ICERs) presented in Tables 5-27, 5-42, 5-47, 5-62 and 5-63 of the evidence submission.

B8: Section 5.7, page 240. Please clarify why a threshold of >2.5 mmol/L has been selected to define “high risk” population in the LAPLACE-2 analyses. Please also clarify whether patients in the LAPLACE-2 trial were stratified according to LDL-C at baseline (LDL-C≤2.5 mmol/L and LDL-C>2.5 mmol/L). Also, please provide baseline characteristics for those with LDL-C>2.5 mmol/L by treatment group (with p values).

A LDL-C threshold of > 2.5mmol/L was selected to define a high risk population for the economic evaluation based on clinical expert advice regarding the patient population that would be anticipated to be treated with evolocumab in clinical practice. Therefore, this LDL-C threshold was used to allow appropriate baseline CVD risk estimation in alignment with anticipated clinical practice for the purposes of the cost-effectiveness analysis. Patients were not stratified according LDL-C (≤ 2.5 mmol/L and >2.5 mmol/L) at baseline in LAPLACE-2.

Please find an additional *post hoc* analysis (Table B-5) of baseline characteristics and lipid-lowering therapy use for patients in LAPLACE-2 with LDL-C > 2.5 mmol/L by treatment group (with p-values) as requested. The included characteristics are aligned with the overall study level characteristics presented in Table 4-7 of the evidence submission.

Table B-5 LAPLACE-2: Baseline characteristics for subjects with baseline LDL-C > 2.5 mmol/L

	PBO + any statin without EZE		PBO + any atorvastatin with EZE		EvoMab + any statin		p-values for EvoMab + any statin vs.	
	Q2W (N = 149)	QM (N = 157)	PBO Q2W (N = 72)	PBO QM (N = 64)	140 mg Q2W (N = 310)	420 mg QM (N = 322)	PBO + any statin without EZE	PBO + any atorvastatin with EZE
Demographics								
Age, years (SD)	59.0 (10.5)	59.2 (11.2)	60.6 (9.1)	61.5 (9.2)	58.6 (10.0)	59.6 (10.4)	0.97	0.048
Male, n (%)	75 (50.3)	84 (53.5)	34 (47.2)	71 (52.2)	180 (58.1)	181 (56.2)	0.14	0.29
Race, n (%)								
White	142 (95.3)	153 (97.5)	68 (94.4)	59 (92.2)	289 (93.2)	304 (94.4)	0.67	0.73
Black	6 (4.0)	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)		
Asian	1 (0.7)	0 (0)	1 (1.4)	1 (1.6)	1 (0.3)	2 (1.5)		
Other	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.6)	1 (0.3)		
Lipid parameters								
LDL-C, mean mmol/L ^a	3.38	3.48	3.42	3.19	3.44	3.52	0.67	0.06
ApoB, mean g/L	1.01	1.05	1.04	0.97	1.05	1.04	0.43	0.14
Lp(a), median nmol/L	54.0	40.0	37.0	44.0	47.5	51.0	0.76	0.77
ApoA1, mean g/L	1.50	1.55	1.49	1.51	1.52	1.56	0.44	0.29
HDL-C, mean mmol/L	1.38	1.44	1.39	1.39	1.37	1.45	0.27	0.049
Non-HDL-C, mean mmol/L	4.06	4.21	4.09	3.92	4.25	4.22	0.13	0.81
Free PSCK9, mean nmol/L	4.59	4.85	5.25	4.38	4.95	4.82	0.43	0.14
CHD characteristics, n (%)								
Coronary artery disease	38 (25.5)	43 (27.4)	10 (13.9)	16 (25.0)	73 (23.5)	78 (24.2)	0.39	0.23
Cerebrovascular or peripheral arterial disease	13 (8.7)	19 (12.1)	8 (11.1)	3 (4.7)	40 (12.9)	30 (9.3)	0.78	0.3
CV risk factors, n (%)								

	PBO + any statin without EZE		PBO + any atorvastatin with EZE		EvoMab + any statin		p-values for EvoMab + any statin vs.	
	Q2W (N = 149)	QM (N = 157)	PBO Q2W (N = 72)	PBO QM (N = 64)	140 mg Q2W (N = 310)	420 mg QM (N = 322)	PBO + any statin without EZE	PBO + any atorvastatin with EZE
Current smoking	21 (14.1)	23 (14.6)	14 (19.4)	8 (12.5)	54 (17.4)	44 (13.7)	0.65	0.85
Diabetes mellitus type 2	12 (8.1)	22 (14.0)	8 (11.1)	13 (20.3)	49 (15.8)	31 (9.6)	0.5	0.38
Hypertension	80 (53.7)	85 (54.1)	35 (48.6)	35 (54.7)	199 (64.2)	162 (50.3)	0.35	0.23
Family history premature CHD	37 (24.8)	28 (17.8)	14 (19.4)	13 (20.3)	61 (19.7)	80 (24.8)	0.71	0.53
Low HDL-C	49 (32.9)	38 (24.2)	20 (27.8)	14 (21.9)	85 (27.4)	62 (19.3)	0.086	0.66
≥ 2 risk factors	60 (40.3)	59 (37.6)	28 (38.9)	24 (37.5)	131 (42.3)	113 (35.1)	0.93	0.94
NCEP risk categories, n (%)								
High	56 (37.6)	69 (43.9)	26 (36.1)	27 (42.2)	123 (39.7)	113 (35.1)	0.3 (high vs. others)	0.72 (high vs. others)
Moderately high	21 (14.1)	13 (8.3)	6 (8.3)	10 (15.6)	35 (11.3)	50 (15.5)		
Moderate	36 (24.2)	35 (22.3)	20 (27.8)	14 (21.9)	97 (31.3)	77 (23.9)		
Low	36 (24.2)	40 (25.5)	20 (27.8)	13 (20.3)	55 (17.7)	82 (25.5)		
Lipid-lowering therapy at study entry (%) ^b								
Statins	102 (68.5)	126 (80.3)	54 (75.0)	40 (62.5)	227 (73.2)	231 (71.7)	0.51	0.43
Bile acid sequestrants	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.15	N/A
Nicotinic acid	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.15	N/A
Ezetimibe	18 (12.1)	25 (15.9)	11 (15.3)	5 (7.8)	35 (11.3)	46 (14.3)	0.6	0.74
Concomitant lipid-lowering therapy use post-baseline (%) ^c								
Statins	6 (9.0)	2 (3.3)	5 (6.9)	2 (3.1)	14 (11.6)	2 (1.7)	0.53	0.86
Bile acid sequestrants	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.15	N/A
Nicotinic acid	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.15	N/A
Ezetimibe	1 (1.5)	1 (1.7)	1 (1.4)	1 (1.6)	0 (0.0)	0 (0.0)	0.29	0.31

	PBO + any statin without EZE		PBO + any atorvastatin with EZE		EvoMab + any statin		p-values for EvoMab + any statin vs.	
	Q2W (N = 149)	QM (N = 157)	PBO Q2W (N = 72)	PBO QM (N = 64)	140 mg Q2W (N = 310)	420 mg QM (N = 322)	PBO + any statin without EZE	PBO + any atorvastatin with EZE
References: Data on file.								
Note: Data presented by randomised IP treatment groups across statin cohorts for brevity.								
^a Calculated LDL-C								
^b Prior to randomisation to statins and IP								
^c Other than study-dispensed statins or IP								
ApoA1, apolipoprotein A1, ApoB, apolipoprotein B; CHD, coronary heart disease; CSR, clinical study report; CV, cardiovascular; EvoMab, evolocumab; EZE, ezetimibe; FAS, full analysis set; HDL-C, high-density lipoprotein cholesterol; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); N/A, not applicable; NCEP, National Cholesterol Education Program; non-HDL-C, non-high-density lipoprotein cholesterol; PAD, peripheral arterial disease; PBO, placebo; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; QM, monthly; SD, standard deviation								

B9: Section 5.5, page 229. The model includes only the costs of atorvastatin 20mg/80mg. Please justify why other statins were not included in the model. Please also provide details on how this assumption corresponds to the experience in the evolocumab trials and the high-risk LAPLACE-2 population included in the model.

As described in the evidence submission, NICE CG181¹⁴ and CG71¹³ provide the following recommendations for lipid modification therapy for primary and secondary prevention of CVD and treatment of HeFH:

- Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD (CG181).
- Start statin treatment in people with CVD with atorvastatin 80 mg (CG181).
- When a decision is made to prescribe a statin use a statin of high intensity and low acquisition cost (CG181).
- Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment) (CG71).

Therefore, the economic evaluation was based on atorvastatin 20 mg for patients without existing CVD and atorvastatin 80 mg for patients with existing CVD to represent the relevant background statin therapy in accordance with the recommendations from NICE CG181. Atorvastatin 80 mg was also selected in the absence of a recommendation for a specific high-intensity statin agent in patients with HeFH (CG71) for consistency. We acknowledge the availability of a range of different statin agents and have provided additional information to support the selection of atorvastatin alone (20 mg and 80 mg) in the economic evaluation.

These alternative statin agents and their respective acquisition costs are summarised in Table B-6.

Table B-6 Statin agents and acquisition costs

Statin	Generic	High-intensity	Strength (mg)	Pack size (tablets)	Cost/pack	Cost/year
Atorvastatin	Yes	No	10	28	£1.18	£15.38
Atorvastatin	Yes	Yes	20	28	£1.41	£18.38
Atorvastatin	Yes	Yes	40	28	£1.59	£20.73
Atorvastatin	Yes	Yes	80	28	£2.71	£35.33
Fluvastatin	Yes	No	20	28	£2.48	£32.33
Fluvastatin	Yes	No	40	28	£2.72	£35.46
Pravastatin	Yes	No	10	28	£1.19	£15.51
Pravastatin	Yes	No	20	28	£1.44	£18.77
Pravastatin	Yes	No	40	28	£1.78	£23.20
Rosuvastatin	No	No	5	28	£18.03	£235.03
Rosuvastatin	No	Yes	10	28	£18.03	£235.03
Rosuvastatin	No	Yes	20	28	£26.02	£339.19
Rosuvastatin	No	Yes	40	28	£29.69	£387.03
Simvastatin	Yes	No	10	28	£0.90	£11.73
Simvastatin	Yes	No	20	28	£1.02	£13.30

Simvastatin	Yes	No	40	28	£1.14	£14.86
Simvastatin	Yes	Yes	80	28	£2.01	£26.20
References: NHS Drug Tariff 2015 ²⁴						

The Clinical Practice Research Datalink (CPRD) study discussed in the evidence submission assessed statin treatment patterns in patients at CVD risk or those with history of CVD (evidence submission Appendix XV, Table 12). For example, of patients with existing CVD treated with a statin; simvastatin and atorvastatin represented the majority of statin therapy use (61.7% and 30.5%, respectively). Fluvastatin, pravastatin and rosuvastatin represented only 0.5%, 3.9% and 3.4%, respectively. Notably, the CPRD study enrolled patients from 2005 onwards; therefore, additional data for statin treatment patterns are also provided below, given the potential change in statin treatment patterns over time.

Prescription cost analysis data from the NHS Business Services Authority (data from April 2015) indicate the following use of statins in the NHS across all statin agents and doses (Table B-7).²⁵

Table B-7 NHS prescription cost analysis, statins (April 2015)

Statin	Quantity	Percentage
Atorvastatin	66,524,947	39.0%
Fluvastatin	357,881	0.2%
Pravastatin	7,403,858	4.3%
Simvastatin	91,327,744	53.6%
Rosuvastatin	4,746,870	2.8%
Total	170,361,300	100.0%
Reference: NHS Prescription Cost Analysis 2015 ²⁵		

When considering statin prescribing in the context of NICE CG181 recommendations for the use of high-intensity statins (described in Table B-6), atorvastatin 20 mg, 40 mg and 80 mg represent 92.5% of total high-intensity statin use. Simvastatin (80 mg) and rosuvastatin (10 mg, 20 mg and 40 mg) represent 1.6% and 5.9% of high-intensity statin use, respectively (Table B-8). As such, atorvastatin is the most commonly used high-intensity statin (> 90%) and also a low cost statin agent. Therefore, atorvastatin represents the most appropriate choice for background lipid-lowering therapy in the base case analysis and also consistent with the recommendations in NICE CG181.

Table B-8 NHS prescription cost analysis, high-intensity statins (April 2015)

Statin	Strength (mg)	Quantity	Percentage
Atorvastatin	20	23,706,152	43.2%
Atorvastatin	40	20,184,454	36.8%
Atorvastatin	80	6,806,663	12.4%
Simvastatin	80	871,696	1.6%
Rosuvastatin	10	1,933,329	3.5%
Rosuvastatin	20	1,041,270	1.9%
Rosuvastatin	40	270,197	0.5%

Total	-	54,813,761	100.0%
Reference: NHS Prescription Cost Analysis 2015 ²⁵			

The evidence submission (Section 5.5, page 228) states ‘*The impact of alternative costs of statins is assessed in a univariate sensitivity analysis*’. We acknowledge that the alternative costs were not fully assessed in the univariate sensitivity analysis. Therefore a sensitivity analysis of the impact of different statin costs has been provided below using the following ranges based on costs from the NHS Drug Tariff²⁴ (Table B-9 and Table B-10). The lower bound of costs was based on atorvastatin 10 mg in patients without existing CVD, and atorvastatin 20 mg for patients with existing CVD and patients with HeFH. The upper bound of costs was based on simvastatin 80 mg for patients without existing CVD (highest cost high-intensity statin that offers similar LDL-C reduction). For patients with existing CVD, and patients with HeFH, a weighted average cost of atorvastatin (20 mg, 40 mg and 80 mg) and rosuvastatin (10 mg, 20 mg and 40 mg) is used for the upper bound based on treatment patterns from the NHS prescription cost analysis (Table B-8).

Table B-9 Statin costs; base-case, lower and upper bound of sensitivity analysis

Population	Base-case	Cost	Lower	Upper
Without existing CVD	Atorvastatin 20 mg	£18.38	£15.38	£26.20
With existing CVD	Atorvastatin 80 mg	£35.33	£18.38	£51.96
HeFH	Atorvastatin 80 mg	£35.33	£18.38	£51.96
CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia.				

Table B-10 Univariate sensitivity analysis

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
Without existing CVD							
Base case	██████	£9,868	██████	12.15	11.84	0.31	██████
Lower bound	██████	£9,820	██████	12.15	11.84	0.31	██████
Upper bound	██████	£9,991	██████	12.15	11.84	0.31	██████
With existing CVD							
Base case	██████	£20,302	██████	8.06	7.62	0.44	██████
Lower bound	██████	£20,093	██████	8.06	7.62	0.44	██████
Upper bound	██████	£20,507	██████	8.06	7.62	0.44	██████
HeFH							
Base case	██████	£19,431	██████	10.17	9.02	1.15	██████
Lower bound	██████	£19,217	██████	10.17	9.02	1.15	██████
Upper bound	██████	£19,642	██████	10.17	9.02	1.15	██████
CVD, cardiovascular disease; EvoMab; evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

As requested, a summary of background statin treatment for the high-risk LAPLACE-2 population based on CVD history is provided in Table B-11 and Table B-12). Details of the

background statin treatment in the evolocumab trials is provided in Section 4 of the evidence submission and accompanying CSRs.

Table B-11 LAPLACE-2: Summary of statin background therapy intensities and regimens at baseline for primary prevention subjects with baseline LDL-C > 2.5 mmol/L

Statin therapy intensity	PBO + any statin without EZE		PBO + any atorvastatin with EZE		EvoMab + any statin	
	Q2W (N = 100) n (%)	QM (N = 102) n (%)	PBO Q2W (N = 55) n (%)	PBO QM (N = 45) n (%)	140 mg Q2W (N = 213) n (%)	420 mg QM (N = 229) n (%)
High intensity						
Atorvastatin 80 mg OD	12 (12.0)	11 (10.8)	15 (27.3)	14 (31.1)	27 (12.7)	22 (9.6)
Rosuvastatin 20 mg OD	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
Rosuvastatin 40 mg OD	6 (6.0)	15 (14.7)	0 (0.0)	0 (0.0)	24 (11.3)	16 (7.0)
Moderate intensity						
Atorvastatin 10 mg OD	34 (34.0)	23 (22.5)	40 (72.7)	31 (68.9)	57 (26.8)	64 (27.9)
Rosuvastatin 5 mg OD	23 (23.0)	28 (27.5)	0 (0.0)	0 (0.0)	63 (29.6)	63 (27.5)
Simvastatin 20 mg OD	3 (3.0)	2 (2.0)	0 (0.0)	0 (0.0)	7 (3.3)	4 (1.7)
Simvastatin 40 mg OD	22 (22.0)	22 (21.6)	0 (0.0)	0 (0.0)	34 (16.0)	57 (24.9)
Low intensity						
Simvastatin 10 mg OD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)
Reference: Data on file. Notes: N=number of primary prevention subjects subjects with baseline LDL-C > 2.5 mmol/L randomised and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); Q2W = every 2 weeks (subcutaneous); QM = monthly (subcutaneous); OD = once a day (oral tablet). Primary prevention subjects do not have a history of angina, MI, CABG, PCI, TIA, VAD, PAD, heart failure or stroke Background therapies reflect the randomised therapies. Four subjects had concomitant medication statin records at baseline in addition to the randomised therapies: 11521017002 (conmed: atorvastatin 20 mg QD, assigned: atorvastatin 80 mg QD), 11521017004 (conmed: rosuvastatin 20 mg QD, assigned: atorvastatin 10 mg QD), 11565005040 (conmed: rosuvastatin 5 mg QD, assigned: rosuvastatin 5 mg QD), and 11566005007 (conmed: simvastatin 40 mg QD, assigned: atorvastatin 10 mg QD). Subjects 11521017003 (assigned: atorvastatin 10 mg QD), 11566055002 (assigned: rosuvastatin 5 mg QD), and 11566030005 (assigned simvastatin 40 mg QD) were not receiving the assigned statins at baseline.						

Table B-12 LAPLACE-2: Summary of statin background therapy intensities and regimens at baseline for secondary prevention subjects with baseline LDL-C > 2.5 mmol/L

Statin therapy intensity	PBO + any statin without EZE		PBO + any atorvastatin with EZE		EvoMab + any statin	
	Q2W (N = 49) n (%)	QM (N = 55) n (%)	PBO Q2W (N = 17) n (%)	PBO QM (N = 19) n (%)	140 mg Q2W (N = 97) n (%)	420 mg QM (N = 93) n (%)
High intensity						
Atorvastatin 80 mg OD	11 (22.4)	9 (16.4)	8 (47.1)	6 (31.6)	14 (14.4)	15 (16.1)
Rosuvastatin 20 mg OD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)	1 (1.1)
Rosuvastatin 40 mg OD	3 (6.1)	5 (9.1)	0 (0.0)	0 (0.0)	9 (9.3)	11 (11.8)
Moderate intensity						
Atorvastatin 10 mg OD	10 (20.4)	17 (30.9)	9 (52.9)	13 (68.4)	23 (23.7)	18 (19.4)
Rosuvastatin 5 mg OD	13 (26.5)	13 (23.6)	0 (0.0)	0 (0.0)	18 (18.6)	26 (28.0)
Simvastatin 20 mg OD	2 (4.1)	2 (3.6)	0 (0.0)	0 (0.0)	3 (3.1)	5 (5.4)
Simvastatin 40 mg OD	9 (18.4)	9 (16.4)	0 (0.0)	0 (0.0)	27 (27.8)	16 (17.2)
Low intensity						
Simvastatin 10 mg OD	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.1)
Reference: Data on file. Notes: N=number of primary prevention subjects subjects with baseline LDL-C > 2.5 mmol/L randomised and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); Q2W = every 2 weeks (subcutaneous); QM = monthly (subcutaneous); OD = once a day (oral tablet). Secondary prevention subjects have a history of angina, MI, CABG, PCI, TIA, VAD, PAD, heart failure or stroke Background therapies reflect the randomised therapies. Four subjects had concomitant medication statin records at baseline in addition to the randomised therapies: 11521017002 (conmed: atorvastatin 20 mg QD, assigned: atorvastatin 80 mg QD), 11521017004 (conmed: rosuvastatin 20 mg QD, assigned: atorvastatin 10 mg QD), 11565005040 (conmed: rosuvastatin 5 mg QD, assigned: rosuvastatin 5 mg QD), and 11566005007 (conmed: simvastatin 40 mg QD, assigned: atorvastatin 10 mg QD). Subjects 11521017003 (assigned: atorvastatin 10 mg QD), 11566055002 (assigned: rosuvastatin 5 mg QD), and 11566030005 (assigned simvastatin 40 mg QD) were not receiving the assigned statins at baseline.						

In LAPLACE-2, the background moderate- to high-intensity statin therapies used were generally consistent with the recommendations in NICE CG181 and used in UK clinical practice (Appendix VIII of the evidence submission). In RUTHERFORD-2, most patients received high-intensity statin therapy which is consistent with NICE CG71. We acknowledge the differences between the economic evaluation and the experience in the evolocumab RCTs (including the high-risk LAPLACE-2 population) based on the intensity and type of statin agent. The evolocumab studies were global in nature and not designed specifically to meet the anticipated needs of the decision problem. We have additionally assessed the impact of alternative costs of background statin therapy and demonstrated the cost-effectiveness results are not sensitive to this variable.

B10: Section 5.3, page 196. Please clarify why LDL-C was the only surrogate used for CVD risk. Please clarify whether other markers were considered.

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. This evidence comes from a range of studies including epidemiological studies, genetic variants (both gain-of-function and loss-of-function), and interventional studies with LDL-C-lowering therapies.²⁶⁻⁴⁰ In contrast, 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. Therefore, other markers were not considered.

Although evolocumab also has a significant positive effect on other lipid markers (e.g. non-HDL-C and Lp[a]), the primary effects of evolocumab are on LDL-C. We anticipate that improvements in these other markers may contribute to reduction in CV risk, but in the absence of data supporting the impact of altering these markers on CV risk, they were not used in the model as a surrogate.

B11 (PRIORITY QUESTION): Section 5.2, pages 174–181. Please comment on the advantages of using combined health states compared with the approach used in the NICE clinical guideline 181, particularly with respect to the number of assumptions required and the availability of data to inform the outcomes associated with these health states. Please also comment on whether the approach taken, whereby the highest transition probability, lowest utility and highest cost is selected for combined health states, had been used in any of the previous economic analyses identified in the cost-effectiveness review presented in Section 5.1.

As acknowledged in NICE CG181; *‘Markov models also do not preserve memory of past events, and so the risk of experiencing a further stroke for someone in the post-stroke state is equal whether they have previously experience one stroke or several strokes’*. As stated in the evidence submission (Section 5.2, pages 176 to 178), the use of combined health states is an approach to overcome the memory-less condition of Markov models, otherwise there may be modelled scenarios in which patients may encounter improvements in health status (or reduction in costs) by having certain recurrent CV events which is not clinically plausible.

With respect to assumptions, for combined health states involving an acute event, the risks and costs are always based on those of the acute event. Utilities are generally those of the

acute event, with the exception of 'acute ACS', which has a utility higher (0.7700) than the 'post-IS' (0.7064) and 'post-HF' (0.7222) health states.

For combined health states involving long-term health states only, the economic model needs to consider a long-term cost, utility, and risk:

- The health status of a patient can only remain the same or become worse by having further CV events, therefore the minimum utility is used. This is a conservative assumption compared with a memory-less Markov model, as treatment with evolocumab maintains patients in the long-term health states by avoiding more CV events compared with alternative scenarios without evolocumab.
- The long-term patient costs can only remain the same or increase by having further CV events; therefore, we are taking the maximum individual cost. This is a conservative assumption compared to a memory-less Markov model, as evolocumab keeps patients in the long-term health states by avoiding CV events compared to alternative scenarios without evolocumab.
- The long-term patient risks are anticipated to remain the same or increase due to further CV events; therefore we are using the maximum risk.

We are not aware of data availability on costs and risks conditional on CV event recurrence, or whether it is readily available in sources such as CPRD, to enable these assumptions to be assessed.

We have also further assessed whether this approach has been utilised in previous economic evaluation studies (as identified in the SLR). Four studies were identified presenting multiple health event states (Ara et al., 2009, Ara et al., 2012, Taylor et al., 2009, Wagner et al., 2009).⁴¹⁻⁴⁴ Moreover, three studies were identified which included recurrent event states in their model (Khoury et al., 2009, Nagata-Kobayashi et al., 2005, Peura et al., 2008).⁴⁵⁻⁴⁷

The economic evaluations by Ara et al., (2009)⁴¹ and Ara et al., (2012)⁴², used a Markov model with the following health states:

- Unstable angina (UA)
- Myocardial infarction (MI)
- Revascularisation
- Hospitalisation for UA
- Non-fatal MI with history of acute coronary syndrome (ACS)
- Non-fatal stroke with history of ACS
- Non-fatal MI with history of stroke
- Non-fatal stroke with history of stroke and ACS
- Hospitalisation for UA with history of stroke and ACS
- Non-CVD mortality
- CVD mortality.

Most of the health states are combined health states to compensate for memory-less attribute with regards clinical history, and only the costs and health consequences associated with the current health state are applied in a Markov model.

For the combined health states, it was assumed that the transition probabilities for future events will be the highest transition probabilities of the experienced events. In clinical practice, it is plausible that patients can experience a severe CV event followed by a less severe CV event. To represent that in the models developed by Ara et al., (2009) and Ara et al., (2012), costs and utilities of the combined health states were adjusted in such a way that a patient who experienced a subsequent event would not benefit in terms of ongoing costs, health-related quality of life, or subsequent risks compared with previous experienced events. For utilities, based on clinical advice, an additional 10% reduction was applied for subsequent CV events.

The health states included in Taylor et al., (2009)⁴³ are divided into:

- major CV events: MI, stroke, congestive heart failure (CHF), revascularisation, and resuscitated cardiac arrest (RCA);
- minor CV events: peripheral artery disease [PAD], transient ischaemic attack (TIA), and documented angina; and
- death.

The major CV event status can be a single event or a combination of two major events (allowing for all possible combinations of events excluding RCA). Rates of second major events were conditional on the type of the first-event. In order to simplify the model, second major events were considered in the analysis only if they occurred within the first year of the first major event. Utilities and costs were assigned to each health state. Patients in major event states were subjected to long-term utilities and mortality consequences, while minor events resulted only in short-term cost and utility consequences, reflecting the transient nature of these conditions. Patients in the combined major event states were assigned the larger mortality multiplier of the two individual events.

Wagner et al., (2009)⁴⁴ presented a Markov model with a lifetime horizon to predict major and minor CV events, survival, costs, and quality-adjusted life years in the Canadian context for CHD patients. The model comprised of four health states:

- Stable CHD
- Single major CV event
- Double major CV event
- Death.

Patients could suffer a single (first) major CV event or suffer two major CV events within the same year. A major CV event was defined as MI, stroke, CHF, RCA, or revascularisation either by coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). A minor CV event (PAD, TIA, or documented angina) could occur at any point in the model but did not cause transition of the patient to a different health state. For patients who experienced a second major event during the same year, the mortality rate of the first event was applied. In the case patients survived two major events in one year; the mortality multiplier of the more severe event was used.

Khuoury et al., (2009),⁴⁵ used a Markov model that modelled patients with diabetes with a prior MI. This model included 5 health states:

- Well (no history of a CV event)

- Event history
- Second event history
- Event death
- Other death (i.e. death due to non-CV events).

Patients in the event history health state were at risk of experiencing a second coronary heart disease (CHD) or stroke event. The risk of having a second event was increased by 2.3 times for CHD and 1.89 times for stroke, to reflect clinical reality. Relative risk ratios for secondary CHD and stroke events were derived from additional literature. Utility decrements were used for CHD (-0.03) and stroke (-0.16). Utility decrements were assumed to be cumulative.

Nagata-Kobayashi et al., (2005)⁴⁶ and Peura et al., (2008)⁴⁷ used a Markov model to follow one type of CV-event (MI). Both divided health states into the time before the onset of the CHD ('CHD free, primary prevention') and the states when the individual has experienced a MI ('CHD, secondary prevention' and 'recurrent MI'). In both of these studies, no decrement or correction on utilities or correction on costs were applied for recurrent events, as patients could only experience the same CV event again.

As described, previous economic evaluations have attempted to account for combined health states by ensuring the appropriate application of risks, utilities and costs to prevent patients from benefiting from specific sequences of CV events which would not be clinically plausible. Our economic model has included the full set of possible combined health states and has applied the same principles to introduce memory of prior CV events for risk, utilities, and costs, as implemented only partially in earlier economic evaluation studies. Furthermore, during the economic model development, clinical and economic advisors supported these assumptions as reasonable and conservative in the absence of robust data.

B12: Section 5.3, page 184. Please provide further details on why the Framingham equation was used instead of the QRISK2 equation. Were data on the additional risk factors required by QRISK2 available in the LAPLACE-2, GAUSS-2 and RUTHERFORD-2 trials? Please also justify how the threshold analysis, which assumes that CV risk is calculated with QRISK, fits in with the model in which CV risk is based on Framingham.

Table B-13 describes the QRISK2 predictors and whether information was recorded in the evolocumab RCTs to allow completion. This indicates that of the 14 predictors, six were recorded, four were partial recorded (definitions not fully aligned) and four were not recorded at baseline in the evolocumab RCTs.

Table B-13 QRISK2 predictors and evolocumab studies

Predictor		QRISK2	Evolocumab studies	Alignment
1	Ethnicity	White or not stated, Indian, Pakistani, Bangladeshi, other Asian, Black Caribbean, Black African, Chinese, Other Ethnic Group	American Indian, Alaska Native, Asian, Black or African America, Native Hawaiian or Other Pacific, White, Other	Partial
2	Age	Years	Collected	Yes
3	Deprivation	Townsend score	Not collected	No
4	Gender	Male/female	Male/female	Yes
5	Smoking status	Non-smoker, ex-smoker, light smoker (less than 10), moderate smoker (11 to 19) and heavy smoker (20 or over)	Current cigarette use, former cigarette use	Partial
6	Family history of CHD	Family history of CHD < 60 years	Family history of premature CHD in first degree relative male at ≤55 or female ≤65 years	Partial
7	Atrial fibrillation	Yes/No	Current, or former atrial fibrillation or flutter	Partial
8	Chronic renal disease	Yes/No	Study exclusion criteria	No
9	Rheumatoid arthritis	Yes/No	Not collected	No
10	Diabetes mellitus	No, Type I or Type II	Type I diabetes was study exclusion criteria	Partial
11	Treated hypertension	Yes/No	Potential to estimate based on hypertension and concomitant medicines	Partial
12	BMI	Continuous	Continuous	Yes
13	SBP	Continuous	Continuous	Yes
14	Total cholesterol	Continuous	Continuous	Yes
15	TC/HDL-C ratio	Continuous	Continuous	Yes
References: Hippisley-Cox et al., (2008) ⁴⁸ BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein-cholesterol; SBP, systolic blood pressure; TC, total cholesterol.				

The adjusted hazard ratios for CVD using QRISK2 are presented in Table B-14. Since data for some of the variables were not recorded, or are not fully aligned with data collected in the evolocumab RCTs (either through different definitions or potential to estimate based on certain completed information), the estimation of CVD risk using QRISK2 would be challenging. For example, deprivation based on the Townsend score was not recorded in the evolocumab RCTs; as such this would result in two missing explanatory variables (Townsend score and Age* Townsend score interaction) for the CVD risk estimations.

Table B-14 Adjusted hazard ratios (95% CI) for cardiovascular disease for QRISK2 model in derivation cohort with interactions

Variable	Women	Men
White/not recorded	1	1
Indian	1.43 (1.24 to 1.65)	1.45 (1.29 to 1.63)
Pakistani	1.80 (1.5 to 2.17)	1.97 (1.70 to 2.29)
Bangladeshi	1.35 (1.06 to 1.72)	1.67 (1.40 to 2.01)
Other Asian	1.15 (0.86 to 1.54)	1.37 (1.09 to 1.72)
Black Caribbean	1.08 (0.94 to 1.24)	0.62 (0.53 to 0.73)
Black African	0.58 (0.42 to 0.82)	0.63 (0.47 to 0.85)
Chinese	0.69 (0.44 to 1.10)	0.51 (0.32 to 0.83)
Other	1.04 (0.85 to 1.28)	0.91 (0.75 to 1.10)
Age (10% increase)*	1.66 (1.65 to 1.68)	1.59 (1.58 to 1.60)
BMI (5 unit increase)	1.08 (1.06 to 1.10)	1.09 (1.07 to 1.11)
Townsend score (5 unit increase)	1.37 (1.34 to 1.40)	1.18 (1.16 to 1.20)
SBP [†]	1.20 (1.18 to 1.22)	1.19 (1.17 to 1.20)
TC/HDL-C ratio	1.17 (1.16 to 1.18)	1.19 (1.18 to 1.20)
Family history coronary heart disease	1.99 (1.92 to 2.05)	2.14 (2.08 to 2.20)
Current smoker	1.80 (1.75 to 1.86)	1.65 (1.60 to 1.70)
Treated hypertension	1.54 (1.45 to 1.63)	1.68 (1.60 to 1.77)
Type 2 diabetes	2.54 (2.33 to 2.77)	2.20 (2.06 to 2.35)
Rheumatoid arthritis	1.50 (1.39 to 1.61)	1.38 (1.25 to 1.52)
Atrial fibrillation	3.06 (2.39 to 3.93)	2.40 (2.07 to 2.79)
Renal disease	1.70 (1.43 to 2.03)	1.75 (1.51 to 2.02)
Age ^a BMI interaction	0.976 (0.970 to 0.982)	0.985 (0.979 to 0.991)
Age ^a Townsend interaction (5 unit increase in score)	0.938 (0.930 to 0.946)	0.973 (0.967 to 0.980)
Age ^a SBP interaction ^b	0.966 (0.961 to 0.971)	0.964 (0.960 to 0.969)
Age ^a family history interaction	0.927 (0.914 to 0.940)	0.923 (0.912 to 0.935)
Age ^a smoking interaction	0.931 (0.920 to 0.943)	0.932 (0.922 to 0.942)
Age ^a treated hypertension interaction	0.952 (0.934 to 0.971)	0.916 (0.901 to 0.931)
Age ^a type 2 diabetes interaction	0.904 (0.877 to 0.931)	0.902 (0.881 to 0.924)
Age ^a atrial fibrillation interaction	0.858 (0.795 to 0.926)	0.893 (0.852 to 0.935)
References: Hippisley-Cox et al., (2008) ⁴⁸		
^a All age terms expressed as 10% increase in age (for example, 50 to 55 years)		
^b 20 unit increase		
BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol		

Our evidence submission states that *‘evolocumab represents both a clinically- and cost-effective treatment option for the NHS in patients without existing CVD but at high residual risk due to additional risk factors (based on QRISK2 score)’*. The estimates of the minimum

baseline CVD risk required for patients without existing CVD are described on the basis of QRISK2 to align with the risk assessment method specified in NICE CG181,¹⁴ although the numbers are based on the Framingham risk equation used in the model. We believe this can be considered a conservative estimate, given that the Framingham study includes a broader definition of CV events (i.e. any estimated CVD risk based on the Framingham definition of CVD will likely be higher than derived from QRISK2). We acknowledge the error in Section 5.15, page 284, where this is incorrectly stated as '*Framingham study includes a narrower definition...*'.

QRISK2 includes a narrower definition of CV events compared with that in economic models designed to model the natural course of CVD. For example, the QRISK2 definition of a first CV event does not include PAD or HF. As such, previous economic evaluations such as that for NICE CG181 have amended the CV risk estimated from QRISK2 to a 'total CV risk'. For example, a QRISK2 derived absolute 10-year CVD risk of 10% has been calculated as being equivalent to a 'total CV risk' of 14.7% (NICE CG181 Appendices, pages 597 to 598¹²).

In the absence of evidence to allow calibration of Framingham-based and QRISK2-based risk estimates in the high risk population for the UK, a minimum 10-year CVD risk based on Framingham was adopted. A patient without existing CVD estimated to have an absolute 10-year CVD risk of 40% for a primary event using QRISK2 is anticipated to be lower risk in terms of 'total CV risk' compared with a patient without existing CVD with the same absolute risk using Framingham, given the narrower definition of events from QRISK2. As such, the estimates in the threshold analyses provide a reasonable conservative estimate of the minimum 10-year risk required in order to demonstrate cost-effectiveness.

B13 (PRIORITY QUESTION): Please clarify why the UKPDS risk engine was not used to assess CV risk in the diabetic population. Please also discuss the limitations of using the Framingham equations in the diabetic population in the CPRD dataset.

The UK Prospective Diabetes Study (UKPDS) risk equation is indeed relevant for estimating risk of a first CV event in a diabetic population without existing CVD. As a diabetic population was not specifically modelled, we did not feel it was necessary to use this risk equation to estimate baseline CV risk. Furthermore, since the proportion of patients with diabetes mellitus (type II) in the high-risk LAPLACE-2 population with existing CVD was approximately 10%, it was also deemed unnecessary to use two different underlying risk equations to estimate risk in the diabetic and non-diabetic populations.

With respect to the CPRD dataset, studies have previously identified that the Framingham risk equations may be unreliable when applied in diabetic populations. Despite a diabetes specific risk equation not being used, the calibration exercise using CPRD (see response to Question B33) allowed us to ensure the predictions from Framingham matched real-world observed CV rates for the diabetic cohort used as a proxy for primary prevention.

B14 (PRIORITY QUESTION): Section 5.3, page 184. The company's submission suggests that calibration is necessary irrespective of whether the QRISK2 or Framingham equation is used. If the QRISK2 risk equation was used, why would this require calibration?

We believe it is good practice to conduct calibration of predicted events from risk equations to observed events in the population of interest since this supports external validity when modelling different patient profiles. As such, calibration should be conducted irrespective of the risk equation underpinning the estimation of a primary CV event risks (QRISK2 or Framingham).

There are two primary reasons for this; the definition of predicted primary CV events from QRISK2 (fatal or non-fatal angina, MI, TIA or stroke) is narrower than the CV events than those modelled (and previously modelled, in economic evaluations such as NICE CG181). The broader definition in the economic model better reflects the natural course of the disease and includes CV events such as PAD and HF. Secondly; we have specifically modelled a higher risk population in comparison with the primary cohort in QRESEARCH UK that informs QRISK2. Therefore, calibration is required to ensure the model is not under- or over-predicting the occurrence of CV events using risk equations such as Framingham or QRISK2, compared with observed CV events within the population of interest. This supports the external validity of the cost-effectiveness analyses.

B15: Section 5.13, page 275–282. Please clarify why for the subgroup analysis, all patients from LAPLACE-2 included in the model were assumed to have diabetes, LDL>3, LDL> 3.5, rather than selecting the smaller subgroup of patients who actually have these particular characteristics?

In the subgroup analysis, the patients from LAPLACE-2 the baseline CV risk were assumed to have diabetes and alternative baseline LDL-C levels rather than selecting the smaller subgroups of patients who actually have these characteristics due to the small sample sizes (total n = 330 for all patients with existing CVD). These subgroups were also assumed for consistency in our modelling approach throughout the subgroup analyses for both modelled subgroups with 1 and 2 additional risk factors (e.g. diabetes mellitus ± 2 vascular beds).

We have provided additional baseline CV event rate estimations by comparing the estimated CV event rates of patients actually with diabetes mellitus in LAPLACE-2 (n = 61) with our modelled approach. This analysis indicates that the predicted rates of recurrent non-fatal and fatal CV events using the REACH risk equation are consistent irrespective of whether diabetic status was assumed or estimates were based on subgroup data (actual) in males and females (Table B-15).

Table B-15 Predicted CV rates for patients with existing CVD based on actual and assumed diabetes mellitus

Prediction based on Wilson 2012	LAPLACE-2 SP and DM (model) LDL-C >2.5mmol/L				LAPLACE-2 SP and DM LDL-C >2.5mmol/L			
	n	Mean	CI lower	CI upper	n	Mean	CI lower	CI upper
Next event (male)	219	0.0780	0.0752	0.0809	44	0.0796	0.0740	0.0851
Death (male)	219	0.0257	0.0242	0.0272	44	0.0263	0.0233	0.0292
Next event (female)	111	0.0798	0.0754	0.0842	17	0.0710	0.0578	0.0842
Death (female)	111	0.0249	0.0226	0.0271	17	0.0209	0.0140	0.0278

CI, confidence interval; DM, diabetes mellitus; SP, secondary prevention

B16: Section 5.14, page 283. Please provide details of the number and positions of clinical advisors who informed the development of the model.

The economic model development has taken place over several years based on input from clinical and economic advisors through regular feedback or annual advisory boards. Over this period, more than 15 clinical advisors (including cardiologist and internal medicine specialists) from several European countries were involved (Table B-16).

Table B-16 Summary of clinical and economic advisors involved in the economic model development

Name	Advisor	Institution	Year
Ron Akehurst	Economic	University of Sheffield, UK	2012
Alberico Catapano	Economic	University of Milan, Italy	2012, 2014
Annie Chicoye	Economic	ESSEC Santé Business School, France	2012
Luca degli Esposti	Clinical	ClinCon Srl, Italy	2012
Michael Khan	Clinical	University Hospital of Coventry & Warwick, UK	2012
Wolfgang Koenig	Clinical	University of Ulm Medical School, Germany	2012, 2013
Jose Mostaza	Clinical	Hospital Carlos III, Spain	2012, 2013
Uwe Siebert	Economic	University of Health Sciences, Medical Informatics and Technology, Austria	2012
Julio Lopez Bastida	Economic	University Castilla-La Mancha, Spain	2013
Danny Liew	Clinical	University of Melbourne, Australia	2013, 2014
Lorenzo Mantovani	Economic	University of Naples, Italy	2013
Jean Ferrieres	Clinical	Toulouse University School of Medicine, France	2013
Frank-Ulrich Fricke	Economic	Nuremberg Institute of Technology, Germany	2013
Paul Oh	Clinical	University Health Network, Canada	2013, 2014
Richard Hobbs	Clinical	Oxford University, UK	2013
Ben van Hout	Economic	University of Sheffield, UK	2013-ongoing
Peter Lindgren	Economic	IVBAR, Sweden	2013-ongoing
Stephen Palmer	Economic	University of York, UK	2013, 2014
Livia Pisciotta	Clinical	University of Genoa, Italy	2013
Lars-Åke Levin	Economic	Linköping University, Sweden	2013
Olivier Wong	Clinical	Private Practice, France	2013

David Wood	Clinical	Imperial College London, UK	2014
Lieven Annemans	Economic	Ghent University & Brussels University, Belgium	2014
Octavio Berwanger	Clinical	Research Institute-Cardiac Hospital, São Paulo, Brazil	2014
Denis Duboc	Clinical	Paris-Descartes University & Cochin Hospital, France	2014
Michel Farnier	Clinical	Point Médical, Rond Point de la Nation, France	2014
Kees Hovingh	Clinical	Academic Medical Centre, Amsterdam, the Netherlands	2014
Claudio Jommi	Economic	Bocconi University of Milan, Italy	2014
Bengt Jonsson	Economic	Stockholm School of Economics, Sweden	2014
Gerald Klose	Clinical	Zentralkrankenhauses Links der Weser, Germany	2014
Reiner Leid	Economic	Ludwig-Maximilians University, Germany	2014
Lluís Masana Marin	Clinical	Saint Joan University Hospital, Reus, Spain	2014
Ken Redekop	Economic	Erasmus University, the Netherlands	2014

B17 (PRIORITY QUESTION): Company's model. Please explain the following values in the "population" sheet of the model:

- cells V43:59 are multiplied by a hard-coded value of 8.15
- cells W43:59 are multiplied by a hard-coded value of 6.95
- cells X43:59 are multiplied by a hard-coded value of 6.35
- cells Y43:59 are multiplied by a hard-coded value of 8.55
- cells Z43:59 are multiplied by a hard-coded value of 7.3
- cells AA43:59 are multiplied by a hard-coded value of 6.5

Please clarify the source of these values. Please clarify whether these multipliers were applied to the probability or the rate of each event. Please also clarify whether D'Agostino and the REACH risk equations produce rates or probabilities.

In the threshold analysis for patients without existing CVD, all the primary prevention event rates are artificially increased by a multiplier (hard-coded values) in the "Populations" worksheet of the economic model. These multipliers are applied to the rates of events (i.e. they are rate ratios) and are based on the calculated level of risk increase required in order to demonstrate cost-effectiveness according to the willingness-to-pay thresholds. The derivation of the multiplier values can be seen in "Risk Frontier Tracking" worksheet, column A, of the economic model. Based on the clarification request dated 11th August 2015, these threshold analyses have been removed from the updated version of the economic model for the NHS list price analysis.

The D'Agostino (Framingham)⁴⁹ and the REACH⁵⁰ risk equations are based on Cox proportional hazards models and therefore they produce probabilities. These probabilities have been converted to rates using the formula proposed in NICE CG181 (exponential distribution) whereby, $\text{risk} = 1 - \exp^{-\text{rate}}$.

B18: Section 5.3, page 192. Please explain where the data contained in Table 5-9 are applied in the model.

Table 5-9 is descriptive and was included to provide context regarding CVD risk for the different populations. The absolute 10-year CVD risk in Table 5-9 is derived from the economic model based on amending the modelled time horizon to 10 years (and converting the predicted rates to probabilities). The baseline LDL-C (mean mmol/L) is based on the patient characteristics from LAPLACE-2 and RUTHERFORD-2 for the relevant populations.

B19 (PRIORITY QUESTION): Table 5-10, page 193. The treatment effects used for the combination with statin therapy (from LAPLACE-2) relate to the treatment difference compared with background statin therapy. The treatment effects for monotherapy (from GAUSS-2) relate to the mean percentage change from baseline, which does not account for the change in LDL-C on placebo treatment. Please clarify the evidence for assuming that there will be no change in response in the placebo group, or alternatively, how this issue has been addressed in the cost-effectiveness model?

As described in the evidence submission (Section 4.2, Table 4-2), GAUSS-2 assessed evolocumab monotherapy versus ezetimibe monotherapy. There was no placebo alone arm in GAUSS-2 since it would have been unethical to conduct a RCT in patients with primary hypercholesterolaemia and mixed dyslipidaemia with statin intolerance with LDL-C ≥ 2.6 mmol/L (patients with CHD or CHD risk equivalent) to ≥ 4.9 mmol/L (patients without diagnosed CHD or CHD risk equivalent, with no additional risk factors) who had not already been offered optimal treatment with currently available therapies e.g. ezetimibe. Therefore, this is no direct evidence in the evolocumab RCTs for a change in response in a placebo alone population with statin intolerance.

In the absence of evidence, no assumption was made for a hypothetical placebo response by attempting to attribute a proxy effect based on the observed placebo responses from LAPLACE-2, RUTHERFORD-2 or DESCARTES.

This was indirectly addressed in the cost-effectiveness analyses based on the univariate sensitivity analysis for both evolocumab and ezetimibe according to the lower and upper 95% confidence intervals of the relative LDL-C reduction treatment effect from GAUSS-2.

B20: Table 5-10, page 193. Please clarify the method for the “post hoc pooled analysis” that was used to provide the pooled treatment effects for ezetimibe 10mg.

The *post hoc* pooled analysis for LAPLACE-2 involved pooling all placebo arms and all ezetimibe arms to generate a pooled treatment difference for ezetimibe versus placebo for the mean percent change from baseline in calculated LDL-C at the mean of weeks 10/12. As there were no placebo arms in GAUSS-2, both ezetimibe arms were pooled to generate a pooled ezetimibe mean percent change from baseline in calculated LDL-C at the mean of weeks 10/12.

Aside from the pooling of data, this *post hoc* analysis was conducted using methods in accordance with the main study analyses presented in the submission.

An updated version of Table 5-10 is provided below with additional text underlined to clarify these data and the methodology for the *post hoc* ezetimibe analysis (Table B-17).

Table B-17 Mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe when used in combination with statins or as monotherapy

	Evolocumab 140 mg Q2W	Evolocumab 420 mg QM	Ezetimibe 10 mg OD^b
Combination with a statin (based on LAPLACE-2)			
<u>Treatment difference in mean percent change from baseline vs. placebo^a</u> (95% CI) [SE]	-71.77 (-74.69, -68.85) [1.49]	-69.12 (-73.49, -64.76) [2.23]	-26.56 (-30.70, -22.42) [2.11]
Monotherapy (based on GAUSS-2)			
Mean percent change from baseline ^a (95% CI) [SE]	-57.10 (-60.84, -53.36) [1.90]	-55.82 (-58.88, -52.76) [1.55]	-17.83 (-21.01, -14.65) [1.62]
References: LAPLACE-2 CSR ¹⁷ Table 14-4.2.13 and LAPLACE-2 supplementary data table 14-4.6.2 ⁵¹ ; GAUSS-2 CSR ⁵² Tables 10-4 and 14-4.1.3 and GAUSS-2 supplementary data table 14-4.9.1 ⁵³			
^a Least squares mean from the repeated measures model which includes treatment group, stratification factors (from IVRS), scheduled visit, dose frequency and the interaction of treatment with scheduled visit as covariates.			
^b Based on <i>post hoc</i> pooled analysis of all ezetimibe arms <u>and all placebo arms</u> in LAPLACE-2, <u>and all ezetimibe arms</u> in GAUSS-2. <u>Aside from the pooling of data, this <i>post hoc</i> pooled analysis was conducted in accordance with the main analyses for LAPLACE-2 and GAUSS-2.</u>			
CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; OD, once daily; Q2W, every 2 weeks; QM, monthly; SE, standard error			

B21 (PRIORITY QUESTION): Section 5.3, Figure 5-7 and Table 5-11. Please clarify how the effect of the combination treatment is generated? For example, for scenario 4, treatment effects from LAPLACE-2 are used. For ezetimibe there was a treatment effect of -27% mean change from baseline. For evolocumab there was a treatment effect of -72 % mean change from placebo, or -64 % mean change from baseline. Assuming a baseline LDL-C of B for a given individual, would the calculated LDL-C after treatment be:

- 1) $B \times (1 - 0.27) \times (1 - 0.64)$ or
- 2) $B \times (1 - 0.27 - 0.64)$

Also, was the evidence from the relevant DESCARTES subgroup (that assessed evolocumab and ezetimibe in combination) considered to inform this treatment effect?

The effect of the combination treatment is generated in the economic model based on sequential LDL-C lowering from baseline (background statin therapy) stated above in equation 1.

We acknowledge the mean percent change from baseline in LDL-C at week 52 was -49.3% ($p < 0.001$) for evolocumab versus placebo in this subgroup from DESCARTES in the relevant subgroup of (diet + atorvastatin 80mg + ezetimibe). This subgroup level treatment effect from DESCARTES was not used given the overall consistency of LDL-C reduction for evolocumab in addition to background lipid-lowering therapy across the RCTs.

Additionally, in accordance with our response to question B26, no reduction in CV event rate is associated with LDL-C levels < 1.03 mmol/L after treatment. This conservative assumption based on sequential LDL-C lowering primarily reduces the efficacy of the combination treatment of evolocumab, ezetimibe and statin since patients with baseline LDL-C ≤ 4.5 mmol/L achieve LDL-C levels < 1.03 mmol/L after treatment.

B22: Section 5.2, pages 173–174. Please clarify why baseline characteristics from DESCARTES have not been used in the health economic analysis.

Inclusion of patients from DESCARTES was not considered during the patient-level CVD risk estimation exercise. Inclusion of patient-level data from DESCARTES in those receiving patients lipid-lowering therapies (and LDL-C > 2.5 mmol/L criterion as per LAPLACE-2) could have been used to supplement the overall cohort for individual CVD risk assessment. Table B-18 indicates the predicted recurrent non-fatal and fatal CV rates using REACH risk equation in males and females from LAPLACE-2 ($n = 330$) and LAPLACE-2 and DESCARTES ($n = 412$). The mean predicted CV rates are not significantly different between the LAPLACE-2 and LAPLACE-2/DESCARTES combined patient cohorts.

Table B-18 Predicted CV rates for patients with existing CVD based LAPLACE-2 and DESCARTES

Prediction based on Wilson 2012	LAPLACE-2 SP LDL-C >2.5mmol/L				LAPLACE-2 and DESCARTES SP LDL-C >2.5mmol/L			
	n	Mean	CI lower	CI upper	n	Mean	CI lower	CI upper
Next event (male)	219	0.0585	0.0560	0.0610	269	0.0570	0.0548	0.0592
Death (male)	219	0.0182	0.0170	0.0193	269	0.0174	0.0164	0.0184
Next event (female)	111	0.0581	0.0547	0.0615	143	0.0568	0.0539	0.0598
Death (female)	111	0.0169	0.0152	0.0185	143	0.0162	0.0148	0.0175

CI, confidence interval; SP, secondary prevention

B23: Section 5.3, page 193. Please clarify why the treatment effect from RUTHERFORD-2 has not been used to inform the analyses in the HeFH population. Please comment on the differences in treatment effect for evolocumab vs. placebo (plus background statins) observed in LAPLACE-2 and RUTHERFORD-2.

As described in the evidence submission (Section 5.3, pages 192 to 193), the treatment effects from LAPLACE-2 were selected for the HeFH population in the absence of head-to-head data in HeFH for evolocumab plus statin versus ezetimibe plus statin. A network meta-analysis was attempted to synthesise comparative efficacy in this population, however, it was deemed neither appropriate nor feasible on assessment of available data.

The treatment effect of mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe from LAPLACE-2 and RUTHERFORD-2 is summarised in Table B-19.

Table B-19 Mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe when used in combination with statins in LAPLACE-2 and RUTHERFORD-2

	Evolocumab 140 mg Q2W	Evolocumab 420 mg QM	Ezetimibe 10 mg OD^b
Combination with a statin (based on LAPLACE-2)			
Treatment difference in mean percent change from baseline vs. placebo ^a (95% CI)	-71.8 (-74.7, -68.9)	-69.1 (-73.5, -64.8)	-26.6 (-30.7, -22.4)
Combined with background lipid-lowering therapy (RUTHERFORD-2)			
Treatment difference in mean percent change from baseline vs. placebo ^a (95% CI)	-61.3 (-67.2, -55.4)	-66.2 (-71.9, -60.6)	Not available
References: LAPLACE-2 CSR ¹⁷ Table 14-4.2.13 and LAPLACE-2 supplementary data table 14-4.6.2 ⁵¹ ; RUTHERFORD-2 CSR ⁵⁴ Tables 10-3 and 14-4.1.2			
^a Least squares mean from the repeated measures model which includes treatment group, stratification factors (from IVRS), scheduled visit, dose frequency and the interaction of treatment with scheduled visit as covariates.			
^b Based on <i>post hoc</i> pooled analysis of all ezetimibe arms and all placebo arms in LAPLACE-2			
CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; OD, once daily; Q2W, every 2 weeks; QM, monthly;			

As noted in our evidence submission, since the treatment effect of evolocumab was demonstrated to be consistent regardless of patient population and patient characteristics, in the absence of evidence, it was also deemed clinically reasonable to assume the treatment effect for ezetimibe would also be consistent regardless of patient population. Therefore, the treatment effects from LAPLACE-2 were used for in the cost-effectiveness analysis of evolocumab and statin versus ezetimibe and statin in HeFH population. This approach was also used of the statin intolerant or contraindicated population whereby the treatment effects from GAUSS-2 were used in the HeFH population.

B24: Section 5.3, page 193. The relative treatment effects for evolocumab in the statin-intolerant population are taken from the GAUSS-2 trial. However, the modelled risk of CVD is based on baseline characteristics from LAPLACE-2 or RUTHERFORD-2. Please clarify why patient-level data from the GAUSS-2 trial have not been used to derive the CVD risk as per the approach used for LAPLACE-2 and RUTHERFORD-2.

As stated in our evidence submission (Section 5.2, page 174), “GAUSS-2 enrolled patients with primary hypercholesterolaemia and mixed dyslipidaemia unable to tolerate any statins or a statin dose high enough to control their LDL-C levels. However, for the purposes of the economic evaluation, the patient populations from LAPLACE-2 and RUTHERFORD-2 were

used since statin intolerance or contraindication is considered a subgroup of the primary hypercholesterolaemia and mixed dyslipidaemia, and HeFH populations.”

Statin intolerance is associated with adverse events such as, muscle-related symptoms, elevation in serum creatine kinase or persistent elevations in transaminase levels. The incidence of these adverse events is typically biochemical in nature and unrelated to patient characteristics used for CVD risk estimation. Patients with statin intolerance are anticipated to be similar to patients without statin intolerance except for baseline LDL-C due to differential background lipid-lowering therapies. Consequently, it was deemed appropriate to use the LAPLACE-2 and RUTHERFORD-2 populations for estimating baseline CVD risk across the primary hypercholesterolaemia and mixed dyslipidaemia and HeFH populations, vary baseline LDL-C (severity of hypercholesterolaemia), and use the GAUSS-2 treatment effects to assess the cost-effectiveness in a statin intolerant population.

B25: Section 5.3, Table 5-5, page 183. The number of vascular beds (VB) and proportion of patients with atrial fibrillation (AF) are based on the mean observed in the REACH study. Please comment on the potential biases associated with this. Please also confirm that this information is not available from the LAPLACE-2, DESCARTES, RUTHERFORD-2 or GAUSS-2 trials.

The number of vascular beds and proportion of patients with atrial fibrillation were based on the means observed in the REACH registry. The REACH equations are based on a Cox proportional hazards model considering mean-centred risk factors. In the absence of information for these risk factors in the modelled populations, considering the mean value reported in Wilson et al., (2012)⁵⁰ means these risk factors have no impact on the CVD risk predictions:

- Vascular beds: The REACH registry assesses the role of previously diagnosed vascular disease using an ordinal variable to test for the effects of 1, 2, or 3 vascular beds involved. We have conducted an exploratory assessment of patients with existing CVD in LAPLACE-2 and RUTHERFORD-2 on the basis of assuming the number of vascular beds is equivalent to individual peripheral, coronary and cerebrovascular beds. This indicates that the LAPLACE-2 and RUTHERFORD-2 patients with existing CVD have 1.227 and 1.333 vascular beds, respectively, in comparison with 1.212 reported in the REACH registry. This slightly higher estimate from this exploratory assessment would indicate we have undertaken a conservative approach in estimating CVD risk from these RCTs compared with the REACH registry. Further, the number of vascular beds is a dynamic risk factor that could be adjusted on the basis of when a CV event occurs in a new vascular bed (peripheral, coronary or cerebrovascular) if the definitions are assumed to be the same. For simplicity, the number of vascular beds is kept static as we are using a cohort model (as opposed to patient-level simulations), and as such would be conservative when assessing a cohort experiencing recurrent CV events. Counterfactually, we can anticipate that we are over-estimating risk in a population without existing CVD in the short term following a CV event. This population would be anticipated to have 1 vascular bed following a first CV event as opposed to 1.212 based on the REACH registry.
- Atrial fibrillation (AF): the proportion of patients with AF is based on the REACH registry (11.7%) since patients with uncontrolled serious cardiac arrhythmia (including AF) in the past 3 months prior to randomisation were excluded from the relevant RCTs. Therefore,

the estimate from the REACH registry was deemed a more appropriate estimate for the purposes of CVD risk estimation. Assessment of the CPRD study indicated that 13.6% of patients with existing CVD had a diagnosis of AF. This would suggest that the REACH registry estimate for this cardiovascular condition could be a reasonable estimate for prevalence in the absence of this from the RCTs due to the exclusion of patients with uncontrolled AF.

B26 (PRIORITY QUESTION): Section 5.3, page 198. Please clarify why no reduction in CV event rate associated with LDL-C levels when lower than 1.03mmol/L from baseline (equivalent to 40mg/dL) was assumed?

None of the studies included in the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis, used as key data source for translating LDL-C reductions to CV events included an intervention that reduced LDL-C below 1.03mmol/L.²⁸ Therefore, a conservative approach was adopted in favour of alternative strategies since only patients treated with evolocumab can experience such intensive LDL-C reductions on the basis of different severities of hypercholesterolaemia (baseline LDL-C) thereby achieving LDL-C levels below this threshold. Table B-20 indicates the modelled LDL-C levels following treatment for the different scenarios with values in bold denoting the scenarios and corresponding baseline LDL-C levels where cohorts are anticipated to achieve an LDL-C level below the defined threshold.

Table B-20 Modelled LDL-C levels after treatment according to severity of hypercholesterolaemia (baseline LDL-C)

Treatment scenarios	Baseline LDL-C (mmol/L)							
	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
Evolocumab 140mg Q2W	0.71	0.85	0.99	1.13	1.27	1.41	1.55	1.69
Evolocumab 420mg QM	0.77	0.93	1.08	1.24	1.39	1.54	1.70	1.85
Evolocumab 140mg Q2W [SI]	1.07	1.29	1.50	1.72	1.93	2.15	2.36	2.57
Evolocumab 420mg QM [SI]	1.10	1.33	1.55	1.77	1.99	2.21	2.43	2.65
Evolocumab 140mg Q2W and ezetimibe 10mg OD	0.52	0.62	0.73	0.83	0.93	1.04	1.14	1.24
Evolocumab 420mg QM and ezetimibe 10mg OD	0.57	0.68	0.79	0.91	1.02	1.13	1.25	1.36
Evolocumab 140mg Q2W and ezetimibe 10mg OD [SI]	0.88	1.06	1.23	1.41	1.59	1.76	1.94	2.12
Evolocumab 420mg QM and ezetimibe 10mg OD [SI]	0.91	1.09	1.27	1.45	1.63	1.82	2.00	2.18
Note: all scenarios include background lipid-lowering therapy with statins except those statin intolerant scenarios								
LDL-C, low-density lipoprotein cholesterol; OD, once daily; Q2W, every two weeks; QM, monthly; SI, statin intolerant or contraindicated								

We have included additional scenario analyses where this assumption has been removed (Table B-21 and Table B-22) in patients with existing CVD, and patients with HeFH. These scenario analyses have been completed based on amending the values in "Parameters List" worksheet, cells F236 and G236 from '40' to '0' and replicating the analyses assessing severity of hypercholesterolaemia (evidence submission, Table 5-58 and Table 5-59).

Table B-21 Existing CVD and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin, scenario 1) based on LDL-C threshold for CV event reduction

Baseline LDL-C	LDL-C threshold for CV event reduction (1.03 mmol/L)			No LDL-C threshold for CV event reduction			Difference
	ΔCost	Δ QALYs	ICER	ΔCost	Δ QALYs	ICER	
3.0 mmol/L	██████	0.35	██████	██████	0.39	██████	██████
3.5 mmol/L	██████	0.43	██████	██████	0.44	██████	██████
4.0 mmol/L	██████	0.48	██████	██████	0.48	██████	██████
4.5 mmol/L	██████	0.51	██████	██████	0.51	██████	██████
5.0 mmol/L	██████	0.54	██████	██████	0.54	██████	██████
5.5 mmol/L	██████	0.56	██████	██████	0.56	██████	██████
6.0 mmol/L	██████	0.59	██████	██████	0.59	██████	██████

CVD, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

Table B-22 Heterozygous familial hypercholesterolaemia and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin, scenario 1) based on LDL-C threshold for CV event reduction

Baseline LDL-C	LDL-C threshold for CV event reduction (1.03 mmol/L)			No LDL-C threshold for CV event reduction			Difference
	ΔCost	Δ QALYs	ICER	ΔCost	Δ QALYs	ICER	
3.0 mmol/L	██████	0.79	██████	██████	0.91	██████	██████
3.5 mmol/L	██████	1.00	██████	██████	1.03	██████	██████
4.0 mmol/L	██████	1.14	██████	██████	1.14	██████	██████
4.5 mmol/L	██████	1.25	██████	██████	1.25	██████	██████
5.0 mmol/L	██████	1.34	██████	██████	1.34	██████	██████
5.5 mmol/L	██████	1.43	██████	██████	1.43	██████	██████
6.0 mmol/L	██████	1.51	██████	██████	1.51	██████	██████

CVD, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

B27: Section 5.4, pages 219–220. Please clarify why utilities from NICE clinical guideline 181 were assumed when the company’s submission includes a new systematic review of health-related quality of life literature.

As NICE CG181¹⁹ is a recent clinical guideline including an economic evaluation, it was used to support development of the current economic model. As such, the utilities used in CG181 fit reasonably well and appropriate to the current economic model structure. However, the utility values applied in NICE CG181 were sourced from primary documents that were published between the mid-1990s and mid-2000s. Therefore, we undertook a SLR to check if more recent utility values of equal relevance had been published.

The SLR identified 173 studies which included potential utility data for one or more health-states in the economic model. Each of the identified studies was assessed in order to

identify the utility values which had greatest relevance to the economic model, and the NICE reference case (for example, those which provided EQ-5D utility estimates). The following studies were deemed to be most consistent with the NICE reference case (Table B-23, please refer Appendix XIII of the evidence submission, Table XIII-11 for more detailed information).

Table B-23 Consistency of identified HRQoL studies with NICE reference case

Author and Year	Appropriateness of Health State	Appropriateness Notes	Consistency with Reference Case	Reference Case Notes
Ali K, Warusevitane A, Lally F, et al. The Stroke Oxygen Pilot Study: A Randomized Controlled Trial of the Effects of Routine Oxygen Supplementation Early after Acute Stroke—Effect on Key Outcomes at Six Months. PLOS ONE. June 2013, 8 (6), 1-8	Partially matches target	Stroke (type not specified) at 6 months	Consistent	EQ-5D in patients in a trial with UK tariffs
Bowen A, Hesketh A, Patchick E, et al. Clinical effectiveness, cost-effectiveness and service users' perceptions of early, well-resourced communication therapy following a stroke: A randomised controlled trial (the ACT noW study). Health Technology Assessment. 2012;16(26):1-159.	Partially matches target	Stroke values after 6 months of treatment; type of stroke is not specified	Consistent	EQ-5D is used on patients in a clinical trial and UK tariffs are applied
Dennis, M., et al. Effect of intermittent pneumatic compression on disability, living circumstances, quality of life, and hospital costs after stroke: secondary analyses from CLOTS 3, a randomised trial. Lancet Neurol. 2014; 13: 1186-92	Partially matches target	Stroke type unclear, time period 6 months post-stroke	Consistent	EQ-5D with patients in RCT using UK tariff
Dennis, M., Sandercock, P., Reid, J., et al. The Effect of Graduated Compression Stockings on Long-term Outcomes After Stroke The CLOTS Trials 1 and 2. Stroke. 2013; 44: 1075-1079	Partially matches target	Stroke type unclear, time period 6 months post-stroke	Consistent	EQ-5D with patients in RCT using UK tariff (Dolan 1995)
Kim J, Henderson RA, Pocock SJ, et al. Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation MI: one-year results of the third Randomized Intervention Trial of unstable Angina (RITA-3). Journal of the American College of Cardiology. Jan 18 2005;45(2):221-228.	Partially matches target	Matches disease state; time since intervention known; time since event unknown.	Consistent	EQ-5D; measured in a trial, UK tariff
Kohn CG, Parker MW, Limone BL, Coleman CI. Impact of angina frequency on health utility values of patients with chronic stable angina. Health and Quality of Life Outcomes. 2014, 12: 39	Does not match target	Patients have chronic stable angina	Consistent	EQ-5D in patients in a clinical trial with UK tariff; (Mapping equation #2; Goldsmith 2010)
Levin, L. A., Wallentin, L., Bernfort, L., Andersson, D., Storey, R. F., Bergstrom, G., Lamm, C. J., Janzon, M., Kaul, P.. Health-related quality of life of ticagrelor versus clopidogrel in patients with acute coronary syndromes - Results from the PLATO Trial. Value in Health. 2013. 16:574-580	Partially matches target	Type of disease state not specified; time since event unknown	Consistent	EQ-5D; in patients measured in a trial, UK tariff

Lewis, E. F., Li, Y., Pfeffer, M. A., Solomon, S. D., Weinfurt, K. P., Velazquez, E. J., Califf, R. M., Rouleau, J. L., Kober, L., White, H. D., Schulman, K. A., Reed, S. D. Impact of cardiovascular events on change in quality of life and utilities in patients after myocardial infarction. A VALIANT Study (Valsartan in acute myocardial infarction). JACC: Heart Failure. 2014. 2:159-165	Partially matches target	Time since event not specified	Consistent	EQ-5D; in patients measured in a trial, UK tariff
Logan, P. A., Armstrong, S., Avery, T. J., Barer, D., Barton, G. R., Darby, J., Gladman, J. R. F., Horne, J., Leach, S., Lincoln, N. B., Mehta, S., Newell, O., O'Neil, K., Sach, T. H., Walker, M. F., Williams, H. C., Woodhouse, L. J., Leighton, M. P.. Rehabilitation aimed at improving outdoor mobility for people after stroke: A multicentre randomized controlled study (the getting out of the house study). Health Technology Assessment. 2014. 18:1-73	Partially matches target	Type of stroke not specified	Consistent	EQ-5D; in patients measured in a trial, UK tariff
Muller-Werdan, U., Stockl, G., Ebelt, H., Nuding, S., Hopfner, F., Werdan, K.. Ivabradine in combination with beta-blocker reduces symptoms and improves quality of life in elderly patients with stable angina pectoris: Age-related results from the ADDITIONS study. Experimental Gerontology. 2014. 59:34-41	Partially matches target	Current angina, stability unclear	Consistent	EQ-5D in patients in trial with UK tariff
Sandercock, P.. Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial [IST-3]): 18-month follow-up of a randomised controlled trial. The Lancet Neurology. 2013. 12:768-776	Partially matches target	Time since event not within one year or equal to subsequent years	Consistent	EQ-5D; in patients measured in a trial, UK tariff reported
Whynes DK, Sprigg N, Selby J, Berge E, Bath PM. Testing for Differential Item Functioning within the EQ-5D. Med Decis Making 2013;33:252–260	Partially matches target	Stroke type not specified, timepoint 3 months	Consistent	EQ-5D with patient data from trial, UK tariff
Whynes DK. Does the correspondence between EQ-5D health state description and VAS score vary by medical condition? Health and Quality of Life Outcomes 2013, 11:155	Partially matches target	Stroke type not specified, timepoint 3 months	Consistent	EQ-5D with patient data from several clinical trials, UK tariff
EQ-5D, EuroQol-5 Dimension; RCT, randomised controlled trial.				

None of these studies were deemed to be more robust or relevant than the utility values used in NICE CG181, and as such, that source was chosen (with minor adjustments) for the model base case. As noted in the full submission document, 19 of the papers identified in the HRQoL SLR conducted for this submission provided utility data that were reported directly or indirectly (cited through other secondary sources) in the NICE CG181 on lipid modification, thus demonstrating the comparability and relevance of the source to the decision problem.

B28: Section 5.5, Table 5-20, pages 227–228. Please clarify why the resource use/cost review focuses only on Markov models with lifetime horizon relating to a UK setting? Please clarify how these studies were used to inform the de novo health economic analysis.

Thank you for identifying this typographic error. The table heading summarising the results of resource use/cost review should state '*Cost summary data extraction of UK studies*'. No model-based limitations were applied during this review.

The SLR was broad and covered 13 European countries. In order to present the identified studies most relevant to the current submission, a summary table containing only the UK studies presenting costs from the past 10 years was presented in the evidence submission. A full data extraction table was provided in Appendix XIV, Table XIV-8 of the evidence submission.

B29: Section 5.3, Table 5-12, page 197. Please clarify why rate ratio for the “more vs less” is used for non-fatal CV events (based on 5 trials), whereas the rate ratio for all lipid agents (n=26 trials) is used for fatal CV events. Please also clarify why only ischaemic stroke (rather than other forms of stroke) is included in the model.

The CTTC meta-analysis for '*more versus less intensive statin therapy*' was used since this meta-analysis specifically considered whether larger reductions in LDL-C safely produce further reductions in major vascular events, since several trials have compared more intensive versus less intensive statin regimens.²⁸ This meta-analysis (2 trials in patients with ACS and 3 trials in patient with stable coronary disease) was deemed to be more representative of the high-risk CV population and clinical intent for patients who would be treated with evolocumab as opposed to the '*standard versus control*' meta-analysis which is generally based on studies of lower intensity statins versus placebo.

The '*more versus less intensive statin therapy*' meta-analysis was not used for fatal events for two reasons. Firstly, the rate ratio per mmol/L reduction of LDL-C was not reported for ischaemic stroke (IS) in this meta-analysis; however, it was reported in the '*standard versus control*' meta-analysis. Secondly, CV outcomes trials typically assess major vascular events as a composite endpoint (e.g. coronary death, non-fatal MI, coronary revascularisation, or stroke). As such, due to the lower frequency of coronary deaths across the five trials, the '*more versus less intensive statin therapy*' reports a non-significant reduction in coronary death (rate ratio per mmol/L reduction in LDL-C of 0.85, 95% CI: 0.62 to 1.15. The authors state that after differences in the absolute reductions in LDL-C were accounted for, the proportional reduction in the incidence of major vascular events per mmol/L was slightly larger (heterogeneity $p=0.03$) in the trials of '*more versus less intensive therapy*' than in

those of '*statin versus control*'. It is reasonable to assume that this would also be the case with more data for coronary death, since there is no clinical reason for a differential finding for this major vascular event. Therefore, to gain alignment with the source for the rate ratio for fatal IS, the rate ratios for fatal events were used from the '*statin versus control*' meta-analysis.

IS was only assessed in the economic model because available evidence from the CTTC meta-analysis indicated that the rate ratio per mmol/L LDL-C reduction for both non-fatal and fatal haemorrhagic strokes were non-significant.

B30: Section 5.3, pages 196–198. The company's model focuses on patients deemed to be at high risk of CV events (according to baseline LDL, presence of diabetes etc.). The company uses data from the CTTC meta-analysis for all patients irrespective of baseline LDL, risk factors or history of cardiac event. Please comment on the availability of data on CV risk by baseline risk factors.

The CTTC meta-analysis assessed the effect of major vascular events by baseline LDL-C concentration and reported that the rate ratio per mmol/L LDL-C reduction is consistent irrespective of baseline LDL-C.²⁸ We are not aware of data for other risk factors (e.g. diabetes mellitus).

B31: Company's model. Please clarify why the 10-year risk was calculated for the overall population in the RUTHERFORD-2 trial in the HeFH population; that is, why was the Framingham risk equation applied to patients who have a history of CVD? Why were the primary and secondary prevention populations not evaluated separately?

The Framingham equation was only applied for transitions for HeFH patients without existing CVD (i.e. primary prevention). The primary and secondary prevention populations in HeFH were not evaluated separately to reflect the decision problem. The economic model cannot assess primary and secondary prevention cohorts simultaneously, therefore average cohort patient characteristics from the primary and secondary prevention population from RUTHERFORD-2 are used for the cost-effectiveness analysis.

The economic model has the flexibility to allow evaluation of these primary and secondary prevention populations separately. This can be conducted by selection of the relevant RUTHERFORD-2 primary or secondary prevention population in the 'Main' worksheet (cell I3).

We have included the cost-effectiveness analyses in this clarification request for the HeFH primary and secondary prevention populations based on comparison of evolocumab and statin versus ezetimibe and statin (scenario 1) (Table B-24). These indicate a lower incremental cost per QALY gained versus ezetimibe in the combined cohort compared with the individual primary and secondary prevention population analyses. This is due to the balance between the costs and benefits accrued in a mixed CVD history population when compared with assessing individual cohorts based on CVD history.

Table B-24 Cost-effectiveness results for heterozygous familial hypercholesterolaemia population (all, primary prevention and secondary prevention populations) for evolocumab and statin versus ezetimibe and statin

Population	Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
HeFH (all)	Statin	£18,154	8.24				
	Ezetimibe and statin	£19,431	9.02	£1,277	0.78	£1,640	
	Evolocumab and statin		10.17		1.93		
HeFH primary prevention	Statin	£14,679	9.86				
	Ezetimibe and statin	£16,509	10.75	£1,829	0.89	£2,064	
	Evolocumab and statin		12.03		2.17		
HeFH secondary prevention	Statin	£21,943	6.32				
	Ezetimibe and statin	£22,705	6.92	£762	0.60	£1,265	
	Evolocumab and statin		7.81		1.49		
HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years							

B32: Company's model. Please provide further explanation on how the 10-year risk was adjusted for age in the model, including any assumptions used. In particular, please explain what the calculations in worksheet "Rates & non-CVD Utilities" columns C and E are intended to do.

The average 10-year rate of events predicted from patient-level data was annualised ensuring the sum of the first 10 annual rates (from the starting age) presented in "Rates & non-CVD Utilities" worksheet, columns C (males) and D (females) equals the original 10-year rate prediction. This was done as the 10-year predicted rates include the effect of aging over the follow-up time in the Framingham study; therefore the rates were corrected to remove this effect and avoid overestimation of event risks.⁵⁵

The effect of aging was assumed to be equal to the age coefficient from the Cox proportional hazards models that were used to develop the Framingham equation. The effect of age was removed from the predicted event rate by using a correction factor that represented the cumulative effect of aging beyond the first year. This correction factor is presented in 'Rates & non-CVD Utilities' worksheet (sum of column E [males] and sum of column F [females]). As the Framingham study included the log of age in the prediction model, its correction factor varied with age. For example, the average 10-year rate for RUTHERFORD-2 (male) patients was predicted to be 0.1699 for a starting age of 49 years old. This equals the sum of the 10 annual rates presented in 'Rates & non-CVD Utilities' worksheet (cells C49 to C58).

The same approach was used to annualise the 20-month rates predicted from the REACH equation. In this case, the correction factor is not age-dependent.

B33 (PRIORITY QUESTION): Section 5.3, pages 187–192. The company attempted to calibrate the 10-year risk estimated from the Framingham algorithm using data from the CPRD (20 months from REACH using the HES data).

- Please comment on whether calibration factors are already available in the literature and if so, how these compare with the calibration factors estimated from the CPRD/HES dataset?
- Please clarify why only patients with diabetes were included in the CPRD dataset for primary prevention. Please comment on the potential biases associated with this approach.
- The submission states that about half the patients from the CPRD dataset could not be linked (or did not have information). Please comment on the potential biases resulting from this (for example, selection bias). Please also comment on any differences between patients included and excluded (or those who could not be linked).
- How does this calibration approach compare with the methods used in NICE clinical guideline 181?
- Please explain why the event rates from the CPRD analysis were not used to directly estimate CV risk (as opposed to using Framingham as per the company's model)?

As far as we are aware, there are no published calibration factors for the Framingham or REACH registry risk equations based on comparisons with UK data specific to the populations used in our study. Literature comparing the accuracy of the Framingham risk equation in other countries for the primary prevention population as a whole is available.

However, because the populations in the CPRD study are specific to support assessment of a high-risk population, it would be unexpected to find literature documenting calibration factors for these five specific populations treated with high-intensity statins: prevalent diabetes, prevalent evident CVD, incident ACS, incident IS, and incident HF (in patients with ACS or IS). With respect to REACH, at the time of the CPRD study, we were not aware of any studies that developed calibration factors. This is one of the reasons why we conducted the calibration

We also compared overall CV event rates from three different countries for these five cohorts. Each study was done with different research organisations, so the results are with slightly different methodologies owing to study design and data. For example, rates from Sweden and the UK are during the first 1500 days, and Spain reflects rates over the entire follow-up period. Also, the exclusion of events within the first 30 days for the incident (ACS, IS, and HF) cohorts is handled differently in the three countries. However, their overall concordance suggests that the CPRD findings are not substantially different from those in other countries (Table B-25 to Table B-29).

Table B-25 Diabetes: Overall event rates

Cohort	Age	Events	Patient years	Rate per 1,000 patient years
Sweden				
UK				
Spain	-		-	

Table B-26 Established cardiovascular disease: Overall event rates

Cohort	Age	Events	Patient years	Rate per 1,000 patient years
Sweden				
UK				
Spain	-		-	

Table B-27 Acute coronary syndrome: Overall event rates

Cohort	Age	Events	Patient years	Rate per 1,000 patient years
Sweden				
UK				
Spain	-		-	

Table B-28 Heart failure: Overall event rates

Cohort	Age	Events	Patient years	Rate per 1,000 patient years
Sweden				
UK				
Spain	-		-	

Table B-29 Ischaemic stroke: Overall event rates

Cohort	Age	Events	Patient years	Rate per 1,000 patient years
Sweden	██████	██████	██████	██████
UK	██████	██████	██████	██████
Spain	-		-	██████

Patients with diabetes were selected because they represent the largest group of high-risk primary prevention patients. While there are other risk factors that confer high risk, most do not confer high-risk status in and of themselves, and those that do typically reflect very small subgroups. Therefore, patients with diabetes were selected to represent a large, easily identifiable subgroup of primary prevention patients at high risk of CV events. Most primary prevention risk equations include diabetes as a risk factor, so these equations should appropriately reflect the risk of diabetic patients. As with any risk equation, there may be biases with regards the representativeness of the population used to estimate the risk equation. Even then, the results may not generalise to other countries. Therefore, we developed calibration equations to address this issue.

High-risk patients with diabetes may have a variety of other complications due to associated microvascular disease, and may have a different distribution of CV events than patients with other risk factors that result in the same risk level.

We conducted a brief comparison of patients in CPRD who did and did not have linked hospital episode statistics (HES) data, and found there to be no substantial differences (Table B-30). It should be noted that these comparisons were earlier in the cohort finalisation process, so the HES cohort is not exactly the same as the final cohort used in the analyses. This is because these were exploratory analyses at the point where the HES data were merged with the CPRD data. After this step, additional exclusion criteria were applied, including removing patients who died within 30 days after the index event. Based on these analyses, we feel that there is no substantive effect of selection bias in restricting our cohort to patients with HES data.

Table B-30 CPRD Study: comparison of population characteristics with and without linked Hospital Episodes Statistics data

Population	HES	Number	Mean age (years)	Male (%)	Diabetes (%)
Diabetes	Yes	7627	63.0	50.6	100.0
	No	6019	62.8	50.6	100.0
Established CVD	Yes	9411	68.5	54.2	22.0
	No	7391	68.1	53.1	22.1
ACS	Yes	1654	69.6	58.7	35.4
	No	1512	68.5	58.1	33.1
IS	Yes	432	72.0	54.9	32.4
	No	377	71.0	48.0	35.5
HF	Yes	1267	73.1	62.4	35.0

	No	1091	72.7	60.0	34.5
ACS, acute coronary syndrome; CVD, cardiovascular disease; HES, hospital episode statistics; HF, heart failure; IS, ischaemic stroke.					

In NICE CG181, QRISK2 and UKPDS are recommended as the preferred risk assessment tools for patients without existing CVD and patients with diabetes, respectively,¹³ since the tools have been validated in England and Wales. Therefore, the economic evaluation uses absolute 10-year CV risk (increased to estimate ‘total CV’ risk) as hypothetical outputs for modelling primary prevention cohorts based on age and gender. For modelling secondary prevention, no risk equation was used for a recurrent CV event. The transition probabilities (based on age and gender) between CV health states after the first event had occurred were taken from sources identified in a systematic review. Therefore, no calibration was undertaken since real-world event rates were directly used. Notably, the subsequent CV event transition probabilities were not conditional on the CV risk of a first event (i.e. the risk for secondary prevention was assumed the same irrespective of primary prevention risk). This approach is appropriate for estimating the cost-effectiveness of lipid modification therapies in the context of general population risk in primary and secondary prevention, but does not allow flexibility to assess high-risk patients beyond age and gender. We conducted a critical appraisal of these source publications (Appendix X of the evidence submission) and identified that these studies were generally of high methodological quality. However, some significant limitations were identified in most of these sources. Specifically, the primary sources were based on analyses conducted during the 1980s and 1990s.

As stated in our evidence submission, the priority for use of evolocumab is in those patients who are at the highest residual risk and are most vulnerable to CV events, where evolocumab represents both a clinically- and cost-effective treatment option for the NHS. Consequently, a primary aim was to derive relevant appropriate data to support baseline CV rate estimation that would be applicable in the current clinical setting and high-risk populations with respect to the decision problem. A study was therefore undertaken in the CPRD to estimate CV rates.

The economic model could indeed have directly used the CPRD study event rates to model an overall high-risk population as per the study cohort definitions. However, this approach would not have permitted us to assess specific high-risk populations such as those with existing CVD with 1 or 2 additional risk factors who remain at the highest residual risk.

B34: Section 6, Table 6-7, page 289. Values for evolocumab are presented as 0% throughout. Please also check figures on page 290 and in Tables 6-8 and 6-9.

We can confirm that these figures are correct and are based on the conclusions of the cost-effectiveness analysis for the different populations.

C: Data request

C1: Please provide an Excel worksheet including patient-level data for all patients from LAPLACE-2, in the same form as the “LAPLACE-2 (PP)” worksheet in the model, but also including variables for (1) primary/secondary prevention, (2) statin product and dose at baseline, and (3) randomised treatment group.

An Excel worksheet including this data has been provided in conjunction with this document.

References

1. Lefebvre CM, E; Glanville, J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. Accessed August 2015. 2011.
2. Amgen. Data on file. TAUSSIG interim CSR. Data cut-off, 1st July 2014
3. Bruckert E, Blaha V, Stein E *et al*. Trial Assessing Long-Term Use of PCSK9 Inhibition in Patients with Genetic LDL Disorders (TAUSSIG): Efficacy and Safety in Patients with Familial Hypercholesterolemia Receiving Lipid Apheresis. Poster presented at the AHA (American Heart Association) Scientific Sessions, 15–19 November 2014, Chicago, USA.
4. Fitch K, Goldberg SW, Iwasaki K *et al*. Estimates of commercial population at high risk for cardiovascular events: impact of aggressive cholesterol reduction. *Am Health Drug Benefits* 2009;2:224-32.
5. Amgen. Data on file. RUTHERFORD-2 study protocol. 2012.
6. Raal FJ, Stein EA, Dufour R *et al*. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;385:331-40.
7. Amgen. Data on file. LAPLACE-2 study protocol. 2012.
8. Robinson JG, Nedergaard BS, Rogers WJ *et al*. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* 2014;311:1870-82.
9. Robinson JG, Rogers WJ, Nedergaard BS *et al*. Rationale and design of LAPLACE-2: a phase 3, randomized, double-blind, placebo- and ezetimibe-controlled trial evaluating the efficacy and safety of evolocumab in subjects with hypercholesterolemia on background statin therapy. *Clin Cardiol* 2014;37:195-203.
10. Blom DJ, Hala T, Bolognese M *et al*. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med* 2014;370:1809-19.
11. Amgen. Data on file. DESCARTES study protocol. 2013.
12. National Institute for Health and Care Excellence. NICE CG181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Appendices. July 2014. Available from: <http://www.nice.org.uk/guidance/cg181/evidence> (Accessed May 2015).
13. National Institute for Health and Care Excellence. NICE CG71. Identification and management of familial hypercholesterolaemia. August 2008. Available from: <http://www.nice.org.uk/guidance/cg71> (Accessed May 2015).
14. National Institute for Health and Care Excellence. NICE CG181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. July 2014. Available from: <http://www.nice.org.uk/guidance/cg181> (Accessed May 2015).
15. National Institute for Health and Care Excellence. NICE TA132. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. November 2007. Available from: <http://www.nice.org.uk/guidance/ta132> (Accessed May 2015).
16. Amgen. Data on file.
17. Amgen. Data on file. LAPLACE-2 CSR. 2014.
18. Amgen. Data on file. DESCARTES CSR. 2014.

19. National Institute for Health and Care Excellence. NICE CG181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Full Guideline. July 2014. Available from: <http://www.nice.org.uk/guidance/cg181/evidence/cg181-lipid-modification-update-full-guideline3> (Accessed May 2015).
20. Stone NJ, Robinson JG, Lichtenstein AH *et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2889-934.
21. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013. August 2008. Available from: <http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf> (Accessed August 2015).
22. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;313:275-83.
23. Sabatine MS, Giugliano RP, Wiviott SD *et al.* Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1500-9.
24. NHS. NHS Electronic Drug Tariff. 2015. Available at <http://www.drugtariff.nhsbsa.nhs.uk/#/00175224-FA/FA00175149/Part> VIIIA products (Accessed May 2015).
25. NHS. NHS Business Services Authority. Prescription Cost Analysis (PCA) Data. April 2015. Available at: <http://www.nhsbsa.nhs.uk/PrescriptionServices/3494.aspx> (Accessed May 2015). 2015.
26. Abifadel M, Varret M, Rabes JP *et al.* Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet* 2003;34:154-6.
27. Assmann G, Schulte H, Cullen P. New and classical risk factors--the Munster heart study (PROCAM). *Eur J Med Res* 1997;2:237-42.
28. Baigent C, Blackwell L, Emberson J *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-81.
29. Baigent C, Keech A, Kearney PM *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78.
30. Cohen JC, Boerwinkle E, Mosley TH, Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;354:1264-72.
31. LaRosa JC, Grundy SM, Waters DD *et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-35.
32. LaRosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H. Safety and efficacy of Atorvastatin-induced very low-density lipoprotein cholesterol levels in Patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). *Am J Cardiol* 2007;100:747-52.
33. Perk J, De Backer G, Gohlke H *et al.* European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33:1635-701.
34. Wiviott SD, Cannon CP, Morrow DA *et al.* Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. *J Am Coll Cardiol* 2005;46:1411-6.
35. Cannon CP, Braunwald E, McCabe CH *et al.* Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.

36. Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *J Am Coll Cardiol* 2011;57:1666-75.
37. Leeper NJ, Ardehali R, deGoma EM, Heidenreich PA. Statin use in patients with extremely low low-density lipoprotein levels is associated with improved survival. *Circulation* 2007;116:613-8.
38. Boekholdt SM, Hovingh GK, Mora S *et al*. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol* 2014;64:485-94.
39. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
40. Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. *J Lipid Res* 2009;50 Suppl:S172-7.
41. Ara R, Pandor A, Stevens J, Rees A, Rafia R. Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation. *Health Technol Assess* 2009;13:1-74, 75-118.
42. Ara R, Pandor A, Stevens J *et al*. Prescribing high-dose lipid-lowering therapy early to avoid subsequent cardiovascular events: is this a cost-effective strategy? *Eur J Prev Cardiol* 2012;19:474-83.
43. Taylor DC, Pandya A, Thompson D *et al*. Cost-effectiveness of intensive atorvastatin therapy in secondary cardiovascular prevention in the United Kingdom, Spain, and Germany, based on the Treating to New Targets study. *Eur J Health Econ* 2009;10:255-65.
44. Wagner M, Goetghebeur M, Merikle E *et al*. Cost-effectiveness of intensive lipid lowering therapy with 80 mg of atorvastatin, versus 10 mg of atorvastatin, for secondary prevention of cardiovascular disease in Canada. *Can J Clin Pharmacol* 2009;16:e331-45.
45. Khoury H, Wagner M, Merikle E, Johnson SJ, Roberts C. Cost-Effectiveness of Atorvastatin in the Primary Prevention of Major Cardiovascular Events in Patients with Type 2 Diabetes in Canada. *Canadian Journal of Diabetes* 2009;33:363-374.
46. Nagata-Kobayashi S, Shimbo T, Matsui K, Fukui T. Cost-effectiveness of pravastatin for primary prevention of coronary artery disease in Japan. *Int J Cardiol* 2005;104:213-23.
47. Peura P, Martikainen J, Soini E, Hallinen T, Niskanen L. Cost-effectiveness of statins in the prevention of coronary heart disease events in middle-aged Finnish men. *Curr Med Res Opin* 2008;24:1823-32.
48. Hippisley-Cox J, Coupland C, Vinogradova Y *et al*. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336:1475-82.
49. D'Agostino RB, Sr., Vasan RS, Pencina MJ *et al*. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743-53.
50. Wilson PW, D'Agostino R, Sr., Bhatt DL *et al*. An international model to predict recurrent cardiovascular disease. *Am J Med* 2012;125:695-703 e1.
51. Amgen. Data on file. LAPLACE-2 – supplementary data tables
52. Amgen. Data on file. GAUSS-2 CSR 2014.
53. Amgen. Data on file. GAUSS-2 – supplementary data tables
54. Amgen. Data on file. RUTHERFORD-2 CSR. 2014.
55. Lothgren M, Danese M, Taylor B, Villa G. Data on file. Avoiding overestimation in annualization of event risk from risk functions for use in economic modeling. Abstract submitted to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 18th Annual European Congress, 7–11 November 2015, Milan, Italy. 2015.

Appendices

Appendix I: Details of additional dyslipidaemia clinical efficacy/safety searches

A search for RCTs, ezetimibe and dyslipidaemia was run and combined with the search strategies for the original SLR using Boolean 'NOT'. This would retrieve studies not picked up in the original searches only.

Embase (OvidSP): 1974 to 2015/8/14
Searched: 17.8.15

- 1 dyslipidemia/ (42230)
- 2 (dyslipidemia\$ or dyslipaemia\$ or dyslipemia\$ or dyslipidaemia\$).ti,ab,ot,hw. (51949)
- 3 or/1-2 (51949)
- 4 ezetimibe/ or ezetimibe plus rosuvastatin/ or ezetimibe plus simvastatin/ (7062)
- 5 (ezetimibe or zetia or ezetrol or ezetib or sch 582235 or sch582235 or 163222-33-1).af. (7348)
- 6 or/4-5 (7348)
- 7 3 and 6 (1861)
- 8 Random\$.tw. or clinical trial\$.mp. or exp health care quality/ (3614677)
- 9 animal/ (1685862)
- 10 animal experiment/ (1871341)
- 11 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6002839)
- 12 or/9-11 (6002839)
- 13 exp human/ (16252074)
- 14 human experiment/ (341227)
- 15 or/13-14 (16253520)
- 16 12 not (12 and 15) (4748936)
- 17 8 not 16 (3440189)
- 18 7 and 17 (1253)
- 19 exp hyperlipidemia/ (119546)
- 20 (hypercholesterol?emi\$ or hypercholesterin?emi\$ or cholester?emi\$ or cholesterin?emi\$ or hyperlipid?emi\$ or hyperlipoprotein?emia\$ or lip?emia\$ or lipid?emi\$ or hyperlip?emi\$ or hefh or hofh or fh or hypertriglycerid?emia\$ or mckusick 14575 or triglycerid?emia\$ or (triglyceride adj1 storage adj1 disease\$)).ti,ab,ot,hw. (150050)
- 21 ((cholesterol\$ or lipid\$ or LDL) adj3 (elevat\$ or ascend\$ or increas\$ or high or rais\$)).ti,ab,ot,hw. (140114)
- 22 or/19-21 (260493)
- 23 exp hydroxymethylglutaryl coenzyme A reductase inhibitor/ (104924)
- 24 (statin\$ or hydroxymethylglutaryl coenzyme A reductase inhibit\$ or HMG CoA reductase inhibit\$ or HMGCoA reductase inhibit\$).ti,ab,ot,hw. (83998)
- 25 (atorvastatin or Lipitor or torvast or atorlip or atovarol or ci 981 or ci981 or glustar or lipibec or lowlipen or sortis or storvas or tahor or ym 548 or ym548 or zarator or 134523-00-5 or 134523-03-8).ti,ab,ot,hw,rn,tn. (27887)
- 26 (Bervastatin or ls 2904 or ls2904 or 132017-01-7).ti,ab,ot,hw,rn,tn. (6)
- 27 (crilvastatin or pmd 387 or pmd387 or 120551-59-9).ti,ab,ot,hw,rn,tn. (7)
- 28 (dalvastatin or rg 12561 or 132100-55-1 or 135910-20-2).ti,ab,ot,hw,rn,tn. (14)
- 29 (fluindostatin or Canef or cranoc or fluindostatin sodium or fluvastatin or fluvastatin sodium or fractal lp or lescol or lescol or leucol or lochol or locol or sri 62320 or sri62320 or vastin or xu 62320 or xu62320 or 93957-54-1).ti,ab,ot,hw,rn,tn. (7947)

30 (glenvastatin or hr 780 or hr780).ti,ab,ot,hw,rn,tn. (34)

31 (mevinolin or altocor or altoprev or artein or belvas or Birotin or cholestra or cysin or ellanco or elstatin or l 654969 or lipdip or lipivas or lofacol or lomar or lostatin or lovacel or lovacol or lovalip or lovalord or lovastan or lovastatin or lovasterol or lovastin or lovatadin or lowachol or lozutin or medostatin or mevacor or meverstin or mevinacor or "mk 0803" or mk 803 or mk0803 or mk803 or monacolin K or monakolin k or msd 803 or neolipid or nergadan or ovasta or rodatin rovacor or taucor or 75330-75-5).ti,ab,ot,hw,rn,tn. (14218)

32 (mevinolinic acid or mevinolinate or 75225-51-3).ti,ab,ot,hw,rn,tn. (38)

33 (Monacolin or 76343-78-7 or 79394-47-1).ti,ab,ot,hw,rn,tn. (218)

34 (pitavastatin or alipza or itavastatin or livalo or livazo or nivastatin or nk 104 or nk104 or nks 104 or nks104 or pitava or ribar or vezeptra or 147526-32-7).ti,ab,ot,hw,rn,tn. (1997)

35 (Pravastatin or astin or bristacol or cholestpar or cs 514 or cs514 or elisor or eptastantin or eptastatin or eptastatin sodium or eptastatine or kenstatin or lipemol or lipidal or liplat or lipostat or liprevil or mevalotin or novales or prareduct or prascolend or prastan or prava or pravachol or pravacol or pravaselect or pravasin or pravasine or pravator or pravyl or sanaprav or selektine or selipran or sq 31000 or sq31000 or stanidine or vasopran or vasten or xipral or 81093-37-0 or 81131-70-6).ti,ab,ot,hw,rn,tn. (17517)

36 (Simvastatin or Avastinee or cholestat or clinfar or colastatina or colestricon or covastin or denan or epistatin or esvat or ethical or eucor or ifistatin or kavelor or klonastin or kolestevan or l 644128 or l644128 or lipecor or lipex or lipinorm or liponorm or lipovas or lodales or medipo or mersivas or mk 733 or mk733 or nor-vastina or normofat or orovas or rechol or simbado or simcard or simchol or simovil or simtin or simvacor or simvahex or simvalord or simvastar or simvata or simvatin or simvor or simvotin or sinvacor or simvastatin or sinvinolin or sivastin or starzoco or synvinolin or torio or valemia or vasilip or vasotenol or vazim or vidastat or zimmex or Zocor or zocor forte or zocord or zovast or 79902-63-9).ti,ab,ot,hw,rn,tn. (104789)

37 (Rosuvastatin or crestor or rosuvast or s 4522 or s4522 or zd 4522 or zd4522 or 147098-18 or 147098-20-2).ti,ab,ot,hw,rn,tn. (10113)

38 tenivastatin.ti,ab,ot,hw,rn,tn. (0)

39 or/23-38 (193279)

40 evolocumab/ (214)

41 (evolocumab or 1256937-27-5 or AMG-145 or amg145).af. (302)

42 ezetimibe/ or ezetimibe plus rosuvastatin/ or ezetimibe plus simvastatin/ (7062)

43 (ezetimibe or zetia or ezetrol or ezetib or sch 582235 or sch582235 or 163222-33-1).af. (7348)

44 alirocumab/ or (Alirocumab or regn 727 or regn727 or sar 236553 or sar236553 or 1245916-14-6).af. (277)

45 bococizumab/ or (bococizumab or "pf 04950615" or pf04950615 or rn 316 or rn 316 or 1407495-02-6).af. (79)

46 proprotein convertase subtilisin kexin type 9 protein/ or (((PCSK9 or PCSK 9) adj2 inhibit\$) or (anti-PCSK-9 or anti-PCSK9)).ti,ab,ot,hw. (401)

47 or/40-46 (7789)

48 nicotinic acid/ (18077)

49 acipimox/ or (acipimox or acipemox or olbetam or albermox or 51037-30-0).ti,ab,ot,hw,rn,tn. (763)

50 (vitamin B3 or vitamin PP or 54-86-4 or 59-67-6 or acido nicotinico or acidum nicotinicum or akotin or apelagrin or apo-nicotinic acid or beta pyridine carboxylic acid or bionic or davitamon pp or direktan or direktane or efacin or efasin or enduracin or enduracin or naotin or natinat or niac or niacin\$ or niacor or Niaspan or nicacid or nicangin or nico or nicobid or nicocap or nicocidin or nicocrisina or nicodan or nicodane or nicolar or niconacid or niconacide or nicoseptin wirkstoff or nicosode or nicospan or nicosyl or nicotabs or nicotamin or nicotine or nicotin\$ acid or nicotinat or nicotinate or nicotinese or nicotinipca or nicotyl or nicovasen or nicyl or nikacid or nipellan or novoniacin or nyacine or nyclin or pellagramin or pellagramine or pellagrin\$ or pelonin or pelonine or pepevit or peviton or pp factor or "pyridine 3 carbonic acid" or pyridine beta carboxylic acid or "s 115" or slo niacin or

sodium nicotinate or vasotherm or vitaplex n or wampocap or wampopap).ti,ab,ot,hw,rn,tn. (80899)

51 or/48-50 (81358)

52 colestyramine/ or bile acid sequestrant/ or colestipol/ or colesevelam/ (11899)

53 (((bile adj2 acid) or anion exchange) adj2 (sequestrant\$ or resin\$)).ti,ab,hw,ot. (3856)

54 (chol-less or choles or cholesthexal or cholestyramin\$ or cholybar or cholytar or colestepiril or colestiramina or colestran or colestrol or colestyramin or cuemid or lipocol-merz or lismol or locholest or prevalite or quantalan or questran or resincoles\$ or vasosan or 11041-12-6 or 58391-37-0).ti,ab,ot,hw,rn,tn. (10672)

55 (colestipol or cholestabyl or cholestipol or colestid or lestid or u 26597a or "u 26797 a" or 25085-17-0 or 37296-80-3 or 50925-79-6).ti,ab,ot,hw,rn,tn. (2803)

56 (Colesevelam or cholestagel or gt 31 104 or gt 31 104hb or gt 31-104 or gt 31-104hb or gt31 104 or gt31 104hb or gt31-104 or gt31-104hb or welchol or 182815-43-6 or 182815-44-7).ti,ab,ot,hw,rn,tn. (1084)

57 or/52-56 (15021)

58 exp Fibric acid derivative/ (25993)

59 (fibrate\$ or fibrin acid\$ or arhalofenate or atomid or beclobate or beclobrinic acid or bezafibrate or biclofibrate or binifibrate or choline fenofibrate or ciprofibrate or clinofibrate or clofibrate or clofibrate aluminium or clofibrin acid or clofibrinide or dulofibrate or eniclobate or etofibrate or etofylline clofibrate or fenirofibrat or fenofibrin acid or halofenate or lifibrate or methylclofenapate or nicofibrate or picafibrate or pirifibrate or ponfibrate or ronifibrate or salafibrate or serfibrate or simfibrate or sitofibrate or tazasubrate or tiadenol diclofibrate or timofibrate or tocofibrate or urefibrate or xantifibrate or gemfibrozil).ti,ab,ot,hw,rn,tn. (26573)

60 (Bezafibrate\$ or befizal or benzafibrate or benzofibrate or bezafibrate retard or bezalip or bezatol or bezifal or bezofibrate or bf 759 or bf759 or bm 15075 or bm15075 or cedur or lo 44 or lo44 or norlip or 41859-67-0).ti,ab,ot,tn,rn. (4732)

61 (Ciprofibrate\$ or lipanor or modalim or win 35833 or 52214-84-3).ti,ab,ot,rn,tn. (1297)

62 (Fenofibrate\$ or Antara or apo-feno-micro or aterolis or bisterol\$ or climage or controlip or durafenat or evothyl or fegenor or felosma or fenobrate or fenofanton or fenogal or fenoglide or fenox or fibrafen or "grs 001" or hyperchol or katalip or lexemin or lipanthyl or lipantil or lipantyl or liparison or lipidax or lipidil or lipilo or lipirex or lipoclar or lipofen or lipolin or liposit or lipsin or livesan ge or lofibra or nopic 200 or normalip or nubrex or procetofen or procetofenate or procetofene or proketofen or qualipantyl or rapidil or redose 200 or rorit or secalip or sigurtil or trichol or tricor or triglide or trolip or zerlubron or zumafib or 49562-28-9).ti,ab,ot,hw,rn,tn. (9056)

63 (gemfibrozil or ausgem or bolutol or brozil or chlorestrol or cholespid or ci 719 or ci719 or clearol or decrelip or detrichol or elmogan or fetinor or fibralip or fibrocit or gedum or gemfi\$ or gemizol or gemlipid or gemnpid or gemzil or genfibrozil or gevilon\$ or gozid or grifogemzilo or hidil or hipolixan or ipolipid or jezil or lanaterom or lifibron or lipazil or lipidys or lipigem or lipira or lipison or lipistorol or lipizyl or lipofor or lipolo or lipostorol or lipozil or lipozil or lipur or lopic\$ or low-lip or lowin or manobrozil or mariston or mersikol or normolipor panazil or polyxit or progemzal or recozil or reducelor regulip or synbrozil or triglizil or uragem or zilop or 25812-30-0).ti,ab,ot,hw,rn,tn. (8209)

64 or/58-63 (31458)

65 lomitapide/ or (lomitapide or lojuxta or Juxtapid or 182431-12-5 or 202833-31-6 or 202914-84-9 or 210823-48-6 or aegr 733 or aegr733 or bms 201038\$).af. (326)

66 apheresis/ or apheresis.ti,ab,hw,ot. (13088)

67 anacetrapib/ or (anacetrapib or "mk 0859" or mk 859 or mk0859 or mk859 or 875446-37-0).af. (524)

68 mipomersen/ or (mipomersen or isis 301012 or isis301012 or kynamro or 629167-92-6).af. (474)

69 39 or 47 or 51 or 57 or 64 or 65 or 66 or 67 or 68 (308248)

70 22 and 69 (46873)

71 Random\$.tw. or clinical trial\$.mp. or exp health care quality/ (3614677)

72 animal/ (1685862)

73 animal experiment/ (1871341)
 74 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6002839)
 75 or/72-74 (6002839)
 76 exp human/ (16252074)
 77 human experiment/ (341227)
 78 or/76-77 (16253520)
 79 75 not (75 and 78) (4748936)
 80 71 not 79 (3440189)
 81 70 and 80 (19620)
 82 18 not 81 (293)

Trial filter based on:

Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc 2006;94(1):41-7.

Medline (OvidSP): 1946 to 2015/8/Wk 1

Strategy: JR_Amgen_evolocumab_dyslipidemia_Med1

Searched: 17.8.15

1 Dyslipidemias/ (6948)
 2 (dyslipidemia\$ or dyslipaemia\$ or dyslipemia\$ or dyslipidaemia\$).ti,ab,ot,hw. (21407)
 3 or/1-2 (21407)
 4 (ezetimibe or zetia or ezetrol or ezetib or sch 582235 or sch58235 or 163222-33-1).af. (1891)
 5 3 and 4 (274)
 6 randomized controlled trial.pt. or "randomized controlled trials as topic"/ (503390)
 7 controlled clinical trial.pt. (91347)
 8 random\$.ti,ot. (121794)
 9 placebo.ab. (156211)
 10 drug therapy.fs. (1821671)
 11 random\$.ab. (691199)
 12 trial.ab. (311554)
 13 groups.ab. (1341743)
 14 or/6-13 (3585739)
 15 exp animals/ not (exp animals/ and humans/) (4093181)
 16 14 not 15 (3058635)
 17 5 and 16 (233)
 18 exp hyperlipidemias/ (58405)
 19 (hypercholesterol?emi\$ or hypercholesterin?emi\$ or cholester?emi\$ or cholesterin?emi\$ or hyperlipid?emi\$ or hyperlipoprotein?emia\$ or lip?emia\$ or lipid?emi\$ or hyperlip?emi\$ or hefh or hofh or fh or hypertriglycerid?emia\$ or mckusick 14575 or triglycerid?emia\$ or (triglyceride adj1 storage adj1 disease\$)).ti,ab,ot,hw. (88146)
 20 ((cholesterol\$ or lipid\$ or LDL) adj3 (elevat\$ or ascend\$ or increas\$ or high or rais\$)).ti,ab,ot,hw. (71361)
 21 or/18-20 (144469)
 22 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (29450)
 23 (statin\$ or hydroxymethylglutaryl coenzyme A reductase inhibit\$ or HMG CoA reductase inhibit\$ or HMGCoA reductase inhibit\$).ti,ab,ot,hw. (28933)

- 24 (atorvastatin or Lipitor or torvast or atorlip or atovarol or ci 981 or ci981 or glustar or lipibec or lowlipen or sortis or storvas or tahor or ym 548 or ym548 or zarator or 134523-00-5 or 134523-03-8).ti,ab,ot,hw,rn. (6478)
- 25 (Bervastatin or ls 2904 or ls2904 or 132017-01-7).ti,ab,ot,hw,rn. (0)
- 26 (crilvastatin or pmd 387 or pmd387 or 120551-59-9).ti,ab,ot,hw,rn. (5)
- 27 (dalvastatin or rg 12561 or 132100-55-1 or 135910-20-2).ti,ab,ot,hw,rn. (4)
- 28 (fluindostatin or Canef or cranoc or fluindostatin sodium or fluvastatin or fluvastatin sodium or fractal lp or lescol or lescol or leucol or lochol or locol or sri 62320 or sri62320 or vastin or xu 62320 or xu62320 or 93957-54-1).ti,ab,ot,hw,rn. (1710)
- 29 (glenvastatin or hr 780 or hr780).ti,ab,ot,hw,rn. (12)
- 30 (mevinolin or altocor or altoprev or artein or belvas or Birotin or cholestra or cysin or ellanco or elstatin or l 654969 or lipidip or lipivas or lofacol or lomar or lostatin or lovacel or lovacol or lovalip or lovalord or lovastan or lovastatin or lovasterol or lovastin or lovatadin or lowachol or lozutin or medostatin or mevacor or meverstin or mevinacor or "mk 0803" or mk 803 or mk0803 or mk803 or monacolin K or monakolin k or msd 803 or neolipid or nergadan or ovasta or rodatin rovacor or taucor or 75330-75-5).ti,ab,ot,hw,rn. (5419)
- 31 (mevinolinic acid or mevinolinate or 75225-51-3).ti,ab,ot,hw,rn. (22)
- 32 (Monacolin or 76343-78-7 or 79394-47-1).ti,ab,ot,hw,rn. (125)
- 33 (pitavastatin or alipza or itavastatin or livalo or livazo or nivastatin or nk 104 or nk104 or nks 104 or nks104 or pitava or ribar or vezepa or 147526-32-7).ti,ab,ot,hw,rn. (579)
- 34 (Pravastatin or astin or bristacol or cholepar or cs 514 or cs514 or elisor or epatostantin or eptastatin or eptastatin sodium or eptastatine or kenstatin or lipemol or lipidal or liplat or lipostat or liprevil or mevalotin or novales or prareduct or prascalend or prastan or prava or pravachol or pravacol or pravaselect or pravasin or pravasine or pravator or pravyl or sanaprav or selektine or selipran or sq 31000 or sq31000 or stanidine or vasopran or vasten or xipral or 81093-37-0 or 81131-70-6).ti,ab,ot,hw,rn. (4328)
- 35 (Simvastatin or Avastinee or cholestat or clinfar or colastatina or colestricon or covastin or denan or epistatin or esvat or ethical or eucor or ifistatin or kavelor or klonastin or kolestevan or l 644128 or l644128 or lipecor or lipex or lipinorm or liponorm or lipovas or lodales or medipo or mersivas or mk 733 or mk733 or nor-vastina or normofat or orovas or rechol or simbado or simcard or simchol or simovil or simtin or simvacor or simvahex or simvalord or simvastar or simvata or simvatin or simvor or simvotin or sinvacor or simvastatin or sinvinolin or sivastin or starzoco or synvinolin or torio or valemia or vasilip or vasotenal or vazim or vidastat or zimmex or Zocor or zocor forte or zocord or zovast or 79902-63-9).ti,ab,ot,hw,rn. (62628)
- 36 (Rosuvastatin or crestor or rosuvas or s 4522 or s4522 or zd 4522 or zd4522 or 147098-18 or 147098-20-2).ti,ab,ot,hw,rn. (2243)
- 37 tenivastatin.ti,ab,ot,hw,rn. (0)
- 38 or/22-37 (98635)
- 39 (evolocumab or 1256937-27-5 or AMG-145 or amg145).af. (63)
- 40 (ezetimibe or zetia or ezetrol or ezetib or sch 582235 or sch58235 or 163222-33-1).af. (1891)
- 41 (Alirocumab or regn 727 or regn727 or sar 236553 or sar236553 or 1245916-14-6).af. (50)
- 42 (bococizumab or "pf 04950615" or pf04950615 or rn 316 or rn 316 or 1407495-02-6).af. (2)
- 43 (((PCSK-9 or PCSK9 or PCSK 9) adj2 inhibit\$) or (anti-PCSK-9 or anti PCSK-9)).ti,ab,ot,hw. (164)
- 44 or/39-43 (2070)
- 45 nicotinic acids/ or niacin/ (14288)
- 46 (acipimox or acipemox or olbetam or albermox or 51037-30-0).ti,ab,ot,hw,rn. (304)
- 47 (vitamin B3 or vitamin PP or 54-86-4 or 59-67-6 or acido nicotinico or acidum nicotinicum or akotin or apelagrin or apo-nicotinic acid or beta pyridine carboxylic acid or bionic or davitamon pp or direktan or direktane or efacin or efasin or endur acin or enduracin or naotin or natinat or niac or niacin\$ or niacor or Niaspan or nicacid or nicangin or nico or

nicobid or nicocap or nicocidin or nicocrisina or nicodan or nicodane or nicolar or niconacid or niconacide or nicoseptin wirkstoff or nicosode or nicospan or nicosyl or nicotabs or nicotamin or nicotine or nicotin acid or nicotinat or nicotinate or nicotinese or nicotinipca or nicotyl or nicovasen or nicyl or nikacid or nipellan or novoniacin or nyacine or nyclin or pellagramin or pellagramine or pellagrins or pelonin or pelonine or pepevit or peviton or pp factor or "pyridine 3 carbonic acid" or pyridine beta carboxylic acid or "s 115" or slo niacin or sodium nicotinate or vasotherm or vitaplex n or wampocap or wampopap).ti,ab,ot,hw,rn. (52747)

48 or/45-47 (60343)

49 Cholestyramine Resin/ (2596)

50 (((bile adj2 acid) or anion exchange) adj2 (sequestrant\$ or resin\$)).ti,ab,hw,ot. (2694)

51 (chol-less or choles or cholesthexal or cholestyramin\$ or cholybar or cholytar or colestepiril or colestiramina or colestran or colestrol or colestyramin or cuemid or lipocol-merz or lismol or locholest or prevalite or quantalan or questran or resincoles\$ or vasosan or 11041-12-6 or 58391-37-0).ti,ab,ot,hw,rn. (3368)

52 (colestipol or cholestabyl or cholestipol or colestid or lestid or u 26597a or "u 26797 a" or 25085-17-0 or 37296-80-3 or 50925-79-6).ti,ab,ot,hw,rn. (534)

53 (Colesevelam or cholestagel or gt 31 104 or gt 31 104hb or gt 31-104 or gt 31-104hb or gt31 104 or gt31 104hb or gt31-104 or gt31-104hb or welchol or 182815-43-6 or 182815-44-7).ti,ab,ot,hw,rn. (231)

54 or/49-53 (6089)

55 fibric acids/ or bezafibrate/ or fenofibrate/ or gemfibrozil/ (4751)

56 (fibrate\$ or fibric acid\$ or arhalofenate or atomid or beclobrate or beclobrinic acid or bezafibrate or biclofibrate or binifibrate or choline fenofibrate or ciprofibrate or clinofibrate or clofibrate or clofibrate aluminium or clofibric acid or clofibrade or dulofibrate or eniclobrate or etofibrate or etofylline clofibrate or fenirofibrat or fenofibric acid or halofenate or lifibrate or methylclofenapate or nicofibrate or picafibrate or pirifibrate or ponfibrate or ronifibrate or salafibrate or serfibrate or simfibrate or sitofibrate or tazasubrate or tiadenol diclofibrate or timofibrate or tocofibrate or urefibrate or xantifibrate).ti,ab,ot,hw,rn. (9382)

57 (Bezafibrate\$ or befizal or benzaifibrate or benzofibrate or bezafibrate retard or bezalip or bezatol or bezifal or bezofibrate or bf 759 or bf759 or bm 15075 or bm15075 or cedur or lo 44 or lo44 or norlip or 41859-67-0).ti,ab,ot,hw,rn. (1507)

58 (Ciprofibrate\$ or lipanor or modalim or win 35833 or 52214-84-3).ti,ab,ot,hw,rn. (532)

59 (Fenofibrate\$ or Antara or apo-feno-micro or aterolis or bisterol\$ or climage or controlip or durafenat or evothyl or fegenor or felosma or fenobrate or fenofanton or fenogal or fenoglide or fenox or fibrafen or "grs 001" or hyperchol or katalip or lexemin or lipanthyl or lipantil or lipantyl or liparison or lipidax or lipidil or lipilo or lipirex or lipoclar or lipofen or lipolin or liposit or lipsin or livesan ge or lofibra or nopid 200 or normalip or nubrex or procetofen or procetofenate or procetofene or proketofen or qualipantyl or rapidil or redose 200 or rorit or secalip or sigurtill or trichol or tricor or triglide or trolip or zerlubron or zumafib or 49562-28-9).ti,ab,ot,hw,rn. (2825)

60 (gemfibrozil or ausgem or bolutol or brozil or chlorestrol or cholespid or ci 719 or ci719 or clearol or decrelip or detrichol or elmogan or fetinor or fibralip or fibrocit or gedum or gemfi\$ or gemizol or gemlipidor gemnpid or gemzil or genfibrozil or gevilon\$ or gozid or grifogemzilo or hidil or hipolixan or ipolipid or jezil or lanaterom or lifibron or lipazil or lipidys or lipigem or lipira or lipison or lipistorol or lipizyl or lipofor or lipolo or lipostorol or lipozid or lipozil or lipur or lupid\$ or low-lip or lowin or manobrozil or mariston or mersikol or normolipor panazil or polyxit or progemzal or recozil or reducelor regulip or synbrozil or triglizil or uragem or zilop or 25812-30-0).ti,ab,ot,hw,rn,tn. (1935)

61 or/55-60 (12497)

62 (lomitapide or lojuxta or Juxtapid or 182431-12-5 or 202833-31-6 or 202914-84-9 or 210823-48-6 or aegr 733 or aegr733 or bms 201038\$).af. (62)

63 exp Blood Component Removal/ or apheresis.ti,ab,hw,ot. (18854)

64 (anacetrapib or "mk 0859" or mk 859 or mk0859 or mk859 or 875446-37-0).af. (126)

65 (mipomersen or isis 301012 or isis301012 or kynamro or 629167-92-6).af. (118)

66 38 or 44 or 48 or 54 or 61 or 62 or 63 or 64 or 65 (191046)
 67 21 and 66 (19915)
 68 randomized controlled trial.pt. or "randomized controlled trials as topic"/ (503390)
 69 controlled clinical trial.pt. (91347)
 70 random\$.ti.ot. (121794)
 71 placebo.ab. (156211)
 72 drug therapy.fs. (1821671)
 73 random\$.ab. (691199)
 74 trial.ab. (311554)
 75 groups.ab. (1341743)
 76 or/68-75 (3585739)
 77 animals/ not (animals/ and humans/) (3998271)
 78 76 not 77 (3059128)
 79 67 and 78 (13499)
 80 17 not 79 (84)

Based on Trials filter:

Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Medline In-Process Citations (OvidSP): up to 2015/8/17

Medline Daily Update (OvidSP): up to 2015/8/17

Searched: 17.8.15

1 Dyslipidemias/ (13)
 2 (dyslipidemia\$ or dyslipaemia\$ or dyslipemia\$ or dyslipidaemia\$).ti,ab,ot,hw. (2866)
 3 or/1-2 (2866)
 4 (ezetimibe or zetia or ezetrol or ezetib or sch 582235 or sch58235 or 163222-33-1).af.
 (292)
 5 3 and 4 (46)
 6 randomized controlled trial.pt. or "randomized controlled trials as topic"/ (994)
 7 controlled clinical trial.pt. (57)
 8 random\$.ti.ot. (18231)
 9 placebo.ab. (11252)
 10 drug therapy.fs. (1119)
 11 random\$.ab. (84990)
 12 trial.ab. (33952)
 13 groups.ab. (149665)
 14 or/6-13 (226942)
 15 exp animals/ not (exp animals/ and humans/) (1529)
 16 14 not 15 (226574)
 17 5 and 16 (18)
 18 exp hyperlipidemias/ (14)
 19 (hypercholesterol?emi\$ or hypercholesterin?emi\$ or cholester?emi\$ or
 cholesterin?emi\$ or hyperlipid?emi\$ or hyperlipoprotein?emia\$ or lip?emia\$ or lipid?emi\$ or
 hyperlip?emi\$ or hefh or hofh or fh or hypertriglycerid?emia\$ or mckusick 14575 or
 triglycerid?emia\$ or (triglyceride adj1 storage adj1 disease\$)).ti,ab,ot,hw. (4694)
 20 ((cholesterol\$ or lipid\$ or LDL) adj3 (elevat\$ or ascend\$ or increas\$ or high or
 rais\$)).ti,ab,ot,hw. (5978)

- 21 or/18-20 (9809)
- 22 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (22)
- 23 (statin\$ or hydroxymethylglutaryl coenzyme A reductase inhibit\$ or HMG CoA reductase inhibit\$ or HMGCoA reductase inhibit\$).ti,ab,ot,hw. (3242)
- 24 (atorvastatin or Lipitor or torvast or atorlip or atovarol or ci 981 or ci981 or glustar or lipibec or lowlipen or sortis or storvas or tahor or ym 548 or ym548 or zarator or 134523-00-5 or 134523-03-8).ti,ab,ot,hw,rn. (689)
- 25 (Bervastatin or Is 2904 or Is2904 or 132017-01-7).ti,ab,ot,hw,rn. (0)
- 26 (crilvastatin or pmd 387 or pmd387 or 120551-59-9).ti,ab,ot,hw,rn. (0)
- 27 (dalvastatin or rg 12561 or 132100-55-1 or 135910-20-2).ti,ab,ot,hw,rn. (0)
- 28 (fluindostatin or Canef or cranoc or fluindostatin sodium or fluvastatin or fluvastatin sodium or fractal lp or lescol or lescol or leucol or lochol or local or sri 62320 or sri62320 or vastin or xu 62320 or xu62320 or 93957-54-1).ti,ab,ot,hw,rn. (79)
- 29 (glenvastatin or hr 780 or hr780).ti,ab,ot,hw,rn. (2)
- 30 (mevinolin or altocor or altoprev or artein or belvas or Birotin or cholestra or cysin or ellanco or elstatin or I 654969 or lipidip or lipivas or lofacol or lomar or lostatin or lovacel or lovacol or lovalip or lovalord or lovastan or lovastatin or lovasterol or lovastin or lovatin or lovachol or lozutin or medostatin or mevacor or meverstin or mevinacor or "mk 0803" or mk 803 or mk0803 or mk803 or monacolin K or monakolin k or msd 803 or neolipid or nergadan or ovasta or rodatin rovacor or taucor or 75330-75-5).ti,ab,ot,hw,rn. (184)
- 31 (mevinolinic acid or mevinolinate or 75225-51-3).ti,ab,ot,hw,rn. (0)
- 32 (Monacolin or 76343-78-7 or 79394-47-1).ti,ab,ot,hw,rn. (16)
- 33 (pitavastatin or alipza or itavastatin or livalo or livazo or nivastatin or nk 104 or nk104 or nks 104 or nks104 or pitava or ribar or vezepa or 147526-32-7).ti,ab,ot,hw,rn. (69)
- 34 (Pravastatin or astin or bristacol or cholestpar or cs 514 or cs514 or elisor or eptastatin or eptastatin sodium or eptastatine or kenstatin or lipemol or lipidal or liplat or lipostat or liprevil or mevalotin or novales or prareduct or prascolend or prastan or prava or pravachol or pravacol or pravaselect or pravasin or pravasine or pravator or pravyl or sanaprav or selektine or selipran or sq 31000 or sq31000 or stanidine or vasopran or vasten or xipral or 81093-37-0 or 81131-70-6).ti,ab,ot,hw,rn. (189)
- 35 (Simvastatin or Avastinee or cholestat or clinfar or colastatina or colestricon or covastin or denan or epistatin or esvat or ethical or eucor or ifistatin or kavelor or klonastin or kolestevan or I 644128 or I644128 or lipecor or lipex or lipinorm or liponorm or lipovas or lodales or medipo or mersivas or mk 733 or mk733 or nor-vastina or normofat or orovas or rechol or simbado or simcard or simchol or simovil or simtin or simvacor or simvahex or simvalord or simvastar or simvata or simvatin or simvor or simvotin or sinvacor or simvastatin or sinvinolin or sivastin or starzoco or synvinolin or torio or valemia or vasilip or vasotenal or vazim or vidastat or zimmex or Zocor or zocor forte or zocord or zovast or 79902-63-9).ti,ab,ot,hw,rn. (5729)
- 36 (Rosuvastatin or crestor or rosuvas or s 4522 or s4522 or zd 4522 or zd4522 or 147098-18 or 147098-20-2).ti,ab,ot,hw,rn. (310)
- 37 tenivastatin.ti,ab,ot,hw,rn. (0)
- 38 or/22-37 (9321)
- 39 (evolocumab or 1256937-27-5 or AMG-145 or amg145).af. (15)
- 40 (ezetimibe or zetia or ezetrol or ezetib or sch 582235 or sch58235 or 163222-33-1).af. (292)
- 41 (Alirocumab or regn 727 or regn727 or sar 236553 or sar236553 or 1245916-14-6).af. (18)
- 42 (bococizumab or "pf 04950615" or pf04950615 or rn 316 or rn 316 or 1407495-02-6).af. (2)
- 43 (((PCSK-9 or PCSK9 or PCSK 9) adj2 inhibit\$) or (anti-PCSK-9 or anti PCSK-9)).ti,ab,ot,hw. (51)
- 44 or/39-43 (347)
- 45 nicotinic acids/ or niacin/ (4)
- 46 (acipimox or acipemox or olbetam or albermox or 51037-30-0).ti,ab,ot,hw,rn. (4)

- 47 (vitamin B3 or vitamin PP or 54-86-4 or 59-67-6 or acido nicotinic or acidum nicotinicum or akotin or apelagrin or apo-nicotinic acid or beta pyridine carboxylic acid or bionic or davitamon pp or direktan or direktane or efacin or efasin or enduracin or naotin or natinat or niac or niacin\$ or niacor or Niaspan or nicacid or nicangin or nico or nicobid or nicocap or nicocidin or nicocrisina or nicodan or nicodane or nicolar or niconacid or niconacide or nicoseptin wirkstoff or nicosode or nicospan or nicosyl or nicotabs or nicotamin or nicotine or nicotin acid or nicotinat or nicotinate or nicotinese or nicotinipca or nicotyl or nicovasen or nicyl or nikacid or nipellan or novoniacin or nyacine or nyclin or pellagramin or pellagramine or pellagrin\$ or pelonin or pelonine or pepevit or peviton or pp factor or "pyridine 3 carbonic acid" or pyridine beta carboxylic acid or "s 115" or slo niacin or sodium nicotinate or vasotherm or vitaplex n or wampocap or wampopap).ti,ab,ot,hw,rn. (2833)
- 48 or/45-47 (2839)
- 49 Cholestyramine Resin/ (0)
- 50 (((bile adj2 acid) or anion exchange) adj2 (sequestrant\$ or resin\$)).ti,ab,hw,ot. (262)
- 51 (chol-less or choles or cholesthexal or cholestyramin\$ or cholybar or cholytar or colestepiril or colestiramina or colestran or colestrol or colestyramin or cuemid or lipocol-merz or lismol or locholest or prevalite or quantalan or questran or resincoles\$ or vasosan or 11041-12-6 or 58391-37-0).ti,ab,ot,hw,rn. (54)
- 52 (colestipol or cholestabyl or cholestipol or colestid or lestid or u 26597a or "u 26797 a" or 25085-17-0 or 37296-80-3 or 50925-79-6).ti,ab,ot,hw,rn. (9)
- 53 (Colesevelam or cholestagel or gt 31 104 or gt 31 104hb or gt 31-104 or gt 31-104hb or gt31 104 or gt31 104hb or gt31-104 or gt31-104hb or welchol or 182815-43-6 or 182815-44-7).ti,ab,ot,hw,rn. (29)
- 54 or/49-53 (329)
- 55 fibric acids/ or bezafibrate/ or fenofibrate/ or gemfibrozil/ (3)
- 56 (fibrate\$ or fibric acid\$ or arhalofenate or atomid or beclobrate or beclobrinic acid or bezafibrate or biclofibrate or binifibrate or choline fenofibrate or ciprofibrate or clinofibrate or clofibrate or clofibrate aluminium or clofibric acid or clofibrade or dulofibrate or eniclobrate or etofibrate or etofylline clofibrate or fenirofibrat or fenofibric acid or halofenate or lifibrate or methylclofenapate or nicofibrate or picafibrate or pirifibrate or ponfibrate or ronifibrate or salafibrate or serfibrate or simfibrate or sitofibrate or tazasubrate or tiadenol diclofibrate or timofibrate or tocofibrate or urefibrate or xantifibrate).ti,ab,ot,hw,rn. (351)
- 57 (Bezafibrate\$ or befizal or benzafibrate or benzofibrate or bezafibrate retard or bezalip or bezatol or bezifal or bezofibrate or bf 759 or bf759 or bm 15075 or bm15075 or cedur or lo 44 or lo44 or norlip or 41859-67-0).ti,ab,ot,hw,rn. (72)
- 58 (Ciprofibrate\$ or lipanor or modalim or win 35833 or 52214-84-3).ti,ab,ot,hw,rn. (16)
- 59 (Fenofibrate\$ or Antara or apo-feno-micro or aterolis or bisterol\$ or climage or controlip or durafenat or evothyl or fegenor or felosma or fenobrate or fenofanton or fenogal or fenoglide or fenox or fibrafen or "grs 001" or hyperchol or katalip or lexemin or lipanthyl or lipantil or lipantyl or liparison or lipidax or lipidil or lipilo or lipirex or lipoclar or lipofen or lipolin or liposit or lipsin or livesan ge or lofibra or nopid 200 or normalip or nubrex or procetofen or procetofenate or procetofene or proketofen or qualipantyl or rapidil or redose 200 or rorit or secalip or sigurtill or trichol or tricolor or triglide or trolip or zerlubron or zumafib or 49562-28-9).ti,ab,ot,hw,rn. (261)
- 60 (gemfibrozil or ausgem or bolutol or brozil or chlorestrol or cholespid or ci 719 or ci719 or clearol or decrelip or detrichol or elmogan or fetinor or fibrilip or fibrocit or gedum or gemfi\$ or gemizol or gemlipidor gemnpid or gemzil or genfibrozil or gevilon\$ or gozid or grifogemzilo or hidil or hipolixan or ipolipid or jezil or lanaterom or lifibron or lipazil or lipidys or lipigem or lipira or lipison or lipistorol or lipizyl or lipofor or lipolo or lipostorol or lipozil or lipozil or lipur or lipid\$ or low-lip or lowin or manobrozil or mariston or mersikol or normolipor panazil or polyxit or progemzal or recozil or reducelor regulip or synbrozil or triglizil or uragem or zilop or 25812-30-0).ti,ab,ot,hw,rn,tn. (107)
- 61 or/55-60 (618)

62 (lomitapide or lojuxta or Juxtapid or 182431-12-5 or 202833-31-6 or 202914-84-9 or
 210823-48-6 or aegr 733 or aegr733 or bms 201038\$).af. (29)
 63 exp Blood Component Removal/ or apheresis.ti,ab,hw,ot. (342)
 64 (anacetrapib or "mk 0859" or mk 859 or mk0859 or mk859 or 875446-37-0).af. (18)
 65 (mipomersen or isis 301012 or isis301012 or kynamro or 629167-92-6).af. (33)
 66 38 or 44 or 48 or 54 or 61 or 62 or 63 or 64 or 65 (13210)
 67 21 and 66 (1168)
 68 randomized controlled trial.pt. or "randomized controlled trials as topic"/ (994)
 69 controlled clinical trial.pt. (57)
 70 random\$.ti,ot. (18231)
 71 placebo.ab. (11252)
 72 drug therapy.fs. (1119)
 73 random\$.ab. (84990)
 74 trial.ab. (33952)
 75 groups.ab. (149665)
 76 or/68-75 (226942)
 77 animals/ not (animals/ and humans/) (1526)
 78 76 not 77 (226574)
 79 67 and 78 (427)
 80 17 not 79 (6)

Based on Trials filter:

Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Cochrane Database of Systematic Reviews (CDSR) (Wiley). To Issue 8/August 2015
 Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley). To Issue 7/ July 2015

Database of Abstracts of Reviews of Effects (DARE) (Wiley). To Issue 2/ April 2015
 Searched: 17.8.15

ID	SearchHits
#1	MeSH descriptor: [Dyslipidemias] explode all trees 5025
#2	(dyslipidemia* or dyslipaemia* or dyslipemia* or dyslipidaemia*) 2344
#3	#1 or #2 6627
#4	(ezetimibe or zetia or ezetrol or ezetib or sch 582235 or sch58235 or 163222-33-1) 671
#5	#3 and #4 258
#6	MeSH descriptor: [Hyperlipidemias] explode all trees 4617
#7	(hypercholesterol?emi* or hypercholesterin?emi* or cholester?emi* or cholesterin?emi* or hyperlipid?emi* or hyperlipoprotein?emia* or lip?emia* or lipid?emi* or hyperlip?emi* or hefh or hofh or fh or hypertriglycerid?emia* or mckusick 14575 or triglycerid?emia* or (triglyceride near/1 storage near/1 disease*)):ti,ab,kw 1766
#8	((cholesterol* or lipid* or LDL) near/3 (elevat* or ascend* or increase* or high or rais*)):ti,ab,kw 9283
#9	#6 or #7 or #8 13037
#10	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees 2850
#11	(statin* or hydroxymethylglutaryl coenzyme A reductase inhibit* or HMG CoA reductase inhibit* or HMGCoA reductase inhibit*):ti,ab,kw 5776

Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

#12 (atorvastatin or Lipitor or torvast or atorlip or atovarol or ci 981 or ci981 or glustar or lipibec or lowlipen or sortis or storvas or tahor or ym 548 or ym548 or zarator or 134523-00-5 or 134523-03-8):ti,ab,kw 3006

#13 (Bervastatin or ls 2904 or ls2904 or 132017-01-7):ti,ab,kw 0

#14 (crilvastatin or pmd 387 or pmd387 or 120551-59-9):ti,ab,kw 0

#15 (dalvastatin or rg 12561 or 132100-55-1 or 135910-20-2):ti,ab,kw 0

#16 (fluindostatin or Canef or cranoc or fluindostatin sodium or fluvastatin or fluvastatin sodium or fractal lp or lescol or lescol or leucol or lochol or locol or locol or sri 62320 or sri62320 or vastin or xu 62320 or xu62320 or 93957-54-1):ti,ab,kw 576

#17 (glenvastatin or hr 780 or hr780):ti,ab,kw 14

#18 (mevinolin or altocor or altoprev or artein or belvas or Birotin or cholestra or cysin or ellanco or elstatin or l 654969 or lipidip or lipivas or lofacol or lomar or lostatin or lovacel or lovacol or lovalip or lovalord or lovastan or lovastatin or lovasterol or lovastin or lovatadin or lowachol or lozutin or medostatin or mevacor or meverstin or mevinacor or "mk 0803" or mk 803 or mk0803 or mk803 or monacolin K or monakolin k or msd 803 or neolipid or nergadan or ovasta or rodatin rovacor or taucor or 75330-75-5):ti,ab,kw 846

#19 (mevinolinic acid or mevinolate or 75225-51-3):ti,ab,kw 1

#20 (Monacolin or 76343-78-7 or 79394-47-1):ti,ab,kw 5

#21 (pitavastatin or alipza or itavastatin or livalo or livazo or nivastatin or nk 104 or nk104 or nks 104 or nks104 or pitava or ribar or vezepa or 147526-32-7):ti,ab,kw 172

#22 (Pravastatin or astin or bristacol or cholestpar or cs 514 or cs514 or elisor or eptastantin or eptastatin or eptastatin sodium or eptastatine or kenstatin or lipemol or lipidal or liplat or lipostat or liprevil or mevalotin or novales or prareduct or prascalend or prastan or prava or pravachol or pravacol or pravaselect or pravasin or pravasine or pravator or pravyl or sanaprav or selektine or selipran or sq 31000 or sq31000 or stanidine or vasopran or vasten or xipral or 81093-37-0 or 81131-70-6):ti,ab,kw 1514

#23 (Simvastatin or Avastinee or cholestat or clinfar or colastatina or colestricon or covastin or denan or epistatin or esvat or ethical or eucor or ifistatin or kavelor or klonastin or kolestevan or l 644128 or l644128 or lipecor or lipex or lipinorm or liponorm or lipovas or lodales or medipo or mersivas or mk 733 or mk733 or nor-vastina or normofat or orovas or rechol or simbado or simcard or simchol or simovil or simtin or simvacor or simvahex or simvalord or simvastar or simvata or simvatin or simvor or simvotin or sinvacor or simvastatin or sinvinolin or sivastin or starzoco or synvinolin or torio or valemia or vasilip or vasotenal or vazim or vidastat or zimmex or Zocor or zocor forte or zocord or zovast or 79902-63-9):ti,ab,kw 4304

#24 (Rosuvastatin or crestor or rosuvast or s 4522 or s4522 or zd 4522 or zd4522 or 147098-18 or 147098-20-2):ti,ab,kw 1075

#25 tenivastatin:ti,ab,kw 0

#26 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 11959

#27 (evolocumab or 1256937-27-5 or AMG-145 or amg145) 46

#28 (ezetimibe or zetia or ezetrol or ezetib or sch 582235 or sch582235 or 163222-33-1) 671

#29 (Alirocumab or regn 727 or regn727 or sar 236553 or sar236553 or 1245916-14-6) 31

#30 (((PCSK-9 or PCSK9 or PCSK 9) near/2 inhibit*) or (anti-PCSK-9 or anti PCSK-9)):ti,ab,kw 25

#31 (bococizumab or "pf 04950615" or pf04950615 or rn 316 or rn 316 or 1407495-02-6) 32

#32 #27 or #28 or #29 or #30 or #31 746

#33 MeSH descriptor: [Nicotinic Acids] this term only 333

#34 MeSH descriptor: [Niacin] this term only 312

#35 #33 or #34 636

#36 (acipimox or acipemox or olbetam or albermox or 51037-30-0):ti,ab,kw 132

#37 (vitamin B3 or vitamin PP or 54-86-4 or 59-67-6 or acido nicotinic or acidum nicotinicum or akotin or apelagrin or apo-nicotinic acid or beta pyridine carboxylic acid or bionic or davitamon pp or direktan or direktane or efacin or efasin or enduracin or naotin or natinat or niac or niacin* or niacor or Niaspan or nicacid or nicangin or nico or nicobid or nicocap or nicocidin or nicocrisina or nicodan or nicodane or nicolar or niconacid or niconacide or nicoseptin wirkstoff or nicosode or nicospan or nicosyl or nicotabs or nicotamin or nicotine or nicotin acid or nicotinat or nicotinate or nicotinese or nicotinipca or nicotyl or nicovasen or nicyl or nikacid or nipellan or novoniacin or nyacine or nyclin or pellagramin or pellagramine or pellagrin* or pelonin or pelonine or pepevit or peviton or pp factor or "pyridine 3 carbonic acid" or pyridine beta carboxylic acid or "s 115" or slo niacin or sodium nicotinate or vasotherm or vitaplex n or wampocap or wampopap):ti,ab,kw 4847

#38 #35 or #36 or #37 5245

#39 MeSH descriptor: [Cholestyramine Resin] this term only 258

#40 (((bile near/2 acid) or anion exchange) near/2 (sequestrant* or resin*)):ti,ab,kw 146

#41 (chol-less or choles or cholesthexal or cholestyramin* or cholybar or cholytar or colestepiril or colestiramina or colestran or colestrol or colestyramin or cuemid or lipocolmerz or lismol or locholest or prevalite or quantalan or questran or resincoles* or vasosan or 11041-12-6 or 58391-37-0):ti,ab,kw 411

#42 (colestipol or cholestabyl or cholestipol or colestid or lestid or u 26597a or "u 26797 a" or 25085-17-0 or 37296-80-3 or 50925-79-6):ti,ab,kw 156

#43 (Colesevelam or cholestagel or gt 31 104 or gt 31 104hb or gt 31-104 or gt 31-104hb or gt31 104 or gt31 104hb or gt31-104 or gt31-104hb or welchol or 182815-43-6 or 182815-44-7):ti,ab,kw 99

#44 #39 or #40 or #41 or #42 or #43 677

#45 MeSH descriptor: [Fibric Acids] this term only 37

#46 MeSH descriptor: [Bezafibrate] this term only 201

#47 MeSH descriptor: [Fenofibrate] this term only 360

#48 MeSH descriptor: [Gemfibrozil] this term only 302

#49 #45 or #46 or #47 or #48 848

#50 (fibrate* or fibric acid* or arhalofenate or atomid or beclobrate or beclobrinic acid or bezafibrate or biclofibrate or binifibrate or choline fenofibrate or ciprofibrate or clinofibrate or clofibrate or clofibrate aluminium or clofibric acid or clofibrade or dulofibrate or eniclobrate or etofibrate or etofylline clofibrate or fenirolfibrat or fenofibric acid or halofenate or lifibrate or methylclofenapate or nicofibrate or picafibrate or pirifibrate or ponfibrate or ronifibrate or salafibrate or serfibrate or simfibrate or sitofibrate or tazasubrate or tiadenol diclofibrate or timofibrate or tocofibrate or urefibrate or xantifibrate):ti,ab,kw 1089

#51 (Bezafibrate* or befizal or benzafibrate or benzofibrate or bezafibrate retard or bezalip or bezatol or bezifal or bezofibrate or bf 759 or bf759 or bm 15075 or bm15075 or cedur or lo 44 or lo44 or norlip or 41859-67-0):ti,ab,kw 390

#52 (Ciprofibrate* or lipanor or modalim or win 35833 or 52214-84-3):ti,ab,kw 34

#53 (Fenofibrate* or Antara or apo-feno-micro or aterolis or bisterol* or climage or controlip or durafenat or evothyl or fegenor or felosma or fenobrate or fenofanton or fenogal or fenoglide or fenox or fibrafen or "grs 001" or hyperchol or katalip or lexemin or lipanthyl or lipantil or lipantyl or liparison or lipidax or lipidil or lipilo or lipirex or lipoclar or lipofen or lipolin or liposit or lipsin or livesan ge or lofibra or nolid 200 or normalip or nubrex or procetofen or procetofenate or procetofene or proketofen or qualipantyl or rapidil or redose 200 or rorit or secalip or sigurtil or trichol or tricolor or triglide or trolip or zerlubron or zumafib or 49562-28-9):ti,ab,kw 645

#54 (gemfibrozil or ausgem or bolutol or brozil or chlorestrol or cholespid or ci 719 or ci719 or clearol or decrelip or detrichol or elmogan or fetinor or fibrilip or fibrocit or gedum or gemfi* or gemizol or gemlipidor gemnpid or gemzil or genfibrozil or gevilon* or gozid or grifogemzilo or hidil or hipolixan or ipolipid or jezil or lanaterom or lifibron or lipazil or lipidys or lipigem or lipira or lipison or lipistorol or lipizyl or lipofor or lipolo or lipostorol or lipozid or lipozil or lipur or lipid* or low-lip or lowin or manobrozil or mariston or mersikol or normolipor

panazil or polyxit or progemzal or recozil or reducelor regulip or synbrozil or triglizil or uragem
or zilop or 25812-30-0):ti,ab,kw 531

#55 #49 or #50 or #51 or #52 or #53 or #54 1959

#56 (lomitapide or lojuxta or Juxtapid or 182431-12-5 or 202833-31-6 or 202914-84-9 or
210823-48-6 or aegr 733 or aegr733 or bms 201038*) 5

#57 MeSH descriptor: [Blood Component Removal] explode all trees 739

#58 apheresis:ti,ab,kw 549

#59 (anacetrapib or "mk 0859" or mk 859 or mk0859 or mk859 or 875446-37-0) 37

#60 (mipomersen or isis 301012 or isis301012 or kynamro or 629167-92-6) 29

#61 #26 or #32 or #38 or #44 or #55 or #56 or #57 or #58 or #59 or #60 19706

#62 #9 and #61 4382

#63 #5 not #62 34

Appendix II: Systematic literature review - cost-effectiveness studies

MEDLINE Search Strategy and Results SIGN FILTER

No.	Query	Results
#1	Economics/	26830
#2	"costs and cost analysis"/	43317
#3	Cost allocation/	1969
#4	Cost-benefit analysis/	64044
#5	Cost control/	20696
#6	Cost savings/	9410
#7	Cost of illness/	19702
#8	Cost sharing/	2069
#9	"deductibles and coinsurance"/	1485
#10	Medical savings accounts/	492
#11	Health care costs/	29707
#12	Direct service costs/	1067
#13	Drug costs/	13083
#14	Employer health costs/	1074
#15	Hospital costs/	8442
#16	Health expenditures/	14739
#17	Capital expenditures/	1964
#18	Value of life/	5499
#19	exp economics, hospital/	20677
#20	exp economics, medical/	13920
#21	Economics, nursing/	3933
#22	Economics, pharmaceutical/	2603
#23	exp "fees and charges"/	27813
#24	exp budgets/	12523
#25	(low adj cost).mp.	30006
#26	(high adj cost).mp.	9152
#27	(health?care adj cost\$).mp.	5645
#28	(fiscal or funding or financial or finance).tw.	95203
#29	(cost adj estimate\$).mp.	1603

No.	Query	Results
#30	(cost adj variable).mp.	37
#31	(unit adj cost\$).mp.	1758
#32	(economic\$ or pharmacoeconomic\$ or price\$ or pricing).tw.	197785
#33	or/1-32	520545
#34	cardiovascular diseases/	109138
#35	heart diseases/	57646
#36	myocardial ischemia/	33804
#37	exp angina pectoris/	48776
#38	coronary disease/	128467
#39	coronary artery disease/	41994
#40	exp coronary stenosis/	14319
#41	myocardial infarction/	147710
#42	exp heart failure/	93060
#43	arrhythmias, cardiac/ or atrial fibrillation/	89617
#44	vascular diseases/	27598
#45	hypertension/	200813
#46	atherosclerosis/	23223
#47	peripheral arterial disease/	2902
#48	peripheral vascular diseases/	11290
#49	cerebrovascular disorders/	44689
#50	exp stroke/	95053
#51	exp brain ischemia/	87591
#52	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event\$ or disease\$)).ti,ab.	138585
#53	((coronary or peripheral vascular or heart or peripheral arter\$) adj3 (disease\$ or event\$)).ti,ab.	230024
#54	(mi or myocardial infarct\$ or myocardial infarction).ti,ab.	169179
#55	(cvd or chd or cad or pad or cva or hypertension).ti,ab.	371435
#56	(atheroscleros\$ or arterioscleros\$).ti,ab.	98307
#57	(cerebrovascular accident\$ or stroke\$).ti,ab.	173484
#58	(acs or angina or acute coronary syndrome\$).ti,ab.	68418
#59	(af or atrial fibrillation).ti,ab.	54020
#60	((chronic or congestive) adj2 heart failure).ti,ab.	45211

No.	Query	Results
#61	or/34-60	1463946
#62	exp Lipoproteins, LDL/	45698
#63	(LDL or LDL-C).mp.	81337
#64	low density lipoprotein*.mp.	61633
#65	or/62-64	100181
#66	*Hydroxymethylglutaryl-CoA Reductase Inhibitors/	16541
#67	statin*.ti,ab.	30041
#68	((Hydroxymethylglutaryl-CoA or HMG-CoA) adj3 (reductase or inhibitors)).ti,ab.	7308
#69	exp *simvastatin/	4005
#70	(simvastatin* or zocor).ti,ab.	7367
#71	(atorvastatin* or lipitor).ti,ab.	6213
#72	(rosuvastatin* or crestor).ti,ab.	2255
#73	exp *pravastatin/	1989
#74	(pravastatin* or lipostat).ti,ab.	3581
#75	(fluvastatin* or lescol).ti,ab.	1600
#76	or/66-75	44805
#77	exp anion exchange resins/	3988
#78	((anion exchange or anionic exchange) adj2 resin*).ti,ab.	1354
#79	((anion or anionic) adj2 exchanger*).ti,ab.	2335
#80	(cholestyramin* or colestyramin* or colestimide or cholybar or colextran or colestilan or cholestagel or cholestipol or colestipol or colestid or questran* or quantalan* or cuemid* or colesevelam).ti,ab.	2843
#81	(bile acid adj3 (sequestrant* or sequestering agent* or resin*)).ti,ab.	758
#82	or/77-81	8578
#83	exp fibric acids/	8865
#84	(fibrate* or bezafibrate or clofibrate or fenofibrate or lopid or gemfibrozil or bezalip or tricor or fibracor or lipantil or supralip or modalim or ciprofibrate).ti,ab.	9920
#85	((fibric or fenofibric or clofibric) adj2 acid*).ti,ab.	1281
#86	or/83-85	12648
#87	nicotinic acids/ or niacin/	14292
#88	nicotinic.ti,ab.	24337
#89	niacin.ti,ab.	3915

No.	Query	Results
#90	(nicotinate* or acipimox or acipemox).ti,ab.	1456
#91	(olbetam or niaspan or tredaptive).ti,ab.	89
#92	((3 pyridinecarboxylic or 3-pyridinecarboxylic) adj3 acid).ti,ab.	68
#93	or/87-92	37879
#94	exp fish oils/	21061
#95	fatty acids, unsaturated/ or exp fatty acids, omega-3/	32472
#96	dietary fats, unsaturated/	4687
#97	(fish adj3 oil*).ti,ab.	8716
#98	(omega 3 or omega-3).ti,ab.	9248
#99	((n 3 or n3 or n-3) adj3 ((fatty adj3 acid*) or PUFA*)).ti,ab.	9140
#100	((docosaehaenoic or docosahexenoic or eicosapentaenoic or eicosapentanoic or icosapentaenoic or timnodonic or linolenic or a-linolenic or alpha linolenic) adj2 acid*).ti,ab.	15018
#101	(linolenate or maxepa or omacor).ti,ab.	863
#102	((DHA or ALA or EPA) and (omega 3 or omega-3 or PUFA* or fatty acid*)).ti,ab.	7971
#103	or/94-102	50169
#104	(ezetimibe or zetia).ti,ab.	1879
#105	or/76,82,86,93,103-104	147826
#106	letter/	946861
#107	editorial/	393023
#108	news/	176506
#109	exp historical article/	342246
#110	anecdotes as topic/	4693
#111	comment/	664656
#112	case report/	1766484
#113	(letter or comment*).ti.	110759
#114	or/106-113	3616358
#115	animals/ not humans/	3999797
#116	exp animals, laboratory/	757998
#117	exp animal experimentation/	6839
#118	exp models, animal/	448128
#119	exp rodentia/	2784064

No.	Query	Results
#120	(rat or rats or mouse or mice).ti.	1159525
#121	61 or 65	1519127
#122	33 and 105 and 121	1220
#123	or/114-120	8260401
#124	122 not 123	1094
#125	limit 124 to (abstracts and english language and yr="2000 - 2014")	750

EMBASE Search Strategy and Results (Conference proceeding search utilised the same search strategy)

No.	Query	Results
#1	Socioeconomics/	117868
#2	Cost benefit analysis/	69153
#3	Cost effectiveness analysis/	107873
#4	Cost of illness/	15739
#5	Cost control/	52902
#6	Economic aspect/	105622
#7	Financial management/	104484
#8	Health care cost/	141616
#9	Health care financing/	11812
#10	Health economics/	34709
#11	Hospital cost/	15256
#12	(fiscal or financial or finance or funding).tw.	119960
#13	Cost minimization analysis/	2683
#14	(cost adj estimate\$).mp.	2273
#15	(cost adj variable\$).mp.	171
#16	(unit adj cost\$).mp.	2844
#17	or/1-16	718422
#18	*cardiovascular disease/	77285
#19	*coronary artery disease/	83045
#20	*vascular disease/	20159
#21	*coronary artery atherosclerosis/	9694
#22	*peripheral vascular disease/	9209
#23	*peripheral occlusive artery disease/	17195
#24	*arteriosclerosis/	21947
#25	*ischemic heart disease/	50524
#26	exp *Stroke/ or *stroke patient/	52293
#27	*coronary artery obstruction/	11854
#28	*hypertension/	190545
#29	*heart disease/	40575
#30	*heart arrhythmia/	44463

No.	Query	Results
#31	*heart fibrillation/ or *heart atrium fibrillation/	44727
#32	*heart failure/ or exp *congestive heart failure/	113545
#33	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/	147705
#34	*cerebrovascular disease/	24912
#35	*cerebrovascular accident/	49425
#36	exp *brain ischemia/	61915
#37	*brain infarction/	16743
#38	*atherosclerosis/	55780
#39	exp *cardiovascular risk/	24857
#40	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event\$ or disease\$)).ti,ab.	195396
#41	((coronary or peripheral vascular or heart or peripheral arter\$) adj3 (disease\$ or event\$)).ti,ab.	314137
#42	(MI or myocardial infarct\$).ti,ab.	234407
#43	(CVD or CHD or CAD or PAD or CVA or hypertension).ti.	168763
#44	(atheroscleros\$ or arterioscleros\$).ti,ab.	129877
#45	(cerebrovascular accident\$ or stroke\$).ti,ab.	253953
#46	(ACS or angina or acute coronary syndrome\$).ti,ab.	97785
#47	(AF or atrial fibrillation).ti,ab.	88366
#48	((chronic or congestive) adj2 heart failure).ti,ab.	62568
#49	or/18-48	1620577
#50	exp Lipoproteins, LDL/	57888
#51	LDL*.mp.	93148
#52	low density lipoprotein.mp.	150241
#53	OR/50-52	165382
#54	*Hydroxymethylglutaryl-CoA Reductase Inhibitor/	14022
#55	((Hydroxymethylglutaryl-CoA or HMG-CoA) adj3 (reductase or inhibitors)).ti,ab.	9173
#56	statin*.ti,ab.	46074
#57	exp *simvastatin/	8415
#58	(simvastatin* or zocor).ti,ab.	10957
#59	(atorvastatin* or lipitor).ti,ab.	10065
#60	(rosuvastatin* or crestor).ti,ab.	3944

No.	Query	Results
#61	exp *pravastatin/	4253
#62	(pravastatin* or lipostat).ti,ab.	4845
#63	(fluvastatin* or lescol).ti,ab.	2218
#64	exp *atorvastatin/ or exp *rosuvastatin/	8796
#65	OR/54-64	67665
#66	exp *anion exchange resin/	334
#67	exp *bile acid sequestrant/	95
#68	*colestilan/ or *colestipol/ or *colestyramine/ or *colesevelam/ or *diethylaminoethyl dextran/	5004
#69	((anion exchange or anionic exchange) adj2 resin*).ti,ab.	1792
#70	((anion or anionic) adj2 exchanger*).ti,ab.	2767
#71	(cholestyramin* or colestyramin* or colestimide or cholybar or colextran or colestilan or cholestagel or colestipol or cholestipol or colestid or questran* or quantalan* or cuemid* or colesevelam).ti,ab.	3499
#72	(bile acid adj3 (sequestrant* or sequestering agent* or resin*)).ti,ab.	944
#73	OR/66-72	11311
#74	exp *fibrin acid derivative/	10767
#75	((fibrin or fenofibrin or clofibrin) adj2 acid*).ti,ab.	1500
#76	(fibrate* or bezafibrate or clofibrate or fenofibrate or lopid or gemfibrozil or bezalip or tricor or fibrinor or lipantil or supralip or modalim or ciprofibrate).ti,ab.	12847
#77	OR/74-76	17463
#78	*nicotinic acid/ or *laropiprant plus nicotinic acid/ or *acipimox/	8629
#79	nicotinic.ti,ab.	27349
#80	(niacin or nicotinate* or acipimox or acipemox or olbetam or niaspan or tredaptive).ti,ab.	6736
#81	((3 pyridinecarboxylic or 3-pyridinecarboxylic) adj3 acid).ti,ab.	86
#82	OR/78-81	37324
#83	fish oil/	13728
#84	polyunsaturated fatty acid/	15747
#85	omega 3 fatty acid/	22083
#86	unsaturated fatty acid/ or docosahexaenoic acid/ or icosapentaenoic acid/ or icosapentaenoic acid ethyl ester/ or linolenic acid/ or omega 3 fatty acid ester/	33133
#87	(fish adj3 oil*).ti,ab.	10708

No.	Query	Results
#88	(omega 3 or omega-3).ti,ab.	10660
#89	((n3 or n 3 or n-3) adj3 ((fatty adj3 Acid*) or PUFA*)).ti,ab.	10837
#90	((docosahexaenoic or docosahexenoic or eicosapentaeonic or eicosapentanoic or icosapentaenoic or timnodonic or linolenic or a-linolenic or alpha linolenic) adj2 acid*).ti,ab.	17500
#91	(linolenate or omacor or maxepa).ti,ab.	967
#92	((DHA or ALA or EPA) and (omega 3 or omega-3 or PUFA* or fatty acid*)).ti,ab.	10449
#93	OR/83-92	70815
#94	exp ezetimibe/ or (ezetimibe* or zetia).ti,ab.	6943
#95	or/65,73,77,82,93-94	196102
#96	letter.pt. or letter/	906721
#97	note.pt.	612179
#98	editorial.pt.	487475
#99	case report/ or case study/	2062496
#100	(letter or comment*).ti.	160651
#101	OR/96-100	3907295
#102	randomized controlled trial/ or random*.ti,ab.	1100271
#103	101 not 102	3876763
#104	animal/ not human/	1267888
#105	nonhuman/	4581626
#106	exp animal experiment/	1874458
#107	exp experimental animal/	473799
#108	animal model/	827729
#109	exp rodent/	3074570
#110	(rat or rats or mouse or mice).ti.	1335655
#111	OR/103-110	10475929
#112	49 or 53	1710991
#113	17 and 95 and 112	2089
#114	113 not 111	1761
#115	limit 114 to (abstracts and english language and exclude medline journals and yr="2000 - 2014")	143

Econlit Search Strategy and Results

ID	Search	Hits
#1	LDL {Including Limited Related Terms}	6
#2	Low density lipoprotein {Including Limited Related Terms}	2
#3	1 OR 2	6

NHS EED Search Strategy and Results (2000-2014)

ID	Search	Hits
#1	LDL (all text	117
#2	Low density lipoprotein	121
#3	1 OR 2	129

Data Extraction Form of Included Cost-Effectiveness Studies

Study Country	Summary of model	Patient population (average age in years)	Treatments (treatment and treatment duration)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Fitch et al., 2009 US	Model Type: Three-year event forecast Time horizon: 3 years Cycle Length: 1 year Health States: Well, 1st CHD event, 2nd CHD event, CHD death, other death Data source: NHANES 2003-2006, MedStat MarketScan 2003-2007, TNT Study, HPS Study, Milliman's 2008 Health Cost Guidelines, Perspective: US (commercial)	Patients with history of CHD who are at high-risk, as defined by NCEP III criteria, for CVD events; no treatment history reported Age: 35-69 years	Interventions: Intensive lipid-lowering therapy	Not reported	Not reported	Cost per event avoided: CHD: Cost reduction per target person per month: \$53 (95%CI, \$28-72) Stroke: Cost reduction per target person per month: \$5 (95%CI, \$1-8) CHD + Stroke: Cost reduction per target person per month: \$58 (95%CI, \$29-80)

Appendix III: Clinical efficacy/safety systematic literature review list of unobtainable papers, ongoing studies, and completed studies with no data

Appendix Table-1 List of unobtainable papers

Publication citation
[No authors listed]. [Hypercholesterolemia: when statins are not enough or not tolerated with combination therapy to LDL cholesterol target goal]. <i>MMW Fortschr Med</i> 2012;154(13):86-7.
Kulev BD, Ageev FT. [Effect of various approaches to therapy with statins in high risk patients from the point of view of vascular endothelium]. <i>Kardiologiya</i> 2009;49(5):4-10.
Byington RP, Jukema JW, Salonen JT, Pitt B, Bruschke AV, Hoen H, et al. [Reduction of cardiovascular events with pravastatin. A pooled analysis of clinical events within the scope of the Pravastatin Atherosclerosis Intervention Program]. <i>Fortschr Med</i> 1996;114(8):91-8.
Liakishev AA, Kukharchuk VV, Titov VN, Volkova EI, Konstantinov VO, Lipovetskii BM, et al. [An evaluation of the hypolipidemic effects of lovastatin in primary hypercholesterolemia. A multicenter study]. <i>Kardiologiya</i> 1993;33(11):48-54.
Bays HE, MacLean A, Shah A, Sisk CM, Dong Q, Maccubbin D. The lipid-altering effects of extended-release niacin/laropiprant among different patient subgroups. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 13-16 May 2010; Chicago, IL: United States. <i>J Clin Lipidol</i> 2010;4(3):215.
Yamagishi T. [Efficacy and safety of ezetimibe added on to rosuvastatin (2.5 mg) compared with up-titration of rosuvastatin (5 mg) in hyperlipidemic patients]. <i>Jpn Pharmacol Ther</i> 2010;38(3):305-311.
Gao RL. [The efficacy and safety of rosuvastatin on treating patients with hypercholesterolemia in Chinese: a randomized, double-blind, multi-center clinical trial]. <i>Zhonghua xin xue guan bing za zhi [Chinese journal of cardiovascular diseases]</i> 2007;35(3):207-211.
Tao P, Wu XS, Yu XJ, Zhu J, Tao SQ. Efficacy and safety of cerivastatin 0.1 mg, 0.2 mg and 0.3 mg in Chinese patients with primary hypercholesterolaemia: a multicentre, randomised, double-blind, placebo-controlled study. <i>Journal of Clinical Research</i> 2000;3:29-40.
Carmena R, De Oya M, Gomez-Gerique J, Mata P, Serrano S, Franco M, et al. Pravastatin, cholestyramine, and bezafibrate in patients with heterozygous familial hypercholesterolemia: the Spanish Multicenter Pravastatin Study. <i>Cardiovascular Risk Factors</i> 1996;6(1):55-61.
Behounek BD. [Pravastatin in patients with cardiovascular risk factors. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors]. <i>Fortschr Med</i> 1994;112(5):45-54.
Merck Co Inc. <i>Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease: Merck Protocol Number: 0806-00, 2004</i>
Roth EM, McKenney JM. ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. <i>Future Cardiol.</i> 2015;11(1):27-37.

Appendix Table-2 List of ongoing studies

Trial ID	Publication
AVOCADO/NCT01974297	Yonsei University, Sang Hak Lee. Comparison of the efficacy and safety of atorvastatin monotherapy vs combination atorvastatin/fenofibric acid. NCT01974297. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 10.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01974297 .
ACCENTUATE/NCT02227784	Eli Lilly and Company. A study of evacetrapib (LY2484595) in participants with high cholesterol. NCT02227784. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 27.10.14] [updated October 2014]; Available from: http://clinicaltrials.gov/show/NCT02227784 .
EUCTR2014-000972-24-SE HYDRA	AstraZeneca A. B. A study to evaluate the effect of rosuvastatin on fatty acids in children and adolescents with homozygous familial hypercholesterolemia. EUCTR2014-000972-24-SE. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2014 [accessed 19.3.15] [updated 20/08/2014]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000972-24. NCT02226198. A Study to Evaluate the Efficacy and Safety of Rosuvastatin in Children and Adolescents With Homozygous Familial Hypercholesterolemia. 2014.
FOURIER/Amgen 20110118	Amgen. Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk. NCT01764633. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 10.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01764633. Amgen Inc. A study assessing the impact of additional LDL-cholesterol reduction on major cardiovascular events when AMG 145 is used in combination with statin therapy in patients with clinically evident cardiovascular disease. EUCTR2012-001398-97-FI. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2012 [accessed 9.7.14] [updated 17/10/2012]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-001398-97.
GAUSS-3/Amgen 20120332	Amgen Inc. Study designed to evaluate the safety and efficacy of AMG 145 compared with Ezetimibe treatment, in people with high cholesterol who have experienced side effects whilst taking existing statin treatment. EUCTR2013-000935-29-DE. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2014 [accessed 9.7.14] [updated 28/02/2014]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000935-29 .

Trial ID	Publication
	Amgen Inc. A double-blind, randomized, multicenter study to evaluate the safety and efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor due to muscle related side effects: GAUSS-3 protocol. Thousand Oaks2013. Amgen. Goal achievement after utilizing an anti-PCSK9 antibody in statin intolerant subjects-3. NCT01984424. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 9.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01984424.
Merck, S./MK-0859-042/NCT01841684	Merck Sharp Dohme Corp. Efficacy and tolerability of anacetrapib added to ongoing lipid-lowering therapy in adult participants with homozygous familial hypercholesterolemia (HoFH) (MK-0859-042). NCT01841684. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 11.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01841684. Merck Sharp & Dohme Corp. A worldwide, multicenter, double-blind, randomized, placebo-controlled, 12-week study to assess the efficacy and tolerability of anacetrapib when added to ongoing lipid-lowering therapy in adult patients with homozygous familial hypercholesterolemia (HoFH). EUCTR2012-002434-37-GB. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2012 [accessed 11.7.14] [updated 23/05/2013]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-002434-37.
Merck, S./NCT01860729	Merck Sharp Dohme Corp. A study of the safety and efficacy of anacetrapib (MK-0859) among participants with hypercholesterolemia when added to ongoing statin therapy (MK-0859-022 AM4). NCT01860729. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01860729.
National Taiwan University, H./NCT00965315	National Taiwan University Hospital. A multicenter randomized parallel-group study to investigate the efficacy of a combination of rosuvastatin and fenofibrate in the patients with diabetes or atherosclerotic vascular diseases with metabolic syndrome. NCT00965315. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 [accessed 11.7.14]; Available from: http://ClinicalTrials.gov/show/NCT00965315.
NCT02107898; EFC13672	Sanofi. Efficacy and safety evaluation of alirocumab in patients with heterozygous familial hypercholesterolemia or high cardiovascular risk patients with hypercholesterolemia on lipid modifying therapy. NCT02107898. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 27.10.14] [updated March 2014]; Available from:

Trial ID	Publication
	http://clinicaltrials.gov/show/NCT02107898 .
ODYSSEY CHOICE 1/ NCT01926782	Regeneron Pharmaceuticals Inc. A study to evaluate the effect and safety of a 4 week treatment plan of alirocumab in patients with high cholesterol. EUCTR2013-002343-29-HU. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2013 [accessed 14.7.14] [updated 29/11/2013]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002343-29. Regeneron Pharmaceuticals, Sanofi. Study to evaluate the efficacy and safety of an every four weeks treatment regimen of alirocumab (REGN727/ SAR236553) in patients with primary hypercholesterolemia (ODYSSEY CHOICE 1). NCT01926782. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01926782.
ODYSSEY ESCAPE	Regeneron Pharmaceuticals Inc. A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia undergoing lipid apheresis therapy. EUCTR2014-001917-20. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2015 [accessed 19.3.15]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001917-20. Regeneron Pharmaceuticals, Sanofi. Study of alirocumab (REGN727/SAR236553) in patients with heterozygous familial hypercholesterolemia (HeFH) undergoing low-density lipoprotein (LDL) apheresis therapy. NCT02326220. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT02326220.
ODYSSEY outcomes	Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. Am Heart J. 2014 Nov;168(5):682-9. Sanofi, Regeneron Pharmaceuticals. ODYSSEY Outcomes: evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab SAR236553 (REGN727). NCT01663402. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT01663402.
Pfizer/2014-000478-20	Pfizer Inc. A 52 week, phase 3 double-blind, randomized,

Trial ID	Publication
	placebocontrolled, parallel-group study to assess the efficacy, safety and tolerability of pf-04950615 in subjects with primary hyperlipidemia or mixed dyslipidemia at risk of cardiovascular events. EUCTR2014-000478-20. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2014 [accessed 19.3.15]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000478-20.
Pfizer/NCT02055976	Pfizer. Dose ranging study of bococizumab (PF-04950615; RN316) In hypercholesterolemic Japanese subjects. NCT02055976. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT02055976.
REAL-CAD/NCT01042730	Public Health Research Foundation. Randomized evaluation of aggressive or moderate lipid lowering therapy with pitavastatin in coronary artery disease (REAL-CAD). JPRN-UMIN000002680. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2009 [accessed 15.7.14] [updated 2010/01/01]; Available from: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000003262&language=E.
Regeneron/NCT01604824	Regeneron Pharmaceuticals, Sanofi. A study of alirocumab (REGN727/SAR236553) in patients with ADH and GOFm of the PCSK9 gene or LOFm of the apoB gene. NCT01604824. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT01604824.
Sanofi/NCT02289963	Sanofi. Evaluation of alirocumab in addition to lipid-modifying therapy in patients with high cardiovascular risk and hypercholesterolemia in South Korea and Taiwan. NCT02289963. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT02289963.
SPIRE-1/NCT01975376	Pfizer. The evaluation of PF-04950615 (RN316), in reducing the occurrence of major cardiovascular events in high risk subjects. NCT01975376. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 15.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01975376.
SPIRE-2/NCT01975389	Pfizer. The evaluation of bococizumab (PF-04950615; RN316) in reducing the occurrence of major cardiovascular events in high risk subjects. NCT01975389. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT01975389.
SPIRE-HF/NCT01968980	Pfizer. A 52 week study to assess the use of RN316 (PF-04950615) in subjects with heterozygous familial hypercholesterolemia. NCT01968980. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 15.7.14];

Trial ID	Publication
	Available from: http://ClinicalTrials.gov/show/NCT01968980 .
SPIRE-HR/NCT01968954	Pfizer. Randomized clinical trial Of RN316 (PF-04950615) In subjects with hyperlipidemia or mixed dyslipidemia at risk of cardiovascular events. NCT01968954. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 15.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01968954. Pfizer Inc. A Phase 3 study investigating the efficacy, safety and tolerability of PF-04950615 in subjects with elevated levels of any or all of the lipids or lipoproteins in the blood who are at risk of developing cardiovascular disease. EUCTR2013-002642-37-CZ. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2013 [accessed 15.7.14] [updated 24/01/2014]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002642-37.
SPIRE-LDL/ NCT01968967	Pfizer. Randomized clinical trial of RN316 (PF-04950615) in subjects with hyperlipidemia or mixed dyslipidemia at risk of cardiovascular events. NCT01968967. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 15.7.14] [updated October 2013]; Available from: http://clinicaltrials.gov/show/NCT01968967 .
SPIRE-LL/NCT02100514	Pfizer. Randomized clinical trial of RN316 (PF-04950615) in subjects with primary hyperlipidemia or mixed dyslipidemia at risk of cardiovascular events. NCT02100514. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 27.10.14] [updated October 2014]; Available from: http://clinicaltrials.gov/show/NCT02100514. NCT02100514. Randomized Clinical Trial of Bococizumab (PF-04950615; RN316) in Subjects With Primary Hyperlipidemia or Mixed Dyslipidemia At Risk Of Cardiovascular Events. 2014.
SPIRE-SI/NCT02135029	Pfizer. Randomized clinical trial of RN316 (PF-04950615) in subjects who are intolerant to statins. NCT02135029. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US) 2014 [accessed 27.10.14] [updated May 2014]; Available from: http://clinicaltrials.gov/show/NCT02135029 .
Vukelic 2013	Vukelic K, Bunc M. Effects of ezetimibe+vs usual doses of statins: data from everyday practise. Presented at 10th International Congress on Coronary Artery Disease, ICCAD; 13-16 Oct 2013; Florence: Italy. Cardiology (Switzerland). 2013;126:299. Laboratoires Merck Sharp & Dohme. A randomized, double-blind, active-controlled, multicenter study to assess the LDL-C lowering of switching to a combination tablet ezetimibe/simvastatin (10mg/20mg) compared to rosuvastatin 10mg in patients with primary hypercholesterolemia and high cardiovascular risk and not adequately controlled with a prior statin treatment (IN-CROSS).

Trial ID	Publication
	EUCTR2006-005513-35-FR. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2007 [accessed 15.7.14] [updated 09/02/2007]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-005513-35 .

Appendix Table-3 List of completed studies and publications with no data

Trial ID	Publication
ACTRN12605000777695	Fournier Laboratories Ireland. A multicenter, double-blind, randomized study to compare the efficacy and safety of the combination of 145mg fenofibrate and simvastatin with 40mg simvastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease not adequately controlled by 40 mg simvastatin alone. ACTRN12605000777695. In: Australian New Zealand Clinical Trials Registry (ANZCTR) [Internet]. 2005 [accessed 14.7.14]; Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12605000777695.
AstraZeneca /NCT00235950	AstraZeneca. Assessment of the Lipid Lowering Effect of Rosuvastatin Compared to Atorvastatin in Subjects With Coronary Heart Disease. NCT00235950. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2010 [accessed 14.7.14] [updated January 2004]; Available from: http://clinicaltrials.gov/show/NCT00235950.
DISCOVERY/NCT00239330	AstraZeneca. Direct statin comparison of LDL-C values: an evaluation of rosuvastatin therapy. NCT00239330. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2010 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT00239330.
Eli Lilly 14853/NCT01890967	Eli Lilly Company. A study of LY3015014 in participants with high cholesterol. NCT01890967. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01890967. Eli Lilly and Company. A study comparing several dose levels of LY3015014 in patients with high cholesterol studying the safety and ability of LY3015014 to reduce cholesterol. EUCTR2013-000622-55-CZ. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2013 [accessed 14.7.14] [updated 31/07/2013]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000622-55.
EUCTR2007-002017-39	Merck & Co Inc. A multicenter, randomized, double-blind, parallel group, 12-week study to evaluate the efficacy and safety of extended-release (ER) niacin/laropiprant added to statin versus doubling the dose of statin in patients with primary hypercholesterolemia or mixed dyslipidemia. EUCTR2007-002017-39. In: PharmNet.Bund [Internet]. Cologne: German Institute of Medical Documentation and Information (DIMDI). 2007 [accessed 14.7.14]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-002017-39. Merck & Co Inc. A multicenter, randomized, double-blind, parallel group, 12-week study to evaluate the efficacy and safety of

Trial ID	Publication
	extended-release (ER) niacin/laropirant added to statin versus doubling the dose of statin in patients with primary hypercholesterolemia or mixed dyslipidemia. Extended release niacin/laropirant – lipids. EUCTR2007-002017-39-DK. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2007 [accessed 4.6.14] [updated 11/07/2007]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-002017-39.
Merck, S./MK-0859-021/NCT01717300	Merck Sharp Dohme Corp. A study of the safety and efficacy of anacetrapib (MK-0859) when added to ongoing statin therapy (MK-0859-021). NCT01717300. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 11.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01717300. Merck sharp & Dohme Corp. A 24-week, worldwide, multicenter, double-blind, randomized, parallel, placebo-controlled study to assess the efficacy and tolerability of anacetrapib when added to ongoing statin therapy with or without other lipid modifying medication(s) in patients with high bad cholesterol or low good cholesterol (HDL-C). EUCTR2012-003110-14-NL. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2012 [accessed 11.7.14] [updated 03/12/2012]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003110-14.
Merck, S./NCT01760460	Merck Sharp Dohme Corp. A study of the safety and efficacy of anacetrapib (MK-0859) when added to ongoing statin therapy in Japanese participants with dyslipidemia (MK-0859-051 AM1). NCT01760460. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01760460.
Merck/NCT01824238/MK-0859-050	Merck Sharp Dohme Corp. A study of the safety and efficacy of anacetrapib (MK-0859) when added to ongoing statin therapy in Japanese participants with heterozygous familial hypercholesterolemia (MK-0859-050). NCT01824238. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 15.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01824238.
Pfizer/NCT01342211	Pfizer. A multiple dose study of PF-04950615 (RN316) in subjects on high doses of statins. NCT01342211. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01342211.
Pharmaceutical, J.W./NCT01166633	J. W. Pharmaceutical. Efficacy and safety study of pitavastatin versus atorvastatin to treat hypercholesterolemia. NCT01166633. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01166633.

Trial ID	Publication
Sanofi/EUCTR2008-002849-23-BE	Sanofi-Aventis Recherche and Développement. A multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety and tolerability of AVE5530 when added to ongoing stable statin therapy at high doses in patients with severe primary hypercholesterolemia. EUCTR2008-002849-23-BE. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2008 [accessed 19.3.15] [updated 04/12/2008]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-002849-23 .
Shionogi, I./NCT00459745	Shionogi Inc, Integrium. A study to evaluate daily pravastatin, fenofibrate or pravafen in the treatment of combined hyperlipidemia. NCT00459745. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT00459745 .
Solvay/NCT00349375	Solvay Pharmaceuticals. Comparison of the combination of fenofibrate and 20 mg simvastatin versus 40 mg simvastatin monotherapy. NCT00349375. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT00349375 . A multicenter, double-blind, randomized, active comparator, forced-titration study to compare the efficacy and safety of the combination of 145 mg fenofibrate and 20 or 40 mg simvastatin with 40 mg simvastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease not adequately controlled by 20 mg simvastatin alone. 2005-003270-14. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2005 [accessed 2.6.14]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-003270-14 .
Solvay/NCT00352183	Solvay Pharmaceuticals. Comparison of the combination of fenofibrate and 40 mg simvastatin versus 40 mg simvastatin monotherapy. NCT00352183. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT00352183 .
Solvay/NCT00362206	Solvay Pharmaceuticals. Comparison of the combination of fenofibrate and simvastatin versus pravastatin. NCT00362206. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT00362206 .
Solvay/NCT00362934	Solvay Pharmaceuticals. Comparison of the combination of fenofibrate and simvastatin versus atorvastatin. NCT00362934. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 14.7.14]; Available from: http://ClinicalTrials.gov/show/NCT00362934 .

Trial ID	Publication
SWITCH	Merck Sharp & Dohme Corp. The study is to evaluate the effectiveness and safety of switching to coadministration ezetimibe and atorvastatin compared with doubling the dose of atorvastatin or switching to rosuvastatin in patients with primary hypercholesterolemia and high cardiovascular risk who are not adequately controlled with atorvastatin 10 mg: comparison of the efficacy and safety of switching to coadministration ezetimibe and atorvastatin versus doubling the dose of atorvastatin or switching to rosuvastatin. EUCTR2009-015247-16-GB. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2010 [accessed 15.7.14] [updated 11/10/2010]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-015247-16.
Tingley 2013	Tingley W, Luca D, Leabman M, Budha N, Kahn R, Baruch A, et al. Effects of RG7652, a fully human mAb against proprotein convertase subtilisin/kexin type 9, on LDL-c: A phase I, randomised, double-blind, placebo-controlled, single and multiple-dose study. Presented at 24th Great Wall International Congress of Cardiology, Asia Pacific Heart Congress, International Congress of Cardiovascular Prevention and Rehabilitation; 10-13 Oct 2013; Beijing: China. Heart. 2013;99:A153. Tingley W, Luca D, Leabman M, Budha N, Kahn R, Baruch A, et al. Effects of RG7652, a fully human mAb against proprotein convertase subtilisin/kexin type 9, on LDL-c: a phase I, randomised, double-blind, placebo-controlled, single- and multiple-dose study. Presented at European Society of Cardiology, ESC Congress; 31 Aug - 4 Sept 2013; Amsterdam: Netherlands. Eur Heart J. 2013;34:767.

Appendix IV: Clinical efficacy/safety systematic literature review inclusion/exclusion criteria

Appendix Table-4 Inclusion and exclusion criteria for the broad clinical efficacy/safety systematic literature review

	Inclusion criteria	Exclusion criteria
Population	• Studies in adults (≥ 18 years old) with primary hypercholesterolaemia (including familial and non-familial) who are candidates for treatment of elevated lipid levels (hyperlipidaemia) and consequent reduction in CV events. For patients with HoFH, studies including patients ≥ 12 years old were also included • Where available, data were identified and reported for two specific groups of patients: ▪ Patients whose condition is not adequately controlled or is unlikely to be adequately controlled (according to European lipid targets) with a statin alone ▪ Patients in whom a statin is considered inappropriate or is only tolerated at low dose/intensity. • Data relevant to the following subgroups were identified: ▪ Patients with HeFH; patients with HoFH; patients with IHD, CVD, or PAD; and patients with diabetes mellitus type 2 • Data were also recorded for subgroups defined by gender, age (< 65, ≥ 65 years), and race (white, non-white) where reported	• Studies including patients with organ transplantations and infectious diseases (e.g. HIV) were excluded. In addition, studies including patients with significant heart failure (NYHA grade III-IV) or significant renal dysfunction (Stage 4-5), which are considered to be major confounding comorbidities, were also excluded
Intervention	• Evolocumab used in combination with moderate- or high-dose statins where cholesterol is insufficiently controlled with statin therapy alone and as monotherapy (in for example statin-intolerant patients). The following doses of evolocumab evaluated will be eligible for inclusion: ▪ 140 mg SC Q2W (1 prefilled AI/pen injection) ▪ 420 mg SC QM (3 prefilled AI/pen injections or 1 personal injector injection)	• Studies that do not include either the included intervention or comparator agents as one of their treatment arms
Comparators ^a	<u>Patients whose condition is not adequately controlled with a statin alone</u> • Alternative moderate- to high-intensity statin monotherapies (daily dose lowers LDL-C on average, by approximately $\geq 30\%$): atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin • Or alternatively, statins in combination with any of the following alternative lipid-lowering therapies such as: other alternative PCSK9 inhibitor monotherapies; cholesterol absorption inhibitors; nicotinic acids; fibrates; cholesteryl ester transfer	

	Inclusion criteria	Exclusion criteria
	proteins; and lomitapide, mipomersen, and apheresis (for HoFH) <u>Patients in whom a statin is considered inappropriate or is not tolerated</u> • No treatment/placebo; other alternative PCSK9 inhibitor monotherapies; cholesterol absorption inhibitors; bile acid resins; fibrates; cholesteryl ester transfer proteins; and lomitapide, mipomersen, and apheresis (for HoFH)	
Outcomes	<u>Clinical outcomes</u> • Overall survival; incidence of CV death; incidence of non-CV death; incidence of fatal and non-fatal CV events (composite and individual outcomes) e.g. CV death, MI, ischaemic stroke, TIA, hospitalisation for unstable angina, hospitalisation for worsening heart failure, symptomatic PAD, CHD and coronary revascularisation; time to fatal or non-fatal CV events (composite and individual outcomes) <u>Lipid-related outcomes (absolute values and change from baseline):</u> • LDL-C; triglycerides; HDL-C; VLDL-C; total cholesterol; total cholesterol/ HDL-C ratio; non-HDL-C; ApoB; ApoB/ApoA1 ratio; Lp(a); and incidence of apheresis (HoFH only). <u>Safety outcomes</u> • Incidence of treatment-related adverse events (any event, serious events, and specific individual events such as hepatic events, gastrointestinal events, headaches, muscle-related events, etc.) <u>Patient-reported outcomes (absolute values and change from baseline)</u> • HRQoL	• RCTs that do not assess one of the included outcomes
Study design	RCTs (including randomised dose finding and formulation studies with either a control or active control arm) were eligible for inclusion, if they were of ≥ 12 weeks' duration. This reflects regulatory guidance on the minimum duration of studies to demonstrate the lipid-lowering effects of investigational agents. It is also in line with previous recommendations included in NICE TA132 (ezetimibe for the treatment of hypercholesterolaemia). This STA reported that trials of shorter duration were considered 'unlikely to inform on survival, CVD events, adverse events or HRQoL' and were also 'excluded to allow for the tachyphylaxis effects'.	• Non-randomised studies • Studies < 12 weeks' duration or with < 10 participants per arm • Pre-clinical, phase 1, and animal studies
Language	Searches were not limited by language.	N/A
^aA more detailed list of specific comparator agents is provided in Appendix III of the evidence submission. AI, autoinjector; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; HIV, human immunodeficiency virus; HoFH, homozygous familial hypercholesterolaemia; HRQoL, health-related quality of life; IHD, ischaemic heart disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); MI, myocardial infarction; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; PAD, peripheral arterial disease;		

	Inclusion criteria	Exclusion criteria
	PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; QM, monthly; RCT, randomised controlled trial; SC, subcutaneous; STA, single technology appraisal; TIA, transient ischaemic attack; VLDL-C, very low-density lipoprotein cholesterol	

Appendix V: Details of quality assessment of studies included in the safety section of the submission in addition to the relevant RCTs

Appendix Table-5 GAUSS (Study 20090159) quality assessment

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 via a computer-generated randomisation schedule in a 1:1:1:1:1 ratio.	Yes
Was the concealment of treatment allocation adequate?	Allocation concealment was achieved using an interactive voice response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No major differences existed between the treatment and placebo groups in baseline demographics or clinical characteristics.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Participants and investigators were blinded to treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups?	Treatment groups were generally balanced with respect to discontinuations and withdrawals.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All efficacy and safety assessments listed in the methods were reported in the results section.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The full analysis set (FAS) included all patients who received at least one dose of study drug (i.e. modified intent-to-treat).	Yes

Appendix Table-6 YUKAWA (Study 20110231) quality assessment

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 via a computer-generated randomisation schedule in a 1:1:1:1:1 ratio.	Yes
Was the concealment of treatment allocation adequate?	Allocation concealment was achieved using an interactive voice response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No major differences existed between the treatment and placebo groups in baseline demographics or clinical characteristics.	Yes
Were the care providers, participants and outcome assessors blind to treatment	Participants, care givers and investigators were blinded to treatment.	Yes

allocation?		
Were there any unexpected imbalances in drop-outs between groups?	Treatment groups were generally balanced with respect to discontinuations or withdrawals. The drop-out rate was 3% (10/310) which was relatively low and balanced across groups.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All efficacy and safety assessments listed in methods were reported in the results section.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The full analysis set (FAS) included all patients who received at least one dose of study drug (i.e. modified intent-to-treat).	Yes

Appendix Table-7 RUTHERFORD (Study 20090158) quality assessment

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 via a computer-generated randomisation schedule in a 1:1:1 ratio	Yes
Was the concealment of treatment allocation adequate?	Allocation concealment was achieved using an interactive voice response system	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No major differences existed between the treatment and placebo groups in baseline demographics or clinical characteristics.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Patients, site staff and trial team were blinded and treatments were given in a blinded fashion. Investigators and trial staff were blinded to lipid parameters and measurements were performed by a central laboratory. Safety monitoring was performed by an independent data monitoring committee.	Yes
Were there any unexpected imbalances in drop-outs between groups?	Treatment groups were generally balanced with respect to discontinuations or withdrawals.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All efficacy and safety assessments listed in methods were reported in the results section.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The full analysis set (FAS) included all patients who received at least one dose of study drug (i.e. modified intent-to-treat).	Yes

Appendix Table-8 LAPLACE-TIMI 57 (Study 20101155) quality assessment

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 via a computer-generated randomisation schedule in a 1:1:1:1:1:1:1:1 ratio.	Yes
Was the concealment of treatment allocation adequate?	Allocation concealment was achieved using an interactive voice response system	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No major differences existed between the treatment and placebo groups in baseline demographics or clinical characteristics.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Patients, caregivers and outcome assessors were masked using identical placebo syringes. Also, LDL-C was measured at a central laboratory, and clinical events by blinded endpoint committee.	Yes
Were there any unexpected imbalances in drop-outs between groups?	Treatment groups were generally balanced with respect to discontinuations or withdrawals.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All efficacy and safety assessments listed in methods were reported in the results section.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The full analysis set (FAS) included all patients who received at least one dose of study drug (i.e. modified intent-to-treat).	Yes

Appendix Table-9 MENDEL (Study 20101154) quality assessment

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 via a computer-generated randomisation schedule to 1 of 9 treatment arms in a 1:1:1:1:1:1:1:1:1 ratio	Yes
Was the concealment of treatment allocation adequate?	Allocation concealment was achieved using an interactive voice response system	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No major differences existed between the treatment and placebo groups in baseline demographics or clinical characteristics.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	All subjects, investigators, and investigative staff were blinded to treatment assignments with the exception of ezetimibe therapy, which was provided in	Yes

	tablet form and was self-administered daily by mouth. Trial staff members who were involved in randomisation and biological sample management were un-blinded to treatment assignment information, but they did not have access to subject-level data from the clinical trial database.	
Were there any unexpected imbalances in drop-outs between groups?	Treatment groups were generally balanced with respect to discontinuations or withdrawals. The drop-out rate was 3.4% (14/411) which was relatively low and balanced across groups.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All efficacy and safety assessments listed in methods were reported in the results section.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The full analysis set (FAS) included all patients who received at least one dose of study drug (i.e. modified intent-to-treat).	Yes

Appendix Table-10 MENDEL-2 (Study 20110114) quality assessment

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 via a computer-generated randomisation schedule to 1 of 6 treatment groups in a 2:2:1:1:1:1 ratio	Yes
Was the concealment of treatment allocation adequate?	Allocation concealment was achieved using an interactive voice response system	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No major differences existed between the treatment and placebo groups in baseline demographics or clinical characteristics.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	All subjects, investigators, and investigative staff were blinded to treatment assignments. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP were blinded post-treatment until un-blinding of the clinical database. Only the external independent DMC members and Independent Bio statistical Group had access to un-blinded subject data per the DMC charter.	Yes
Were there any unexpected imbalances in drop-outs between groups?	Treatment groups were generally balanced with respect to discontinuations or withdrawals. The drop-out rate was 5.4% (33/615) which was relatively low and	No

	balanced across groups.	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All efficacy and safety assessments listed in methods were reported in the results section.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The full analysis set (FAS) included all patients who received at least one dose of study drug (i.e. modified intent-to-treat).	Yes

Appendix Table-11 OSLER (Study 20110110) quality assessment

OSLER-1		
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 via a computer-generated randomisation schedule to 1 of 2 treatment groups in a 2:1 ratio.	Yes
Was the concealment of treatment allocation adequate?	Allocation concealment was achieved using an interactive voice response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No major differences existed between the treatment and placebo groups in baseline demographics or clinical characteristics.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	This was an open-label study; blinding was not utilised.	No
Were there any unexpected imbalances in drop-outs between groups?	Treatment groups were generally balanced with respect to discontinuations or withdrawals. The drop-out rate was 12.2% (108/882) in evolocumab group and 10% (44/442) in the control group after 1 year.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All efficacy and safety assessments listed in methods were reported in the results section.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	They performed an interim standard of care controlled analysis which included all subjects randomized in this study. Subjects were analysed according to the treatment group to which they were randomized in year 1. All data from year 1 were summarized, regardless of possible IP discontinuation.	Yes

Appendix Table-12 OSLER-2 (Study 20120138) quality assessment

Study Question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Subjects who completed a qualifying protocol were randomised in a 2:1 ratio stratified by parent study crossed with parent study dose frequency. The randomisation was a block design within each stratum (the sequence of treatments repeats within each block, this was done to keep the overall study close to the 2:1 with a random study size and to handle temporal effects). The randomisation sequence was computer generated	Yes
Was the concealment of treatment allocation adequate?	Allocation concealment was achieved using an Interactive voice response system	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No major differences existed between the treatment and placebo groups in baseline demographics or clinical characteristics.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	This was an open-label study; blinding was not utilized.	No
Were there any unexpected imbalances in drop-outs between groups?	Treatment groups were generally balanced with respect to discontinuations or withdrawals. The drop-out rate was less than 5% in both groups after 1 year.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All efficacy and safety assessments listed in methods were reported in the results section.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	They performed an interim standard of care controlled analysis which included all subjects randomized in this study. Subjects were analysed according to the treatment group to which they were randomized in year 1. All data from year 1 were summarised, regardless of possible IP discontinuation.	Yes

Appendix Table-13 THOMAS-1 (Study 20120348) quality assessment

Study Question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Eligible subjects were assigned equally between two groups on the basis of a computer-generated randomisation schedule in 1:1 ratio using an interactive voice/web response system	Yes

Was the concealment of treatment allocation adequate?	Allocation concealment was achieved using an interactive voice/web response system	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Characteristics of the two treatment groups were similar across all demographic and baseline variables.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	This was an open-label study in which all subjects received evolocumab during the treatment phase. Blinding was not utilised.	No
Were there any unexpected imbalances in drop-outs between groups?	Treatment groups were generally balanced with respect to discontinuations or withdrawals. The drop-out rate was 3.4% (5/149) which was relatively low and balanced across groups.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All efficacy and safety assessments listed in methods were reported in the results section.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The fullanalysis set (FAS) included all patients who received at least one dose of study drug (i.e. modified intent-to-treat).	Yes

Appendix Table-14 THOMAS-2 (Study 20120356) quality assessment

Study Question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Eligible subjects were assigned equally between two groups on the basis of a computer-generated randomization schedule in 1:1 ratio using Interactive voice/web response system	Yes
Was the concealment of treatment allocation adequate?	Allocation concealment was achieved using an Interactive voice/web response system	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Characteristics of the two treatment groups were similar across all demographic and baseline variables.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	This was an open-label study in which all subjects received evolocumab during the treatment phase. Blinding was not utilized.	No
Were there any unexpected imbalances in drop-outs between groups?	Treatment groups were generally balanced with respect to discontinuations or withdrawals. The drop-out rate was 4.3% (7/164) which was relatively low and balanced across groups.	No

Is there any evidence to suggest that the authors measured more outcomes than they reported?	All efficacy and safety assessments listed in methods were reported in the results section.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The full analysis set (FAS) included all patients who received at least one dose of study drug (i.e. modified intent-to-treat).	Yes

Appendix VI: Summary table of economic evaluation studies from the UK

Appendix Table-15 Summary table of economic evaluation studies from the UK

Study	Country	Model type	Time horizon	Other model characteristics	Included in summary table (Yes/no)
Ara et al., 2009 [Ara R, Rafia R, Ward SE et al. Are intensive lipid-lowering regimens an optimal economic strategy in patients with ACS? An acute and chronic perspective. Expert Rev Pharmacoecon Outcomes Res 2009;9:423-33.]	UK	Model Type: Markov model with various adherence scenarios (Secondary prevention)	Time horizon: Lifetime	Cycle Length: 1 year Health States: UA, MI, revascularization, stroke, hospitalization for UA, MI with ACS history, MI + stroke, new stroke + ACS, Hospitalization for UA + stroke + ACS, non-CVD mortality, CVD mortality Data source: NHAR, RITA-2, SLSR, Bayesian mixed treatment meta-analysis Perspective: NHS	Yes
Ara et al., 2012 [Ara R, Pandor A, Stevens J et al. Prescribing high-dose lipid-lowering therapy early to avoid subsequent cardiovascular events: is this a cost-effective strategy? Eur J Prev Cardiol 2012;19:474-83.]	UK	Model Type: Markov model (Secondary prevention)	Time horizon: Lifetime	Cycle Length: 1 year Health States: UA, MI, revascularization, stroke, hospitalization for UA, MI with ACS history, MI + stroke, new stroke + ACS, Hospitalization for UA + stroke + ACS, non-CVD mortality, CVD mortality Data source: RCT meta-analysis, Registries, Bayesian meta-analysis Perspective: Healthcare	Yes
Ara et al., 2008 [Ara R, Pandor A, Tumur I et al. Cost effectiveness of ezetimibe in patients with cardiovascular disease and statin intolerance or contraindications: a Markov model. Am J Cardiovasc Drugs 2008;8:419-27.]	UK	Model Type: Markov (Secondary prevention)	Time horizon: Lifetime	Cycle Length: 1 year Health States: New SA, new UA, new non-fatal MI, new non-fatal stroke, post-SA, post-UA, post-MI, post-TIA, post-stroke, fatal CHD, fatal stroke, fatal other Data source: Meta-analyses of RCTs, UK epi studies Perspective:	Yes

Study	Country	Model type	Time horizon	Other model characteristics	Included in summary table (Yes/no)
				UK department of health	
Ara et al., 2008 <i>[Ara R, Pandor A, Tumur I et al. Estimating the health benefits and costs associated with ezetimibe coadministered with statin therapy compared with higher dose statin monotherapy in patients with established cardiovascular disease: results of a Markov model for UK costs using data registries. Clin Ther 2008;30:1508-23.]</i>	UK	Model Type: Markov (Secondary prevention)	Time horizon: Lifetime	Cycle Length: 1 year Health States: New SA, new UA, new non-fatal MI, new non-fatal stroke, post-SA, post-UA, post-MI, post-TIA, post-stroke, fatal CHD, fatal stroke, fatal other Data source: Meta-analyses of RCTs, UK epi studies Perspective: UK health department	Yes
Ara et al., 2008 <i>[Ara R, Tumur I, Pandor A et al. Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. Health Technol Assess 2008;12:iii, xi-xiii, 1-212.]</i>	UK	Model Type: Markov model (Primary and secondary preventions)	Time horizon: Lifetime	Cycle Length: 1 year Health States: MI, SA, UA, CHD death, TIA, stroke, CVD death, other death, event free Data Source: Systematic review, meta-analysis Perspective: NHS	Yes
AWSMG 1311, 2011 <i>[AWMSG Secretariat Assessment Report. Rosuvastatin (Crestor®) for the prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors. 2011.]</i>	UK	Model Type: Markov (Primary prevention)	Time horizon: lifetime	Cycle Length: 1 year Health States : CVD free, UA, non-fatal MI, TIA, non-fatal stroke, CVD death, death from other cause Data source: Systematic review, Indirect comparisons of PROSPER (PRA) and JUPITER (ROS) Perspective: NHS Wales	Yes

Study	Country	Model type	Time horizon	Other model characteristics	Included in summary table (Yes/no)
Buller et al., 2003 [Buller N, Gillen D, Casciano R, Doyle J, Wilson K. A pharmacoeconomic evaluation of the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study in the United Kingdom. <i>Pharmacoeconomics</i> 2003;21 Suppl 1:25-32.]	UK	Model Type: No model utilized (Secondary prevention)	Time horizon: 16 weeks	Data source: MIRACL RCT Perspective: NHS	No
Davies et al., 2006 [Davies A, Hutton J, O'Donnell J, Kingslake S. Cost-effectiveness of rosuvastatin, atorvastatin, simvastatin, pravastatin and fluvastatin for the primary prevention of CHD in the UK. <i>British Journal of Cardiology</i> 2006; 13(3): 196-202]	UK	Model type: Quasi-Markov (Primary prevention)	Time horizon: 21 years	Cycle Length: 4 years Health States: Angina, MI, post-MI, stroke general, stroke mild, stroke moderate, stroke severe, CHF, PVD, other disease Data source: Framingham risk equations, STELLAR RCT Perspective: NHS	No
Feher et al., 2003 [Feher M-H, Byrne CD. Cost-outcome benefits of fibrate therapy in type 2 diabetes. <i>British Journal of Diabetes and Vascular Disease</i> 2003;3:124-30.]	UK	Model type: Cost-effectiveness model (Primary and secondary prevention)	Time horizon: 5 years	Data source: VA-HIT, DAIS, CARE, 4S, LIPID RCTs Perspective: NHS	No
Fidan et al., 2007 [Fidan D, Unal B, Critchley J, Capewell S. Economic analysis of treatments reducing coronary heart disease mortality in	UK	Model type: CE Analysis (Primary and secondary prevention)	Time horizon: 10 years	Data source: IMPACT model, Meta-analysis Perspective: NHS	No

Study	Country	Model type	Time horizon	Other model characteristics	Included in summary table (Yes/no)
England and Wales, 2000-2010. QJM 2007;100:277-89.]					
Heart Protection Study Group, 2006 [Heart Protection Study C, Mihaylova B, Briggs A et al. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. BMJ 2006;333:1145.]	UK	Model type: Markov (Primary and secondary prevention)	Time horizon: Lifetime	Cycle Length: 1 years Health States: Healthy, death from vascular cause, non-fatal major vascular event, non-fatal other vascular event, death from non-vascular cause Data source: HPS, UK life tables Perspective: NR	Yes
Lindgren et al., 2005 [Lindgren P, Buxton M, Kahan T et al. Cost-effectiveness of atorvastatin for the prevention of coronary and stroke events: an economic analysis of the Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). Eur J Cardiovasc Prev Rehabil 2005;12:29-36.]	Sweden, UK	Model type: No model utilized (Primary prevention)	Time horizon: 3.3 years	Data source: ASCOT-LLA RCT Perspective: Healthcare payer	No
Lorgelly et al., 2010 [Lorgelly PK, Briggs AH, Wedel H et al. An economic evaluation of rosuvastatin treatment in systolic heart failure: evidence from the CORONA trial. Eur J Heart Fail 2010;12:66-74.]	UK	Model type: No model utilized (Secondary prevention)	Time horizon: 3 years	Data source: CORONA RCT Perspective: Healthcare sector	No
Marshall et al., 2003	UK	Model type: CE analysis	Time horizon: 5 years	Data source: Framingham risk equations, Meta-analysis	No

Study	Country	Model type	Time horizon	Other model characteristics	Included in summary table (Yes/no)
[Marshall T. Coronary heart disease prevention: insights from modelling incremental cost effectiveness. <i>BMJ</i> 2003;327:1264.]		(Primary prevention)		Perspective: Health service	
Marshall et al., 2006 [Marshall T. The cost-effectiveness of drug treatments for primary prevention of cardiovascular disease: a modelling study. <i>Eur J Cardiovasc Prev Rehabil</i> 2006;13:523-8.]	UK	Model type: CE analysis (Primary prevention)	Time horizon: 10 years	Data source: Framingham risk equations, Meta-analysis Perspective: Health service	No
McConnachie et al., 2014 [McConnachie A, Walker A, Robertson M et al. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. <i>Eur Heart J</i> 2014;35:290-8.]	UK	Model type: Cost - utility analysis (Primary prevention)	Time horizon: 15 years	Data source: WOSCOPS Perspective: NHS	No
Mihaylova et al., 2005 [Mihaylova B, Briggs A, Armitage J et al. Cost-effectiveness of simvastatin in people at different levels of vascular disease risk: economic analysis of a randomised trial in 20,536 individuals. <i>Lancet</i> 2005;365:1779-85.]	UK	Model type: No model utilized (Primary and secondary prevention)	Time horizon: 5 years	Data source: HPS Perspective: NHS	No
Mihaylova et al., 2006	UK	Model type:	Time horizon:	Cycle Length:	Yes

Study	Country	Model type	Time horizon	Other model characteristics	Included in summary table (Yes/no)
[Mihaylova B, Briggs A, Armitage J et al. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. <i>BMJ</i> 2006;333:1145.]		Markov (Secondary prevention)	Lifetime	Annual Health States: Well, non-fatal major vascular event, non-fatal other vascular event only, death from non-vascular cause, death from vascular cause Data source: HPS risk equations; RCT Perspective: NR	
Nherera et al., 2010 [Nherera L, Calvert NW, Demott K et al. Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolaemia. <i>Curr Med Res Opin</i> 2010;26:529-36.]	UK	Model type: Markov (Primary prevention)	Time horizon: Lifetime	Cycle Length: 1 year Health States: Well, MI, stroke, PAD, CHF, revascularization, UA, death Data source: NICE Technology appraisal of statins, Simon Broome Register, Meta-analysis of 4 RCTs (TNT, IDEAL, PROVE-IT, A to Z) Perspective: NHS	Yes
NICE CG 181 , 2014 [National Institute for Health and Care Excellence. 2014. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease.]	UK	Model type: Markov (Primary [ICERs not available for secondary prevention])	Time horizon: Lifetime	Cycle Length: 1 year Health States: CV death, SA, UA, MI, TIA, CHF, PAD, non-CV death Data source: Systematic review Perspective: UK NHS	Yes
NICE TA 132, Issue date: 2007 Review date: 2010 [National Institute for Health and	UK	Model type: Markov (Primary and secondary)	Time horizon: 20 years and Lifetime	Cycle Length: NR Health States: NR	Yes

Study	Country	Model type	Time horizon	Other model characteristics	Included in summary table (Yes/no)
Care Excellence. NICE TA132. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. November 2007. Available from: http://www.nice.org.uk/guidance/ta132 (Accessed May 2015).]		prevention)		Data source: Framingham risk equations Perspective: NHS	
Raikou et al., 2007 [Raikou M, McGuire A, Colhoun HM et al. Cost-effectiveness of primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes: results from the Collaborative Atorvastatin Diabetes Study (CARDS). <i>Diabetologia</i> 2007;50:733-40.]	UK, Ireland	Model Type: Markov (Primary prevention)	Time horizon: 3.9 years (trial duration) and lifetime	Data source: CARDS RCT Perspective: NHS	No
Reckless et al., 2010 [Reckless J, Davies G, Tunceli K, Hu XH, Brudi P. Projected cost-effectiveness of ezetimibe/simvastatin compared with doubling the statin dose in the United Kingdom: findings from the INFORCE study. <i>Value Health</i> 2010;13:726-34.]	UK	Model Type: Markov decision-analytic model (Secondary prevention)	Time horizon: Lifetime	Cycle Length: 1 year Health States: Well, MI, angina, CHD death, non-CHD death Data source: INFORCE study, Framingham risk equations Perspective: Payer (UK Department of Health)	Yes
Scuffham et al., 2005 [Scuffham PA, Chaplin S. A cost-effectiveness analysis of fluvastatin in patients with diabetes after successful percutaneous coronary	UK	Model type: Markov (Secondary prevention)	Time horizon: 10 years	Cycle Length: Monthly Health States: Healthy, MI, post-PCI, post-CABG, cardiac death, other death Data source: LIPS RCT	No

Study	Country	Model type	Time horizon	Other model characteristics	Included in summary table (Yes/no)
intervention. Clin Ther 2005;27:1467-77.]				Perspective: UK NHS	
Scuffham et al., 2004 [Scuffham PA, Chaplin S. An economic evaluation of fluvastatin used for the prevention of cardiac events following successful first percutaneous coronary intervention in the UK. Pharmacoeconomics 2004;22:525-35.]	UK	Model type: Markov (Secondary prevention)	Time horizon: 10 years	Cycle Length: Monthly Health States: Healthy after PCI, MI, post-PCI, post CABG, cardiac death, other death Data source: LIPS RCT Perspective: UK NHS	No
SMC 725/11, 2011 [Scottish Medical Council. Rosuvastatin, 5mg, 10mg, 20mg, film-coated tablets (Crestor®) SMC No. (725/11). 2011.]	UK	Model type: Markov (Primary prevention)	Time horizon: Lifetime	Cycle Length: NR Health States: Unstable angina, MI, TIA, CVD death, non-CVD death, non-fatal stroke Data source: Untreated population for UK registries, Nottingham Heart Attack Register, South London Stroke Register, systematic review Perspective: SMC	Yes
Taylor et al., 2009 [Taylor DC, Pandya A, Thompson D et al. Cost-effectiveness of intensive atorvastatin therapy in secondary cardiovascular prevention in the United Kingdom, Spain, and Germany, based on the Treating to New Targets study. Eur J Health	UK Spain Germany	Model type: Markov (Primary and secondary prevention)	Time horizon: Lifetime	Cycle Length: 1 year Health States: Stable CHD, one major event, two major events, minor CVD events, and survival Data source: TNT trial Perspective: Payer	No

Study	Country	Model type	Time horizon	Other model characteristics	Included in summary table (Yes/no)
<i>Econ 2009;10:255-65.]</i>					
Ward et al., 2007 <i>[Ward S, Lloyd Jones M, Pandor A et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess 2007;11:1-160, iii-iv.]</i>	UK	Model type: Markov (Pprimary prevention)	Time horizon: Lifetime	Cycle Length: 1 year Health States: Event free, MI, SA, UA, CHD death, TIA, stroke, CVD death, death other, post MI, post SA, post UA, post TIA, post stroke Data source: Algorithm based on UK-specific incidence rates, systematic review, meta-analysis of RCTs Perspective: UK NHS	Yes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia

Addendum

August 2015

File name	Version	Contains confidential information	Date
	Addendum	Yes CIC: Redacted	November 2015

Overview:

This addendum contains revised cost effectiveness analyses associated with the clarification request dated 11th August 2015 from the Evidence Review Group (ERG) during the clarification process.

As noted by the ERG, non-fatal and fatal CV events are estimated independently. As such, in certain extreme scenarios of CV risk, negative transition probabilities may occur. This issue has precipitated in the manufacturer submission (NHS list price) in the threshold analyses for patients 'without existing CVD', whereby such extreme scenarios have been modelled on the basis of CVD risk to demonstrate cost-effectiveness according to willingness-to-pay thresholds. Therefore, we acknowledge that the analyses for this population (at NHS list price) are invalid due to this finding and have been revised.

Additionally, it has been identified that for the heterozygous familial hypercholesterolaemia (HeFH) population with previous history of heart failure, some transition probabilities are negative for patients above 90 years of age. On examination of the Benn, *et al* (2010) publication that has been used as the basis for the HeFH CV event rate calibration, we note that the prevalence of heart failure is not reported. In the absence of this information and additional data, we have removed the heart failure history risk adjustment for HeFH patients. This prevents the occurrence of negative transitions in patients above 90 years of age; and may result in conservative estimates for other younger populations.

Therefore, the cost effectiveness analyses have been updated for these populations:

Patients without existing CVD

- Threshold analysis according to CVD risk and willingness-to-pay thresholds
- Probabilistic sensitivity analyses

Patients with HeFH

- Base case results
- Sensitivity analyses (deterministic and probabilistic)
- Scenario analyses

The original section, table and figure numbering (and relevant associated text) has been retained in this addendum to facilitate cross-reference with the manufacturer evidence submission.

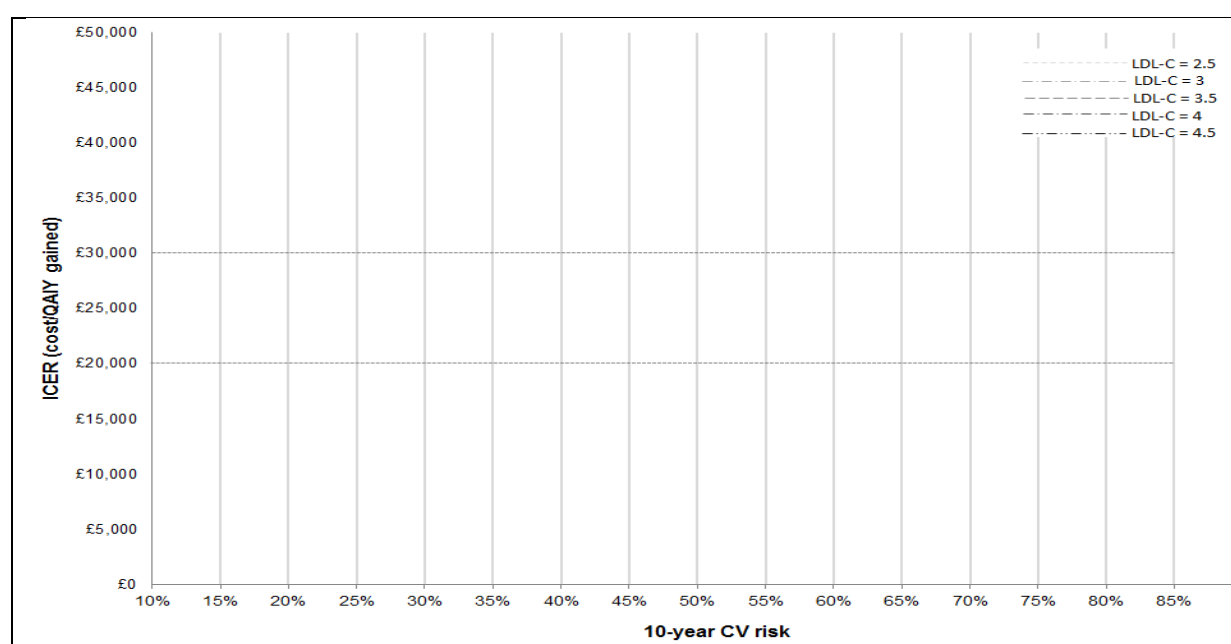
1.4 Summary of the cost-effectiveness analysis

Without existing CVD: Although evolocumab would be beneficial for many patients with existing CVD whose LDL-C remains inadequately controlled by maximally-tolerated doses of statins or who are statin intolerant/contraindicated (per its MA), the priority for use in patients at the highest residual risk. Threshold analyses for various baseline LDL-C levels (2.5 to 4.5mmol/L) were therefore conducted to establish the minimum 10-year CVD risk (measured using a risk assessment tool such as QRISK2) at which treatment with evolocumab in accordance with its MA would be deemed a cost-effective use of NHS resources according to willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained. The minimum absolute 10-year CVD risks required for evolocumab to be cost-effective at these thresholds are presented in Table 1-4 and Figure 1-1.

Table 1-4 Threshold analyses of baseline LDL-C and 10 year CVD risk according to willingness-to-pay thresholds for evolocumab and statin versus ezetimibe and statin

Baseline LDL-C (mmol/L)	10-year CVD risk for £20,000/QALY	10-year CVD risk for £30,000/QALY
2.5	_*	_*
3	_*	_*
3.5	_*	_*
4	_*	_*
4.5	_*	_*
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD; cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year		

Figure 1-1 Threshold analysis of baseline LDL-C and 10-year CVD risk for evolocumab and statin versus ezetimibe and statin



CV, cardiovascular; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year

HeFH: Deterministic analyses indicate that the incremental cost per QALY gained is approximately £[REDACTED] to £[REDACTED] for evolocumab compared with ezetimibe in patients with HeFH. The cost-effectiveness of evolocumab and ezetimibe in the different treatment scenarios is presented in Table 1-8.

Table 1-8 Incremental cost-effectiveness results: HeFH

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Scenario 1						
Statin	£18,154	8.24				
Ezetimibe and statin	£19,431	9.02	£1,277	0.78	£1,640	
Evolocumab and statin	[REDACTED]	10.17	[REDACTED]	1.93	[REDACTED]	[REDACTED]
Scenario 2						
No lipid-lowering therapy	£17,741	8.24				
Ezetimibe alone	£19,817	8.77	£2,076	0.53	£3,916	
Evolocumab alone	[REDACTED]	9.82	[REDACTED]	1.58	[REDACTED]	[REDACTED]
Scenario 3						
Ezetimibe alone	£19,817	8.77				
Evolocumab and ezetimibe	[REDACTED]	10.01	[REDACTED]	1.24	[REDACTED]	[REDACTED]
Scenario 4						
Statin and ezetimibe	£19,431	9.02				
Evolocumab, statin and ezetimibe	[REDACTED]	10.23	[REDACTED]	1.20	[REDACTED]	[REDACTED]
HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

5 Cost effectiveness

5.7 Base case results

The cost-effectiveness analysis has been conducted for the relevant populations within the decision problem according to the four treatment scenarios. Treatment scenarios for evolocumab and statin versus ezetimibe and statin (scenario 1), and evolocumab alone versus ezetimibe alone (scenario 2) are presented in full in this section. For brevity, the cost-effectiveness analyses for evolocumab and ezetimibe versus ezetimibe alone (scenario 3), and evolocumab, statin, and ezetimibe versus statin and ezetimibe (scenario 4) are presented as scenario analyses (Section 0). Summary details of these analyses are provided in Table 5-27.

Table 5-27 Modelled intervention and comparator for patients with and without existing CVD, and patients with HeFH

Pop.	Intervention	Comparator	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Analysis, Section, Tables
Without existing CVD	Evolocumab and statin	Ezetimibe and statin	N/A	N/A	N/A	Analysis A (threshold) according to LDL-C, Table 5-28 and Table 5-29
	Evolocumab alone	Ezetimibe alone	N/A	N/A	N/A	Analysis B (threshold) according to LDL-C, Table 5-30 and Table 5-32
	Evolocumab and ezetimibe	Ezetimibe alone	N/A	N/A	N/A	Not conducted
	Evolocumab, ezetimibe, and statin	Ezetimibe and statin	N/A	N/A	N/A	Not conducted
Existing CVD	Evolocumab and statin	Ezetimibe and statin	██████	0.44	██████	Analysis C, Error! Reference source not found. to Error! Reference source not found.
	Evolocumab alone	Ezetimibe alone	██████	0.42	██████	Analysis D, Error! Reference source not found. to Error! Reference source not found.
	Evolocumab and ezetimibe	Ezetimibe alone	██████	0.49	██████	Analysis E, Error! Reference source not found.
	Evolocumab, ezetimibe, and statin	Ezetimibe and statin	██████	0.44	██████	Analysis F, Error! Reference source not found.

Pop.	Intervention	Comparator	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Analysis, Section, Tables
HeFH	Evolocumab and statin	Ezetimibe and statin	██████	1.15	██████	Analysis G, Table 5-42 to Table 5-46
	Evolocumab alone	Ezetimibe alone	██████	1.05	██████	Analysis H, Table 5-47 to Table 5-51
	Evolocumab and ezetimibe	Ezetimibe alone	██████	1.24	██████	Analysis I, Table 5-62
	Evolocumab, ezetimibe, and statin	Ezetimibe and statin	██████	1.20	██████	Analysis J, Table 5-63
CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year;						

5.8 Without existing CVD

Analysis A: Evolocumab and statin versus ezetimibe and statin

Threshold analyses for evolocumab and statin versus ezetimibe and statin presented in Table 5-28 and Table 5-29 indicate the minimum 10-year CVD risk required for defined willingness-to-pay thresholds. A minimum 10-year risk could not be appropriately estimated based on the proposed price of evolocumab for defined willingness-to-pay thresholds.

Table 5-28 Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin)

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
2.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year							

Table 5-29 Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin)

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
2.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year							

Analysis B: Evolocumab alone versus ezetimibe alone

Threshold analyses for evolocumab alone versus ezetimibe alone presented in Table 5-30 and Table 5-31 indicate the minimum 10-year CVD risk required for defined willingness-to-pay thresholds.

Table 5-30 Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone)

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
2.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year							

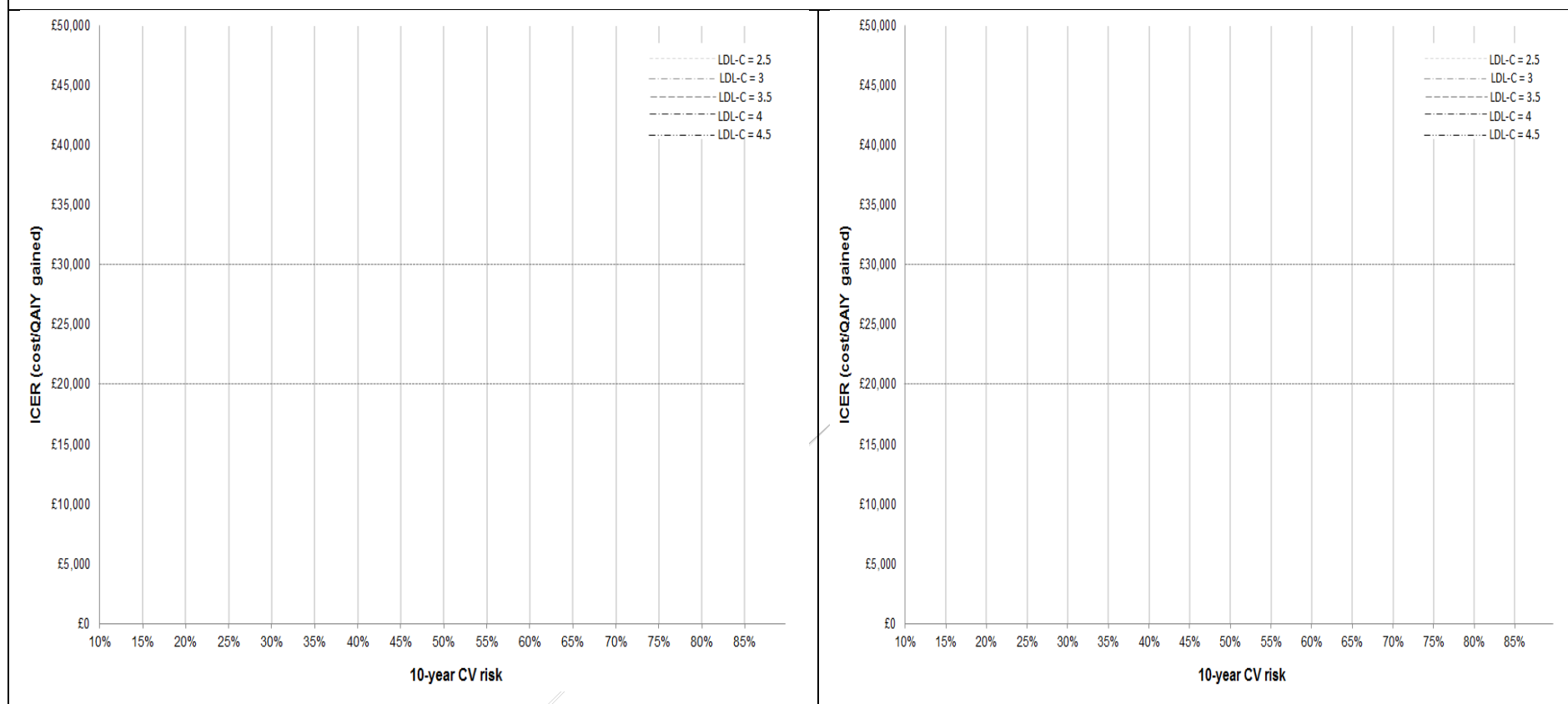
Table 5-32 Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone)

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
2.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)
4	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe and statin	-*	N/A	N/A			
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; QALY, quality-adjusted life-year							

Threshold analyses for various baseline LDL-C levels (2.5 mmol/L to 4.5mmol/L) for the cost-effectiveness of evolocumab and statin compared with ezetimibe and statin, and evolocumab alone compared with ezetimibe alone are presented in Figure 5-11.

Figure 5-11 Threshold analysis for different baseline LDL-C for scenarios 1 and 2



CV, cardiovascular; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year

5.10 Heterozygous familial hypercholesterolaemia

Analysis G: Evolocumab and statin versus ezetimibe and statin

Base case incremental cost-effectiveness results

The incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin in patients with HeFH is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 1.15 (Table 5-42).

Table 5-42 Analysis G: Base case incremental cost, incremental QALYs and ICER for the HeFH population (evolocumab and statin vs. ezetimibe and statin)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£18,154	8.24	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Ezetimibe and statin	£19,431	9.02	£1,277	0.78	£1,640	[REDACTED]
Evolocumab and statin	[REDACTED]	10.17	[REDACTED]	1.93	[REDACTED]	[REDACTED]

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Clinical outcomes – CV events

The base case undiscounted CV event rates for the HeFH population for evolocumab in combination with statin versus ezetimibe in combination with statin are presented in Table 5-43. This indicates that evolocumab and statin is anticipated to prevent approximately 0.74 CV events compared with ezetimibe and statin over the lifetime horizon.

Table 5-43 Analysis G: Base case undiscounted CV event rates

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	1.56	1.19	0.70	-0.49	0.49	61%
IS	0.33	0.24	0.14	-0.10	0.10	13%
HF	0.32	0.29	0.23	-0.05	0.05	7%
CHD death	0.68	0.62	0.49	-0.13	0.13	16%
IS death	0.16	0.18	0.22	0.03	0.03	4%
Total	3.06	2.52	1.78	-0.74	0.81	100%

ACS, acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; IS, ischaemic stroke

Disaggregated results – QALY gains by health state

Disaggregated QALYs for statin, ezetimibe and statin, and evolocumab and statin are presented in Table 5-44. This indicates a total QALY gain of 1.15 for evolocumab and statin compared with ezetimibe and statin.

Table 5-44 Analysis G: Base case summary of QALYs by health state

Health state	QALY: Statin	QALY: Ezetimibe and statin (comparator)	QALY: Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.56	0.41	0.23	-0.18	0.18	9%
IS	0.09	0.06	0.03	-0.03	0.03	2%
HF	0.09	0.08	0.06	-0.02	0.02	1%
ECVD	1.56	1.79	2.12	0.33	0.33	17%
Post-acute	2.61	2.64	2.47	-0.17	0.17	9%
No CVD	3.33	4.04	5.25	1.22	1.22	62%
Total	8.24	9.02	10.17	1.15	1.95	100%
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – costs by health state

The base case disaggregated costs show that there is an anticipated saving of £ [REDACTED] associated with evolocumab and statin compared with ezetimibe and statin. These savings are attributable to a reduction in ACS, IS, HF, CHD death and revascularisation costs (Table 5-45).

Table 5-45 Analysis G: Base case summary of costs by health state

Health state	Cost: Statin	Cost: Ezetimibe and statin (comparator)	Cost: Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	% absolute increment
ACS	£3,127	£2,287	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IS	£767	£540	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HF	£561	£478	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CHD death	£287	£248	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IS death	£169	£178	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ECVD	£1,138	£1,316	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Post-acute	£2,817	£2,838	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Revasc	£7,562	£5,350	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total	£16,427	£13,233	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; Revasc, revascularisation						

Summary of predicted resource use by category of cost

The resource use estimations show increased costs of £ [REDACTED] associated with evolocumab and statin compared with ezetimibe and statin over the time horizon. The summary in Table 5-46 indicates that these are due to additional costs for medication, and monitoring and training for evolocumab.

Table 5-46 Analysis G: Base case summary of resource use by health state

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£413	£4,787	██████	██████	██████	██████
Monitoring and training	£1,314	£1,411	██████	██████	██████	██████
Health states	£16,427	£13,233	██████	██████	██████	██████
Total	£18,154	£19,431	██████	██████	██████	██████

Analysis H: Evolocumab alone versus ezetimibe alone*Base case incremental cost-effectiveness results*

The incremental cost per QALY gained for evolocumab alone versus ezetimibe alone in patients with HeFH is £██████ based on incremental costs of £██████ and incremental QALYs of 1.05 (Table 5-47).

Table 5-47 Analysis H: Base case incremental cost, incremental QALYs, and ICER for the HeFH population

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
No lipid-lowering therapy	£17,741	8.24	██████	██████	██████	██████
Ezetimibe alone	£19,817	8.77	£2,076	0.53	£3,916	██████
Evolocumab alone	██████	9.82	██████	1.58	██████	██████
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Clinical outcomes – CV events

The base case undiscounted CV event rates for the HeFH population (statin intolerant or contraindicated) for evolocumab alone compared with ezetimibe alone are presented in Table 5-48. This indicates that evolocumab alone is anticipated to prevent approximately 0.69 CV events compared with ezetimibe alone.

Table 5-48 Analysis H: Base case undiscounted CV event rates

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	1.56	1.30	0.84	-0.47	0.47	62%
IS	0.33	0.26	0.16	-0.10	0.10	13%
HF	0.32	0.30	0.25	-0.05	0.05	6%
CHD death	0.68	0.64	0.54	-0.11	0.11	14%
IS death	0.16	0.18	0.21	0.03	0.03	4%
Total	3.06	2.69	1.99	-0.69	0.75	100%
ACS, acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – QALY gains by health state

Disaggregated QALYs for statin, ezetimibe and statin, and evolocumab and statin are presented in Table 5-49. This indicates a total QALY gain of 1.05 for evolocumab alone compared with ezetimibe alone.

Table 5-49 Analysis H: Base case summary of QALYs by health state

Health state	QALY: No lipid-lowering therapy	QALY: Ezetimibe alone (comparator)	QALY: Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.56	0.46	0.28	-0.18	0.18	10%
IS	0.09	0.07	0.04	-0.03	0.03	2%
HF	0.09	0.08	0.06	-0.02	0.02	1%
ECVD	1.56	1.71	2.02	0.31	0.31	18%
Post-acute	2.61	2.64	2.55	-0.10	0.10	6%
No CVD	3.33	3.80	4.87	1.06	1.06	63%
Total	8.24	8.77	9.82	1.05	1.70	100%
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established CVD; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – costs by health state

The base case disaggregated costs show that there is an anticipated saving of £ [REDACTED] associated with evolocumab alone versus ezetimibe alone when considering the health states. These savings are attributable to a reduction in ACS, IS, HF, CHD death and revascularisation costs (Table 5-50).

Table 5-50 Analysis H: Base case summary of costs by health state

Health state	Cost: No lipid-lowering therapy	Cost: Ezetimibe alone (comparator)	Cost: Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	£3,127	£2,541	██████	██████	██████	██████
IS	£767	£606	██████	██████	██████	██████
HF	£561	£504	██████	██████	██████	██████
CHD death	£287	£261	██████	██████	██████	██████
IS death	£169	£175	██████	██████	██████	██████
ECVD	£1,138	£1,258	██████	██████	██████	██████
Post-acute	£2,817	£2,845	██████	██████	██████	██████
Revasc	£7,562	£6,011	██████	██████	██████	██████
Total	£16,427	£14,201	██████	██████	██████	██████
ACS, acute coronary syndrome; CHD, coronary heart disease; ECVD, established; CHF, heart failure; IS, ischaemic stroke; Revasc, Revascularisation						

Summary of predicted resource use by category of cost

The resource use estimations show increased costs associated with evolocumab alone compared with ezetimibe alone (£██████). The summary in Table 5-51 indicates that these are due to additional costs for medication, and monitoring and training for evolocumab.

Table 5-51 Analysis H: Base case summary of resource use by health state

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment vs. comparator	Absolute increase	Absolute increment
Medication	£0	£4,235	██████	██████	██████	██████
Monitoring and training	£1,314	£1,380	██████	██████	██████	██████
Health states	£16,427	£14,201	██████	██████	██████	██████
Total	£17,741	£19,817	██████	██████	██████	██████

5.11 Sensitivity analyses

Probabilistic sensitivity analysis

The probabilistic sensitivity analysis was run with 1,000 simulations. Probabilistic sensitivity analysis outputs are represented graphically by plotting incremental cost and effectiveness pairs on the cost-effectiveness plane and presenting the likelihood of evolocumab being the optimal strategy across different maximum willingness-to-pay thresholds. The results of the various baseline LDL-C levels and corresponding 10-year CVD risk are presented in Table 5-52 to Table 5-55 for scenarios 1 and 2. The results of the probabilistic sensitivity analysis depicted as scatter plots are presented in the figures below for patients with existing CVD and HeFH based on scenarios 1 and 2 (Figure 5-12 to Figure 5-15). The ellipses represent the 95% CI and the gradients represent £20,000 and £30,000 incremental cost per QALY gained on the scatterplots.

Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

Table 5-52 Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Probability of optimal strategy at MAICER of £30,000 per QALY
2.5	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
4	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Table 5-53 Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Probability of optimal strategy at MAICER of £20,000 per QALY
2.5	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
3	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
4	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe and statin	-*	N/A	N/A				
	Evolocumab and statin		N/A	N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds								
CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Analysis B: Evolocumab alone versus ezetimibe alone

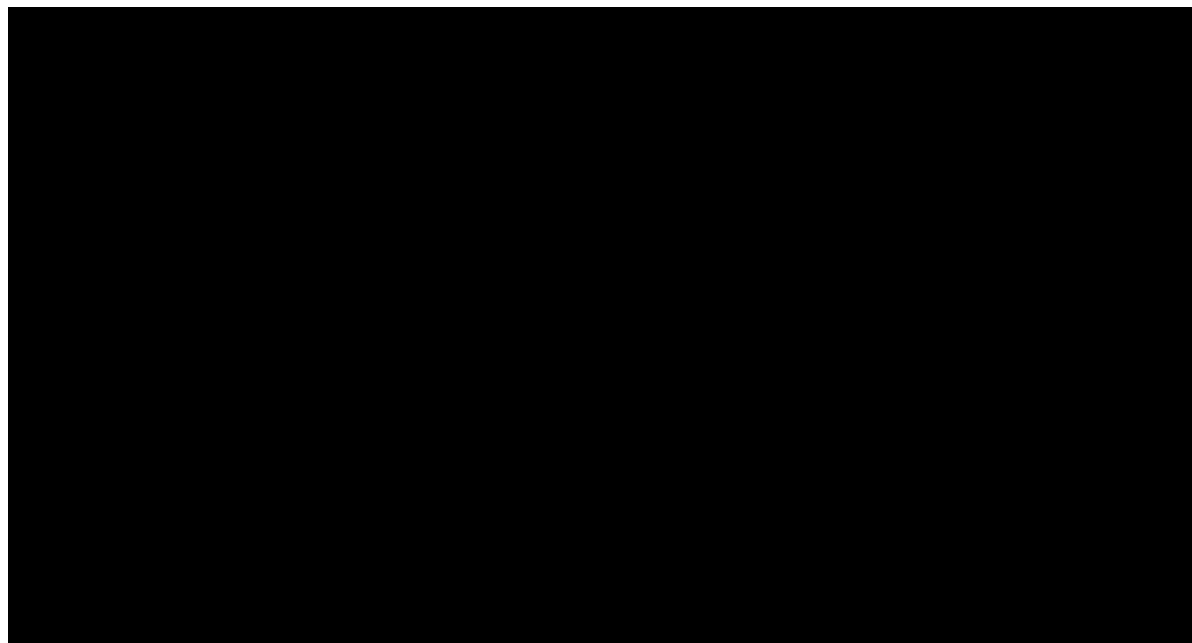
Table 5-54 Threshold analysis (up to £30,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone) [scenario 2]

Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Probability of optimal strategy at MAICER of £20,000 per QALY
2.5	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
3	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
4	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Table 5-55 Threshold analysis (up to £20,000 per QALY gained) for baseline LDL-C and 10-year CVD risk for patients without existing CVD (evolocumab alone versus ezetimibe alone) [scenario 2]

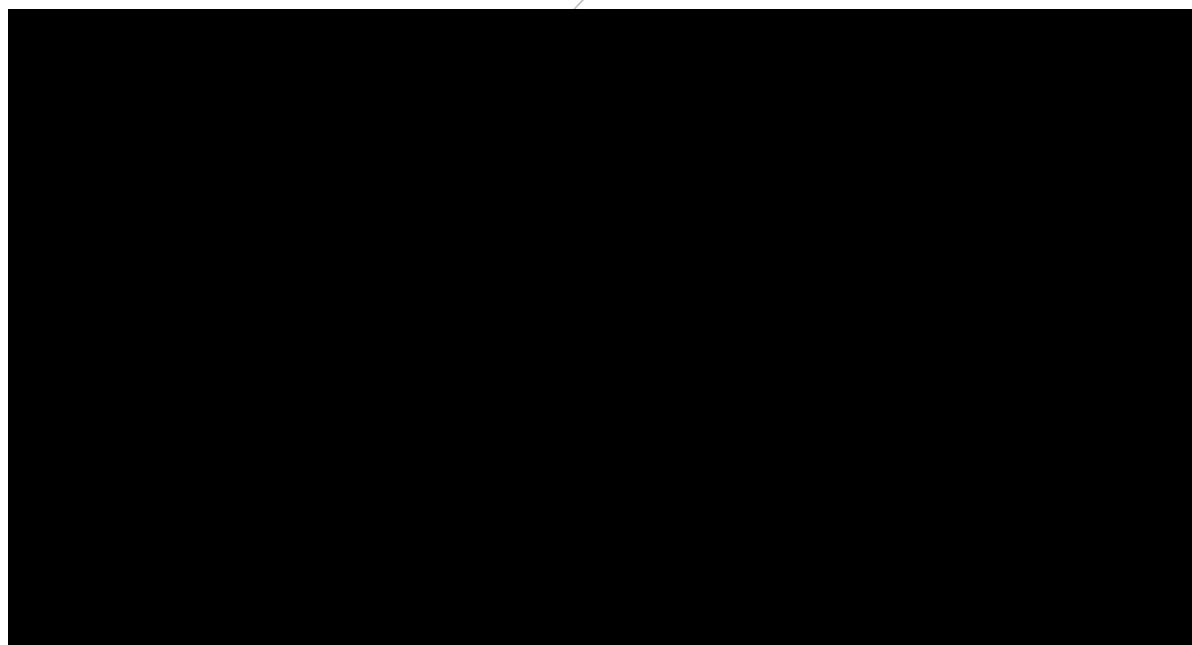
Baseline LDL-C (mmol/L)	Technologies	10-year CVD risk	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Probability of optimal strategy at MAICER of £20,000 per QALY
2.5	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
3	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
3.5	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
4	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
4.5	Ezetimibe alone	-*	N/A	N/A				
	Evolocumab alone		N/A	N/A	N/A	N/A	N/A	N/A
*Not achievable based on threshold analysis for defined willingness-to-pay thresholds								
CVD, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Figure 5-12 Scatterplot for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1]



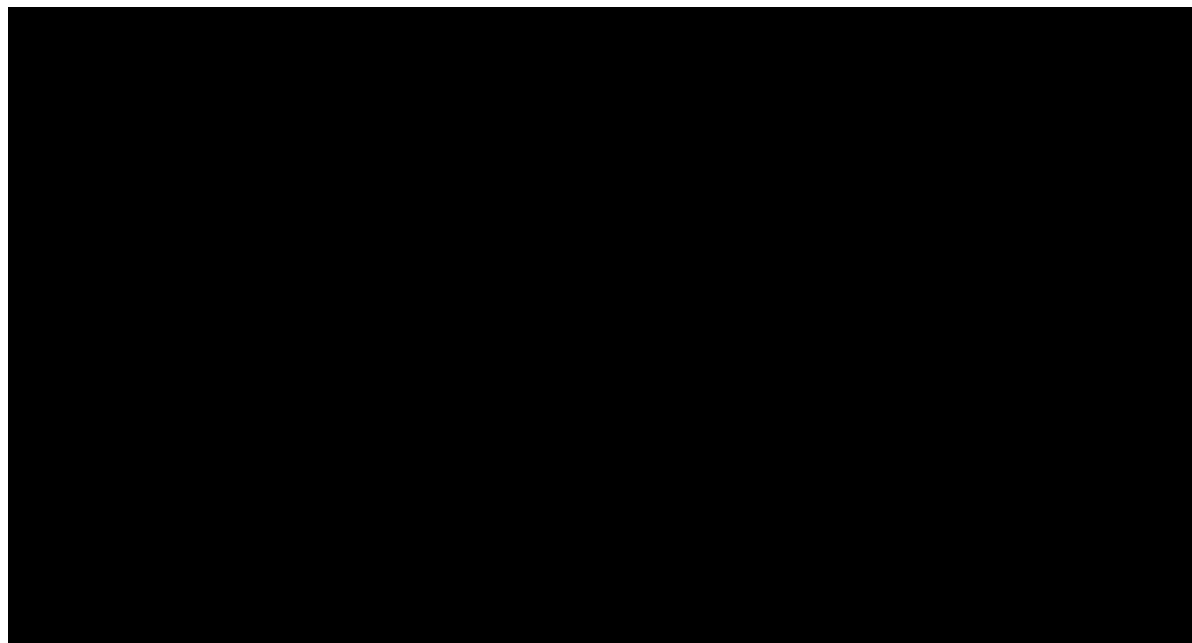
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention

Figure 5-13 Scatterplot for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2]



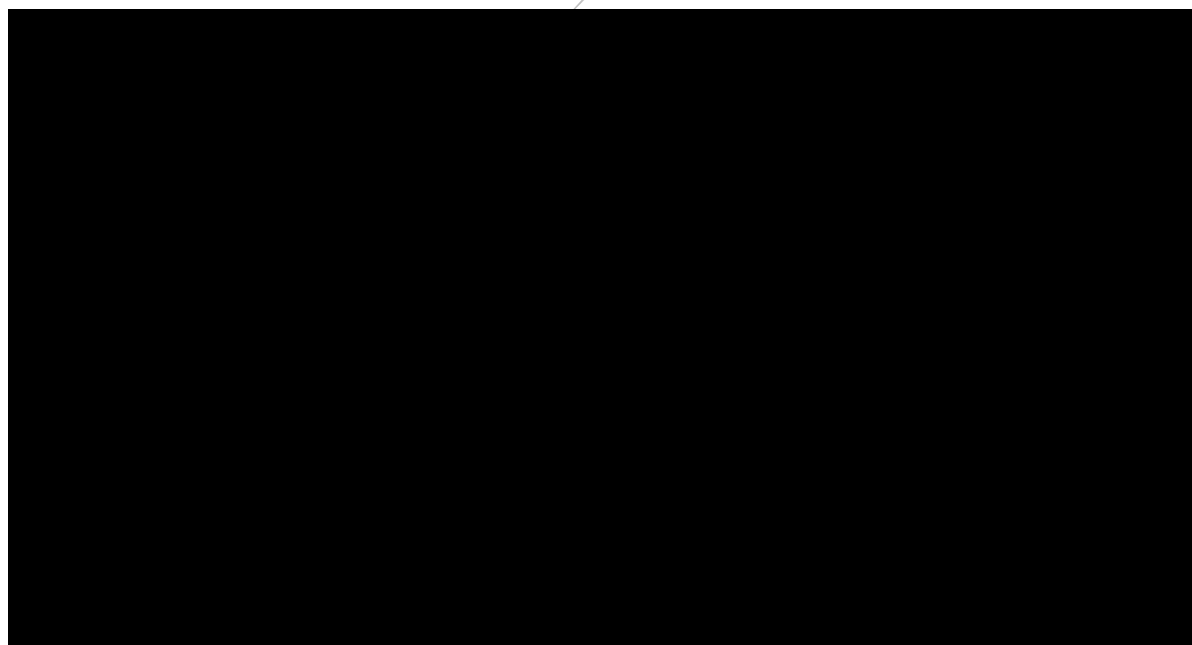
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention

Figure 5-14 Scatterplot for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

Figure 5-15 Scatterplot for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2]

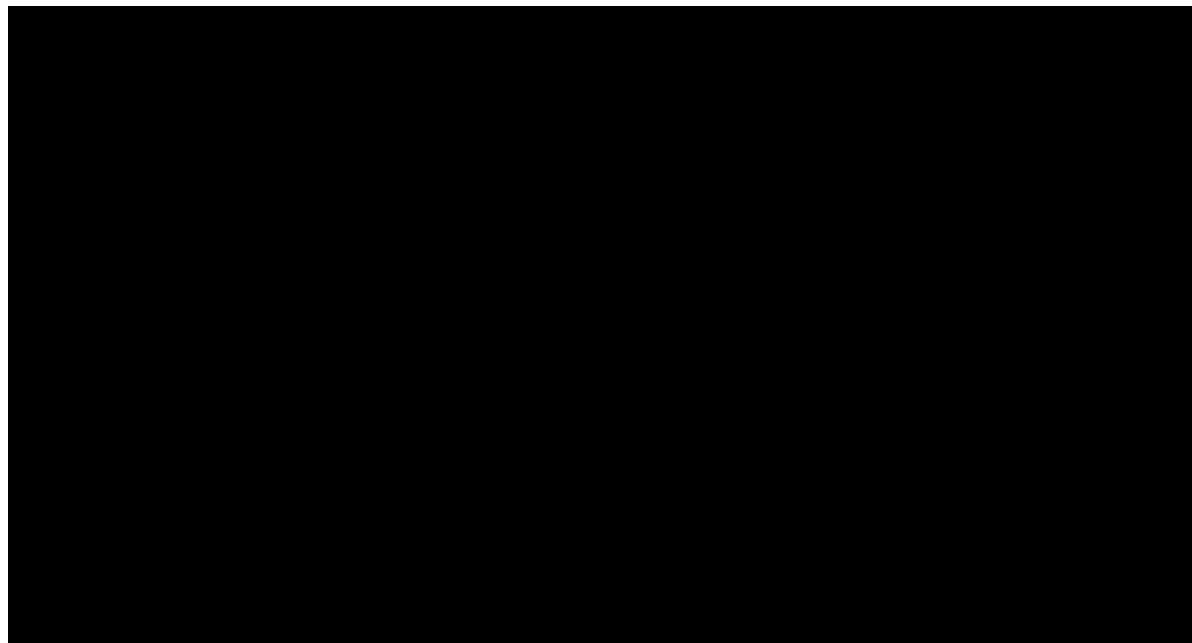


HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

In addition, cost-effectiveness acceptability curves were used to assess the proportion of simulations whereby the different treatment strategies for specific maximum acceptable ICERs. These are presented in Figure 5-16 to Figure 5-19 5-19 and summarised in Table 5- Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

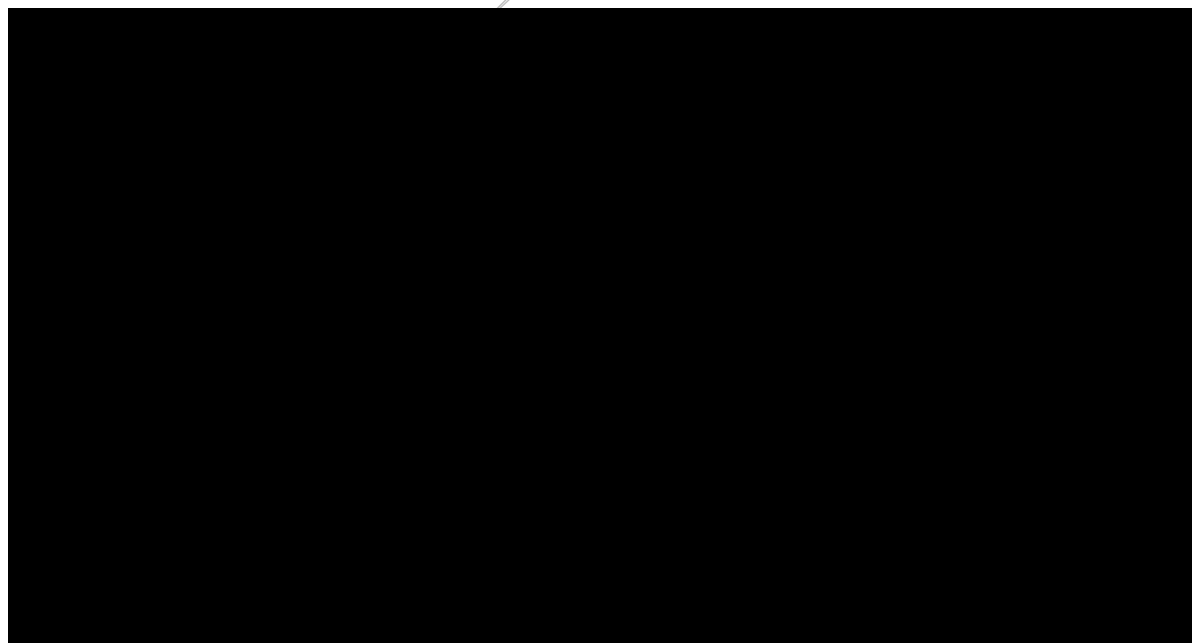
56. Furthermore, a comparison of the base case results for the deterministic and probabilistic analyses are presented in Table 5-57.

Figure 5-16 Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1]



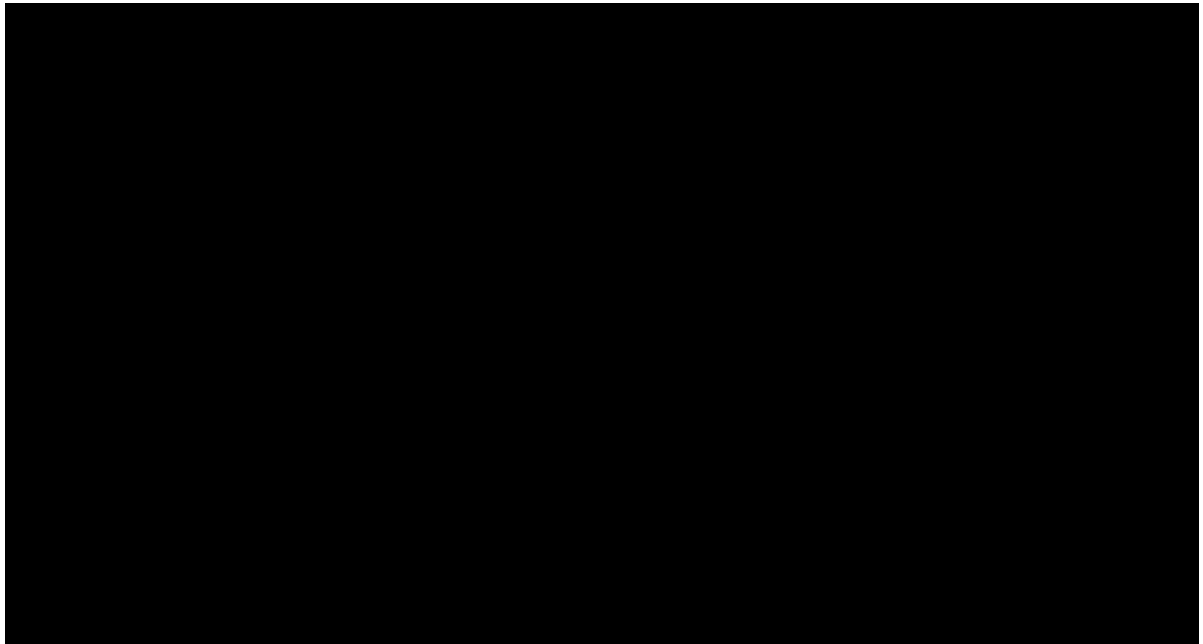
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 5-17 Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2]



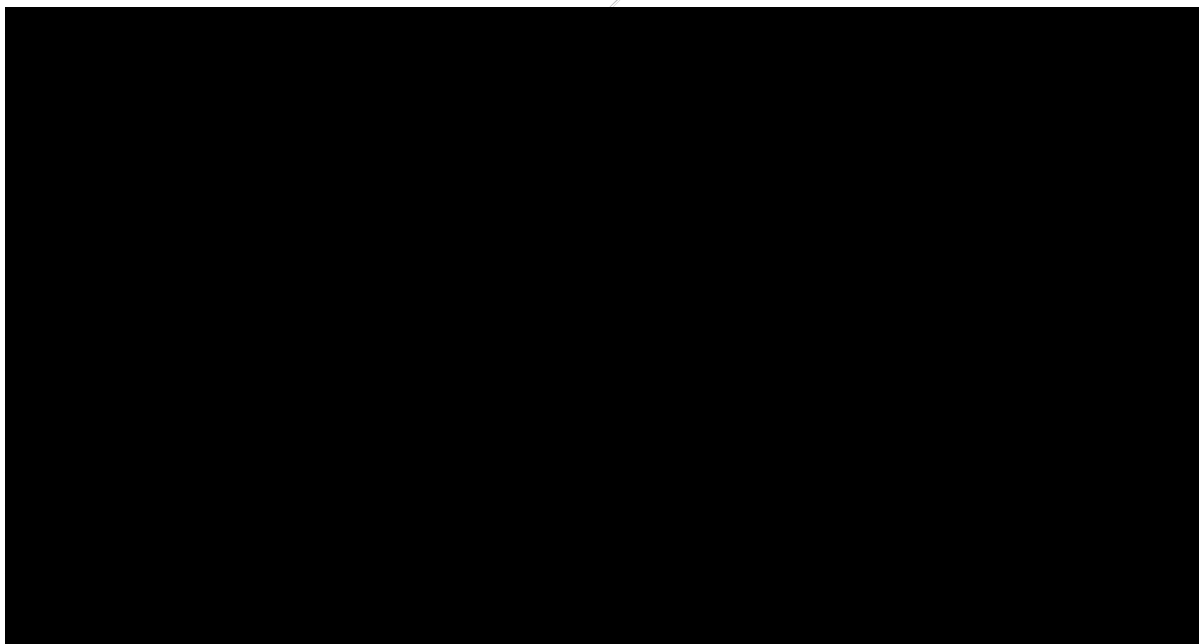
LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 5-18 Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol

Figure 5-19 Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol

Table 5-57 Deterministic and probabilistic incremental cost-effectiveness ratios

Pop.	Intervention	Comparator	ICER	
			Deterministic	Probabilistic
Existing CVD	Evolocumab and statin	Ezetimibe and statin		
	Evolocumab alone	Ezetimibe alone		
HeFH	Evolocumab and statin	Ezetimibe and statin		
	Evolocumab alone	Ezetimibe alone		
HeFH; heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; Pop., population; QALY, quality-adjusted life-year				

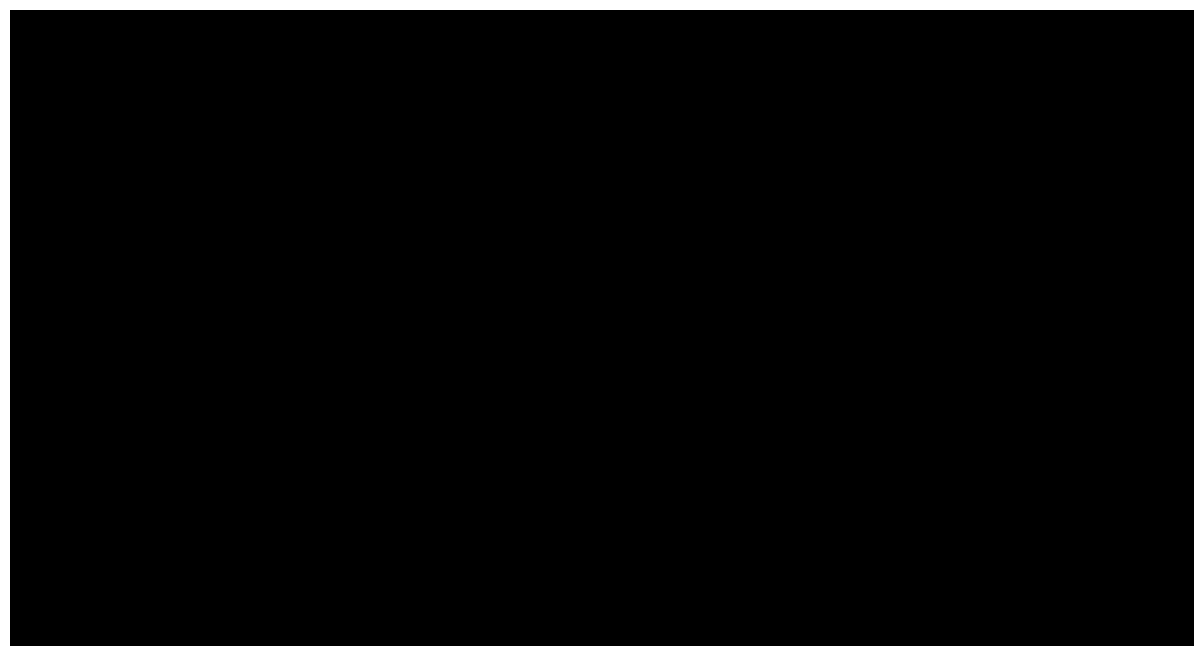
Deterministic sensitivity analysis

Deterministic sensitivity analyses were performed by means of one-way sensitivity analyses, where one parameter was varied relative to its base case value. The method adopted and the parameters tested are described in Section **Error! Reference source not found.** A summary of the results is presented below for patients with and without existing CVD and patients with HeFH for evolocumab and statin versus ezetimibe and statin (scenario 1). The additional scenarios are not presented as the results were not sensitive to the different treatment strategies covered in scenarios 2 to 4. All parameters where the incremental cost per QALY gained was sensitive by > 1% are presented in Tornado plots (**Error! Reference source not found.** to Figure 5-22).

The Tornado plots that indicate the most sensitive parameters for cost-effectiveness of evolocumab versus ezetimibe were:

- CV event rate ratio (HeFH alone)
- CPRD ratio ratios (secondary prevention alone)
- treatment duration
- effect of LDL-C reduction on CV events
- ezetimibe treatment effect
- evolocumab treatment effect
- 'ECVD' and 'post-ACS' health state utility multiplier.

Figure 5-22 Tornado plot: evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]



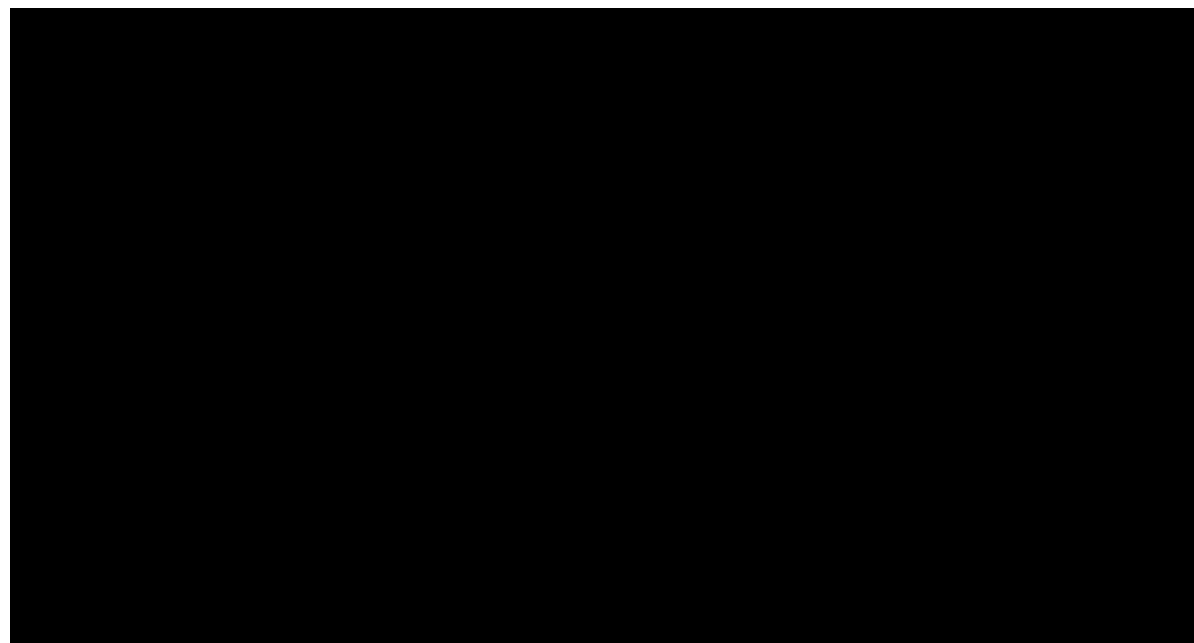
ACS, acute coronary syndrome; CI, confidence interval; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol

5.12 Scenario analysis

HeFH and severity of hypercholesterolaemia

For the HeFH population, the impact of severity of hypercholesterolaemia has been assessed on the basis of the baseline LDL-C level when treatment with evolocumab or ezetimibe would be initiated (scenario 1 modelled). The HeFH population modelled on the basis of RUTHERFORD-2 had a baseline LDL-C of 4.0 mmol/L (Table 5-5). In the UK, the National Audit of Familial Hypercholesterolaemia indicated that the median LDL-C is 3.3 mmol/L⁹⁰ (Figure 3-1). Scenario analysis indicates that evolocumab is anticipated to be a cost-effective treatment option when considering baseline LDL-C in accordance with the UK HeFH population (Figure 5-24 and Table 5-59). As for patients with existing CVD, scenarios 2 to 4 have not been presented based on severity of hypercholesterolaemia.

Figure 5-24 HeFH: Incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin (scenario 1) according to severity of hypercholesterolaemia



HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

Table 5-59 Scenario analyses: HeFH and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Baseline LDL-C	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
3.0 mmol/L	██████	£20,059	██████	9.62	8.83	0.79	██████
3.5 mmol/L	██████	£19,746	██████	9.93	8.92	1.00	██████
4.0 mmol/L	██████	£19,443	██████	10.16	9.02	1.14	██████
4.5 mmol/L	██████	£19,151	██████	10.36	9.11	1.25	██████
5.0 mmol/L	██████	£18,868	██████	10.54	9.20	1.34	██████
5.5 mmol/L	██████	£18,596	██████	10.72	9.29	1.43	██████
6.0 mmol/L	██████	£18,333	██████	10.89	9.38	1.51	██████
EvoMab; evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year							

Additional scenario analyses

Analysis I: Evolocumab and ezetimibe versus ezetimibe alone in HeFH

The incremental cost per QALY for evolocumab and ezetimibe versus ezetimibe alone in patients with HeFH is £██████ based on incremental costs of £██████ and incremental QALYs of 1.24 (Table 5-62).

Table 5-62 Analysis I: Base case incremental cost, incremental QALYs and ICER for patients with HeFH (evolocumab and ezetimibe versus ezetimibe alone)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Ezetimibe	£19,817	8.77			
Evolocumab and ezetimibe		10.01		1.24	
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Analysis J: Evolocumab, statin, and ezetimibe versus statin and ezetimibe in HeFH

The incremental cost per QALY for evolocumab, statin, and ezetimibe versus statin and ezetimibe in patients with HeFH is £ based on incremental costs of £ and incremental QALYs of 1.20 (Table 5-63).

Table 5-63 Analysis J: Base case incremental cost, incremental QALYs, and ICER for patients with HeFH (evolocumab, statin and ezetimibe vs. statin and ezetimibe)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Statin and ezetimibe	£19,431	9.02			
Evolocumab, statin and ezetimibe		10.23		1.20	
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Table 5-66 Scenario analyses – HeFH population (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALY s EZE	Δ QALYs	ICER
Base case	██████	£19,431	██████	10.17	9.02	1.15	██████
Evolocumab QM PFP	██████	£19,431	██████	10.11	9.02	1.09	██████
5-year treatment duration	██████	£17,107	██████	8.78	8.49	0.29	██████
10-year treatment duration	██████	£18,036	██████	9.23	8.69	0.55	██████
20-year treatment duration	██████	£19,070	██████	9.85	8.93	0.92	██████
Discounting: 0% costs, 0% effects	██████	£31,314	██████	15.31	12.99	2.32	██████
Discounting: 0% costs, 6% effects	██████	£31,314	██████	8.03	7.28	0.75	██████
Risk capping 75 years	██████	£19,499	██████	10.22	9.06	1.16	██████
NICE CG181 CV costs	██████	£20,642	██████	10.22	9.06	1.16	██████
TTO study utilities	██████	£19,499	██████	11.04	9.81	1.23	██████
Nurse training 30 minutes	██████	£19,499	██████	10.22	9.06	1.16	██████
Nurse training 2 hours	██████	£19,499	██████	10.22	9.06	1.16	██████
CV, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia [ID765]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. *About you and your organisation*

Your name: [REDACTED] [REDACTED]

Name of your organisation: HEART UK

Your position in the organisation: [REDACTED] [REDACTED]

Brief description of the organisation: HEART UK is the UK's cholesterol charity and provides support, guidance and education services to healthcare professionals and people and families with concerns about cholesterol. HEART UK is registered as a charity with the Charity Commission (charity number 1003904). We do not receive any government funding and are funded through donations from individuals and organisations.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. *Living with the condition*

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Following a Familial hypercholesterolaemia (FH) diagnosis patients can often initially find it difficult to implement new lifestyle decisions, such as being more conscious about what they eat and how often they exercise. However, once these new habits are established and they have found a suitable medication, we find that patients can live care-free lives, unaffected by their disease.

In the long term though, patients can experience concern around passing the condition onto their children. Indeed, carers for children diagnosed with FH can find living with this condition more difficult. Ensuring a young child is on a continual healthy diet and teaching them how to make the right choices themselves when they are offered various foods when they are out of the home, can prove extremely difficult.

3. *Current practice in treating the condition*

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Patients want their cholesterol levels to be normal and their cardiac risk to be reduced to help increase life expectancy to the national average by avoiding any early onset heart problems, preferably with few or no side effects so they can continue to live normal lives.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

For most patients with familial and non-familial hypercholesterolaemia statins are the mainstay of treatment and they are generally well tolerated. Some patients cannot tolerate even a very low dose and in this circumstance alternative treatments such as Ezetimibe are likely to be required and are usually better tolerated.

In some patients, particularly those with more severe hypercholesterolaemia, maximum statin treatment does not reduce their cholesterol sufficiently and add on treatment is required. This is most effectively and easily given by Ezetimibe, but occasionally other treatments such as bile acid sequestrants or fibrates are used. Bile acids often produce gastrointestinal side effects and fibrates are not very efficacious. In extremely severe cases LDL apheresis may be considered, but this is very invasive, time consuming and not available in many parts of the country.

4. *What do patients or carers consider to be the advantages of the treatment being appraised?*

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)

- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Evolocumab, taken in conjunction with a statin and Ezetimibe, helps FH patients reduce their cholesterol up to a further 60 per cent.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Evolocumab is a more preferential option than invasive and debilitating procedures such as apheresis.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

Unknown

5. Some patients find that they are more likely to stick with a singular treatment, involving only one pill a day, rather than having to take Ezetimibe along with a statin as two separate drugs. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)

Appendix G – patient/carer organisation submission template

- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Some patients report experiencing differing advice about statins and the use of secondary drugs, such as Ezetimibe to compliment them.

Please list any concerns patients or carers have about the treatment being appraised.

There are concerns around the expense of the treatment, with some patients concerned about the cost of paying for prescriptions for the remainder of their lives. This is particularly a concern as there is disparity with other genetic or life-long conditions, such as diabetes, where patients are able to have free medication.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

No

6. *Patient population*

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Those patients who have intolerance to statins and/or are at high risk of developing CVD. For further information see section 3 above.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Patients will generally have a similar response to the treatment.

7. *Research evidence on patient or carer views of the treatment*

Is your organisation familiar with the published research literature for the treatment?

☐ Yes

If you answered ‘no’, please skip the rest of section 7 and move on to section 8.

Please comment on whether patients’ experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

During trials patients generally have more intensive and frequent review/guidance to ensure adherence and monitor outcomes.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

No

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not available

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;

- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Those with difficulties injecting as no tablet form of Evolocumab is available. This may be a particular issue for the Asian patients who we know through experience of diabetes have a particular dislike of self-injecting medicines.

9. Other issues

Do you consider the treatment to be innovative?

Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

It is a new class of drug which has the ability to further reduce cholesterol by 60 per cent in addition to current standard of care.

Are there any other issues that you would like the Appraisal Committee to consider?

The availability for Evolocumab is vital for a number of FH patients and their families who currently cannot tolerate statins and are at high risk of developing early onset of cardiac problems without the use of expensive, invasive, time consuming and debilitating procedures.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- If FH is properly managed through lifestyle changes and medications, patients can live care-free lives, unaffected by their disease
- Patients want their cholesterol levels to be normal and their cardiac risk to be reduced to help increase life expectancy
- In some patients, particularly those with more severe hypercholesterolaemia, maximally tolerated statin plus other lipid lowering

Appendix G – patient/carer organisation submission template

medications does not reduce their cholesterol sufficiently, therefore add on treatments such as Evolocumab are necessary to avoiding the development of CVD

- Patients will need support when initiating treatment given the new method of administration (injection)
- Evolocumab is a non-statin with good efficacy that is vital for a number of FH patients and their families and should therefore be accessible by this set of patients

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: ■■■■■

Name of your organisation: ■■■■■/Newcastle upon Tyne Hospitals

Are you (tick all that apply):

- **TICK** a specialist in the treatment of people with the condition for which NICE is considering this technology?
- **TICK** a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- **TICK** an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? **MEMBER**
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

RESPONSE:

The mainstay of treatment for both primary hyperlipidaemia and mixed dyslipidaemia is with statins where tolerated. Other lipid lowering agents including ezetimibe, fibrates, and bile acid sequestrants are safe but less potent and lack of clinical endpoint outcome studies and are not recommended in current NICE guidance (CG181). Fibrates are the mainstay of treatment for severe hypertriglyceridaemia (>10mmol/L).

Patients with familial hypercholesterolaemia (FH) are at greater risk, and according to NICE Guidance (CG71) may benefit from the greater efficacy of combination therapy (statin plus ezetimibe or bile acid sequestrants) but some patients are poorly controlled on maximum combination therapy and if suffering from symptomatic progressive coronary disease, LDL apheresis may be considered as the prognosis is poor.

The expected place for the new anti-PCSK9 antibodies is in people with "primary hypercholesterolaemia or mixed hyperlipidaemia" who are either intolerant of inadequately responsive to high intensity statin treatment in line with current NICE guidance. The definition of an adequate response and statin intolerance require definitions.

At present ezetimibe is the "standard of care" alternative treatment but usage varies widely due to confusion regarding negative surrogate endpoint trials (ENHANCE).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia

Patients with heterozygous FH are at higher risk and should be considered separately. Consideration should be given to identification of a subgroup with severe heterozygous FH e.g. those with baseline LDL-C >8.0 - 8.5 mmol/L who are unlikely to achieve an adequate response to conventional therapy. Patients who have heterozygous FH caused by gain-of-function (GOF) mutations in the PCSK9 gene have severe FH and typically poor response to statins but appear to respond particularly well to anti-PCSK9 therapy

Patients who are intolerant of statins are at higher risk, but present a difficult diagnostic problem there is a lack of consensus on definitions of statin intolerance. These patients should be considered separately from those who are poorly responsive. Patients who have established cardiovascular disease (secondary prevention) and are therefore at the highest level of risk should be considered separately from those requiring treatment for primary prevention.

The technology be used in secondary care, specialist clinics. Additional professional input from specialist nurses would be required for training and troubleshooting, and possibly community nurses may be required to support patients who are unable to self-administer the injections.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

RESPONSE:

I am familiar with the technology having been local PI for two clinical trials which have now entered open-label extension phase. The latter reflects circumstances of UK clinical practice, however patients are likely to require more frequent follow-up

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia

appointments that similar patients treated with statins and ezetimibe (3-6 monthly rather than annually) as development of neutralising antibodies and loss of effectiveness requires monitoring. The trials measured only surrogate outcomes but in FH patients large scale studies with hard outcomes are unlikely to be conducted and long term studies in statin intolerant patients against placebo are not available.

In my experience, the therapy has been well tolerated with only infrequent minor injection site problems (eg. Bruising). Flu-like symptoms and a transient cutaneous eruption remote from the injection site on one occasion were the only other issues, however large databases pooled from the clinical trials will be a more reliable guide, once they become available. Subcutaneous injection therapy is not acceptable to all patients but most patients are happy to self administer injections, store supplies of injectors in their refrigerator and the manage therapy confidently themselves using a patient diary. Most prefer a single, fortnightly injection.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

RESPONSE: NO

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia

RESPONSE

The major issues centre around

1. The need for specialist nursing support to train patients to self-inject, and
2. Development and implementation of pathways for assessment and referral of potentially eligible patients from primary to secondary/tertiary care
3. The capacity for lipid specialist assessment if this is required to determine eligibility and or confirm the case of clinical need e.g. truly statin-intolerant (e.g. statin related muscle toxicity with documents rise in CK >4 ULN versus pseudo-intolerance with non-specific musculoskeletal symptoms)

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

RESPONSE:

There are no major equality issues but the following should be noted

1. There is a need for community nursing support to administer treatment to patients to who cannot self-inject whether due to disability or personal preference
2. Some ethnic groups may be unwilling to accept injection therapy
3. Geographically remote areas may have difficulty accessing specialist clinic support to initiate therapy, but this is much less than the problems of accessing LDL-apheresis

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Anthony S. Wierzbicki

Name of your organisation :

**Guy's & St Thomas Hospitals, London, UK
HEART-Uk nominated clinical expert**

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **No**
- other? (please specify) **Previous Chair (2012-4): NICE Lipid management & cardiovascular disease risk assessment guideline CG181 and clinical expert member NICE Post-MI , Lipids and CVD Risk Quality Standards Committee (2014-15)**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Familial hypercholesterolaemia (FH) is managed by a mixture of secondary and primary care. Specialist lipid clinics do not exist in all locations in the UK and many patients with this condition are not diagnosed or simply receive statin therapy following screening (NHS Health Check) or after review by general cardiology or diabetes and endocrine services.

National and international consensus exists on the management of FH. Most guidelines follow NICE CG71 and TA132 on recommendations for diagnosis, statin and ezetimibe therapy. Some differences exist as to whether a >50% LDL-C reduction is adequate in heterozygous FH (HeFH) or whether patients should be treated to a LDL-C target. Most clinicians follow the 50% recommendation as achieving general population LDL-C targets is very difficult with current agents. New US and UK NICE CG181 guidelines suggest treatment based on underlying cardiovascular disease (CVD) risk rather than LDL-C targets.

Some patients with polygenic elevations in LDL-C can have very high LDL-C (overlapping with genetically diagnosed HeFH) and not respond fully to current therapies despite proof of adequate adherence. They often show aggressive progression of underlying atherosclerosis and CVD driven by a number of factors including inflammation and raised lipoprotein (a).

Statin intolerance has been defined on the basis of failure to tolerate 3 statins (after varying drug, dose and administration interval). They include patients with underlying primary muscle diseases as well as a poorly defined group in whom no predisposing cause is found. The syndrome of statin-related myalgia is real as interference of statin lactones with a CoQ10 binding site in complex 3 of the mitochondrial respiratory chain has been demonstrated. Consensus management algorithms have been evolved originally in Canada and now in Europe including a brief statement in NICE CG181. These patients are at increased CVD risk due to high residual LDL-C concentrations because of the low-efficacy medications that can be used in their management.

Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, Roden M, Stein E, Tokgözoğlu L, Nordestgaard BG, Bruckert E, De Backer G, Krauss RM, Laufs U, Santos RD, Hegele RA, Hovingh GK, Leiter LA, Mach F, März W, Newman CB, Wiklund O, Jacobson TA, Catapano AL, Chapman MJ, Ginsberg HN; European Atherosclerosis Society Consensus Panel.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management.

Eur Heart J. 2015 May 1;36(17):1012-22. doi: 10.1093/eurheartj/ehv043. Epub 2015 Feb 18. Review

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Yes. There is sub-group within patients with HeFH who have increased cardiovascular risk. A preliminary definition of severe HeFH based on the 90th centile of the lipid distribution (LDL-C >8 mmol/L) suggest they have a 25% increase in CVD events even above that seen in the general HeFH population with this increase being over and above that due to classical CVD risk factors.

Besseling J, Kindt I, Hof M, Kastelein JJ, Hutten BA, Hovingh GK. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. Atherosclerosis. 2014 Mar;233(1):219-23. doi: 10.1016/j.atherosclerosis.2013.12.020. Epub 2014 Jan 11.

Patients completely intolerant to statins with derive only small benefits from other currently available agents and have a high residual risk for CVD events. Fibrates deliver a small reduction in non-fatal myocardial infarction (11%; limited use recommended in NICE CG181) while bile acid sequestrants deliver an 18% reduction(on very dated monotherapy trial data; not recommended in CG181). Recent data for ezetimibe (IMPROVE-IT trial; 2015) suggest it will deliver a 17% reduction in CVD events roughly similar to that seen for fibrates (fatal and non-fatal MI/ CVA: 15/1000 vs. 13/1000 patients over 5 years).

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

This technology would be used in secondary care. Training for patients would need to be provided in the use of injection devices. This is best done by specialist lipid or diabetes nurses who are familiar with providing this type of training. Once initiated care could be transferred to primary care for repeat prescription in the long-term though it is likely that most patients on anti-PCSK9 therapy would remain under the care of secondary care clinics (e.g. lipid clinics).

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

No. A few patients receive evolocumab as part of clinical trial extension programmes.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Relevant guidelines include NICE Lipid Modification and Cardiovascular Risk Assessment CG181. This did not include ezetimibe in its scope as this was subject to a Technology Appraisal process update (from TA132) (currently out for consultation).

CG181 moved to a risk-based method of defining individuals likely to benefit from lipid-lowering therapies as opposed to LDL-C targets. It recommended maximising statin therapy in patients with established CVD- ideally Atorvastatin 80mg and the use of Atorvastatin 20mg and if necessary higher doses in primary prevention based on the risk profile of the patient. It highlighted the high probability of the presence of FH in patients with presenting Total Cholesterol > 9mmol/L (extending NICE CG71) and gave a basic management strategy for statin intolerance.

NICE CG71 (Familial Hypercholesterolaemia) is due to be updated but remains the mainstay of clinical practice for diagnosis and management of this disorder. It recognises the utility of maximising statin therapy and where appropriate adding ezetimibe (from TA132)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The technology is an injection and thus more difficult to use than current tablet therapies. Initial training for patients in use of the injection device will be required.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Not applicable

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Evolocumab is an antibody member one of the first of a new class of lipid-lowering agents working by inhibition of PCSK-9 – a protein that controls expression of LDL receptors. This is the first new class of lipid-lowering drugs licensed for 10 years- the previous novel molecule being ezetimibe.

An extensive programme of clinical trials has been conducted with evolocumab across the world. This has included recruitment of patients with a clinical diagnosis of HoFH and a large group with HeFH, patients with moderate dyslipidaemia in the form of hypercholesterolaemia and those with mild (triglycerides <4mmol/L) mixed hyperlipidaemia as well as patients who have proved intolerant to statin therapies. The patients recruited to those trials are representative of the UK population with these disorders attending secondary care settings (HoFH and HeFH), and/or primary care (moderate dyslipidaemia and statin intolerance). The recruitment criteria for the trials did not specify genetic diagnosis of FH as recommended in NICE CG71 but there remains considerable variation in the provision of genetic testing in the UK with most centres in England not providing this diagnostic service. This means that recruitment to the trials and UK clinical practice are likely coincident.

A meta-analysis of the efficacy of all the drugs in the class has recently been published. This shows a consistent efficacy of the drugs with reductions in LDL-C ranging from 50-65% in all populations depending on the dose of the antibody used. Top doses show consistent efficacy with an approximate 60-65% reduction in LDL-C. This compares with a maximum 55% reduction seen in LDL-C with statins or 22% with ezetimibe.

Li C, Lin L, Zhang W, Zhou L, Wang H, Luo X, Luo H, Cai Y, Zeng C.
Efficiency and safety of proprotein convertase subtilisin/kexin 9 monoclonal antibody on hypercholesterolemia: a meta-analysis of 20 randomized controlled trials.
J Am Heart Assoc. 2015 Jun 15;4(6):e001937. doi: 10.1161/JAHA.115.001937.

Trials to date only include LDL-C data. This is a reasonable surrogate for future CVD benefits. Outcomes for the efficacy of reducing LDL-C in producing CVD event reductions comes from randomised controlled trials of ileal bypass surgery (Programme of Surgical Correction of Hyperlipidemia; n=952; 20 years follow-up) as well as statins, bile acid sequestrants (dated) and recently ezetimibe (IMPROVE-IT).

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The side-effects seen in the trials were generally very mild if present at all and no specific signals were detected. Very mild occasional injection site reactions seem to be the only side-effect that are clearly drug attributable. Open label safety and efficacy extension data is now available for evolocumab. A reduction in cardiovascular events is seen but numbers of events are very small and thus this can only be considered as preliminary reassuring data for later validation in large scale trials.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA; Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators.

Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015 Apr 16;372(16):1500-9. doi: 10.1056/NEJMoa1500858. Epub 2015 Mar 15.

There seems to be little distinct side-effect pattern detectable in wider meta-analysis of all the anti-PCSK9 antibodies in the trials (phase 1-3) to date. Longer term safety data would be desirable for the class and will be provided by the on-going large CVD outcome trials with this agent (FOURIER study) and its analogues. These are due to report possibly in late 2016 but likely in 2017.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

No equality or diversity issues expected to be identified.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The single most surprising finding from the evolocumab trial programme was the unexpected efficacy of PCSK-9 inhibition in patients with some sub-types of HoFH. HoFH is strictly defined as the presence of mutations in genes affecting the LDL-receptor pathway present in both maternal and paternally derived alleles. However clinically a mutation cannot be identified in one allele in 25% of HoFH cases leading to their being also described as cases of severe HeFH. Given this overlap/confusion in diagnostic criteria licensing authorities such as the European Medicines Agency have accepted clinical definitions for HoFH using criteria such as untreated Total Cholesterol >15mmol/L and LDL-C >13 mmol/L for the approval of lipid-lowering agents for this orphan indication (e.g. lomitapide). These are also accepted in the European consensus statement on HoFH.

Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjærg-Hansen A, Watts GF, Aversa M, Boileau C, Borén J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia.

Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. 2014 Aug 21;35(32):2146-57. doi: 10.1093/eurheartj/ehu274. Epub 2014 Jul 22.

Criteria for the diagnosis of homozygous familial hypercholesterolaemia

Genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus

OR

An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥8 mmol/L (300 mg/dL)* together with either:

- Cutaneous or tendon xanthoma before age 10 years***

or

- Untreated elevated LDL-C levels consistent with heterozygous FH in both parents***

**** These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH***

HoFH patients show a reasonable (but overall inadequate) response to the weak lipid –lowering agent ezetimibe – 20-23% LDL-C reduction but often show highly variable responses to statin therapy varying from zero-30% LDL-C reduction. Despite their small relative response treatment does result in clinical benefit on cardiovascular outcomes. Data is available from a cohort in whom apheresis was only performed in 19% and porto-caval shunt in 17%.

Raal FJ, Pilcher GJ, Panz VR, van Deventer HE, Brice BC, Blom DJ, Marais AD. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Circulation. 2011 Nov 15;124(20):2202-7. doi: 10.1161/CIRCULATIONAHA.111.042523. Epub 2011 Oct 10.

Data in a cohort of HoFH patients with evolocumab shows efficacy ranging from nil (LDL-receptor) homozygous null patients to 40% LDL-C reduction. This is highly significant as treatment options for HoFH are limited, efficacy of statins is variable and usually reduced. Access to apheresis is highly variable across the UK and the invasive nature of this expensive time-consuming procedure means that acceptability to patients is low with some patients discontinuing this therapy and preferring to take their chances with CVD events and to tolerate the disability of living with angina. A substantial cost-saving to the NHS would be possible through reduction in the number of patients attending apheresis services or at least the in increasing the intervals between treatments.

Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, Wasserman SM, Stein EA; TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):341-50. doi: 10.1016/S0140-6736(14)61374-X. Epub 2014 Oct 1.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

**Most patients would already be attending lipid clinics however an increase in workload is likely to be expected.
Facilities for patient training in injection device use will need to be provided.**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia [ID765]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Steve Forster

Name of your nominating organisation: HeartUK

Do you know if your nominating organisation has submitted a statement?

Yes

Do you wish to agree with your nominating organisation's statement?

Yes

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

Yes

- a carer of a patient with the condition?

No

- a patient organisation employee or volunteer?

No

Do you have experience of the treatment being appraised?

No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. *Living with the condition*

What is your experience of living with the condition as a patient or carer?

Identified the condition in 2009, via routine blood test at GP. Initial shock, my own lack of knowledge and understanding. Feel lucky/thankful to have had the condition identified. The change in diet and lifestyle combined with medication has actually improved my life, I am now fitter healthier. No side effects from medication that I am aware of. Taken opportunities to learn more about the condition. Heart UK helped in the support and dietary advice, also opportunities to share my story in order to encourage others to get checked. Concerned about the general assumptions made by the public regarding high cholesterol and its association with being overweight. Excellent support and encouragement from GP and Lipid clinic. FH has actually changed my life for the better. It's like getting another chance so I'm living it !!

3. *Current practice in treating the condition*

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Contribute to the lowering of total cholesterol in particular LDL and Triglycerides (the bad stuff) combined with few or no side effects. Recognition that no treatments are likely to be a silver bullet and need to be combined with a change of diet and lifestyle which then needs to be maintained alongside the treatment.... I see the diet and lifestyle change as part of the treatment, however there needs to be a degree of self motivation and or support from family, friends, health professionals and health organisations eg Heart UK

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

An excellent GP who had knowledge of high cholesterol and FH she took the time to investigate my family history and then refer me to Lipid clinic. The treatment I have had has been excellent. No hassle with current GP re my bi annual blood tests (occasionally have to ask for blood test result print outs) – being told test is normal not enough information. I continue with the

same medication as prescribed in 2010 and appears to be contributing to treating the condition.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Not sure as I am not aware that I have had any side effects from statin treatment

Please explain any advantages that you think this treatment has over other NHS treatments in England.

An alternative for people with a condition who appear to have side effects and have a true statin intolerance. It could be combined with low dose statin. Potentially a useful diversion for certain elements of the media who seem to be periodically critical of statins ! ☺

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

other than I guess it's not going to "work" for everyone and issues of availability and accessibility are paramount particularly for true statin intolerance patients.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

more concerned about diagnosis than treatment. My experience of treatment has been excellent however had I not been diagnosed I may well have had a cardiovascular incident .. may not be alive today ! Diagnosis and education about the condition is very important.

Please list any concerns you have about the treatment being appraised.

None, the more options that are available for those living with the condition I think is a helpful way forward providing the treatment is accessible.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None

6. *Patient population*

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Possibly those who have a condition that could be describe as severe or chronic and those where current treatments have had limited effects or uncomfortable side effects.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

not sure .. unless there is a reduction of current treatments in preference to this treatment. Hopefully its not an either or ...more of an additional option particularly for people who have a true statin intolerance

7. *Research evidence on patient or carer views of the treatment*

Are you familiar with the published research literature for the treatment?

No

If you answered ‘no’, please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. *Equality*

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. *Other issues*

Do you consider the treatment to be innovative?

Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

Alternative for patients who have a true statin intolerance

Is there anything else that you would like the Appraisal Committee to consider?

How to create an awareness that this treatment is available and accessible

10. *Key messages*

In no more than 5 bullet points, please summarise the key messages of your submission.

- Early diagnosis of the condition is critical
- Information and support for patient
- Treatment available to the right patients- easy access
- Medical intervention is part of a treatment programme
- Continued awareness raising of condition and treatments made available



Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: A Single Technology Appraisal

Produced by	School of Health and Related Research (SchARR), The University of Sheffield
Authors	Christopher Carroll, Reader in Health Technology Assessment, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Paul Tappenden, Reader in Health Economic Modelling, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Rachid Rafia, Research Fellow, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Jean Sanderson, Research Associate, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Duncan Chambers, Research Fellow, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Mark Clowes, Information Specialist, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Paul Durrington, Professor, Cardiovascular Research Group, Core Technology Facility, Manchester, M13 9NT Nadeem Qureshi, Professor, Faculty of Medicine & Health Sciences, Tower Building University Park, Nottingham, NG7 2RD Anthony Wierzbicki, Professor, King's College London, Guy's and St. Thomas' NHS Foundation Trust, Westminster Bridge Road, London, SE1 7EH
Correspondence to	Christopher Carroll, Reader in Health Technology Assessment, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA 22nd September 2015

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 14/177/05.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Matt Stevenson and Iñigo Bermejo, SCHARR, for providing comments on the draft report and Gill Rooney, Programme Manager, SCHARR, for her help in preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Carroll C, Tappenden P, Rafia R, Sanderson J, Chambers D, Clowes M, Durrington P, Qureshi N, and Wierzbicki A. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: A Single Technology Appraisal. School of Health and Related Research (SCHARR), 2015.

Contributions of authors

Christopher Carroll and Duncan Chambers summarised and critiqued the clinical effectiveness data reported within the company's submission. Paul Tappenden and Rachid Rafia critiqued the health economic analysis submitted by the company. Mark Clowes critiqued the company's search strategies. Jean Sanderson critiqued the statistical analysis contained within the company's submission. Paul Durrington, Nadeem Qureshi and Anthony Wierzbicki provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final report.

CONTENTS

1.	SUMMARY	1
1.1	Critique of the decision problem in the company's submission	1
1.2	Summary of clinical effectiveness evidence submitted by the company	3
1.3	Summary of the ERG's critique of clinical effectiveness evidence submitted	4
1.4	Summary of cost effectiveness submitted evidence by the company	6
1.5	Summary of the ERG's critique of cost effectiveness evidence submitted	9
1.6	ERG commentary on the robustness of evidence submitted by the company	10
1.7	Summary of exploratory and sensitivity analyses undertaken by the ERG	11
2	BACKGROUND	12
2.1	Critique of company's description of underlying health problem.	12
2.2	Critique of manufacturer's overview of current service provision	13
3.	CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM	18
3.1	Population	19
3.2	Intervention	20
3.3	Comparators.....	21
3.5	Other relevant factors.....	22
4.	CLINICAL EFFECTIVENES	23
4.1	Critique of the methods of review(s)	23
4.2	Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)	29
4.3	Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison.....	53
4.4	Critique of the indirect comparison and/or multiple treatment comparison	53
4.5	Additional work on clinical effectiveness undertaken by the ERG	54
4.6	Conclusions of the clinical effectiveness section.....	54
5	COST EFFECTIVENESS.....	57
5.1	ERG comment on the company's systematic review of cost-effectiveness evidence.....	57
5.2	Description of the company's model	61

5.3	Critical appraisal of the company's health economic analysis	109
5.4	Conclusions of the cost effectiveness section	133
6	IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG	137
7	END OF LIFE	140
8	OVERALL CONCLUSIONS	141
8.1	Implications for research.....	143
9.	REFERENCES	144

LIST OF TABLES

	Page
Table 1	Decision problem in final NICE scope 18
Table 2	Clinical evidence presented within the CS 19
Table 3	Inclusion and exclusion criteria for the broad clinical efficacy/safety systematic literature review 26
Table 4	Included RCTs: Basic characteristics 30
Table 5	Included RCTs: Populations 32
Table 6	Included RCTs: Interventions and comparators 35
Table 7	Included RCTs: Outcomes 36
Table 8	Mean percentage change from baseline (and 95% CIs) in calculated LDL-C in LAPLACE-2: evolocumab versus ezetimibe arms 38
Table 9	Treatment difference in mean percentage change (and 95% CIs) in calculated LDL-C from baseline in LAPLACE-2: evolocumab versus ezetimibe arms 39
Table 10	Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C in LAPLACE-2: pooled analysis across all statin cohorts 39
Table 11	Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C in LAPLACE-2: pooled analysis across atorvastatin cohorts 40

Table 12	Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C from baseline in GAUSS-2	41
Table 13	Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C from baseline in DESCARTES	42
Table 14	Subgroup analysis of mean percentage change and treatment difference in ultracentrifugation LDL-C from baseline in DESCARTES for patients using ezetimibe at baseline	42
Table 15	Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C from baseline in RUTHERFORD-2	44
Table 16	Subgroup analysis of mean percentage change and treatment difference (and 95% CIs) in calculated LDL-C from baseline in RUTHERFORD-2 for patients using ezetimibe at baseline	44
Table 17	Percentage rates of all AEs	47
Table 18	Percentage rates of SAEs	47
Table 19	Percentage rates of AEs leading to discontinuation	48
Table 20	Percentage rates of nasopharyngitis	48
Table 21	Percentage rates of headache	48
Table 22	Percentage rates of back pain	49
Table 23	Percentage rates of neurocognition AEs	49
Table 24	Percentage rates of upper respiratory tract infection	49
Table 25	Relevant ongoing studies of evolocumab (as of 1st July 2015)	52
Table 26	Scope of the company's health economic analysis	61
Table 27	Health states used in the company's model	65
Table 28	Summary of evidence sources used to inform the company's model parameters	75
Table 29	Framingham risk equations used in company's model (patients without a history of CVD)	78
Table 30	REACH Registry risk equations used in company's model (patients with a history of CVD)	79
Table 31	Calibration estimates applied to Framingham and REACH registry predictions, based on CPRD analysis	81

Table 32	Mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe when used in combination with statins or as monotherapy	83
Table 33	Proportion of change in CVD event risk per mmol/L LDL-C change	85
Table 34	Health utilities used in the company's model	88
Table 35	Description of interventions/comparators assessed in the company's model	89
Table 36	Other costs included in the company's model	90
Table 37	Summary of results presented within the CS	94
Table 38	Summary of company's cost-effectiveness results (deterministic)	96
Table 39	Summary of probabilistic sensitivity analysis results	98
Table 40	Summary of company's scenario analysis results (evolocumab plus ezetimibe - deterministic)	100
Table 41	Amended base case and scenario analysis results for HeFH primary and secondary prevention analyses	107
Table 42	Amended summary of probabilistic sensitivity analysis results	107
Table 43	Adherence of the company's economic analysis to the NICE Reference Case	110
Table 44	Resource use associated with monitoring reported in the CS, NICE CG181 and company's model	128
Table 45	Comparison of company's model and ERG's rebuilt model	132
Table 46	Summary of key concerns identified by the ERG	136

LIST OF FIGURES

		Page
Figure 1	Summary of current UK clinical pathway of care for lipid-lowering therapy for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia based on NICE clinical guidelines and technology appraisal guidance	14
Figure 2	Proposed place of evolocumab in the treatment pathway	16
Figure 3	Simplified representation of the company's model structure	65
Figure 4	Summary of the company's model logic	67
Figure 5	Step-wise sequence of estimating event-specific transition probabilities from patient-level characteristics	68
Figure 6	Company's approach to modelling the effects of LDL-C reduction on	71

	reductions in CV events	
Figure 7	Health state transitions and applied treatment effects	73
Figure 8	ACS long-term period – multinomial model event distribution results by age	83
Figure 9	Tornado diagram for evolocumab plus statins versus ezetimibe plus statins in the primary hypercholesterolaemia LDL-C>2.5mmol/L primary prevention population	101
Figure 10	Tornado diagram for evolocumab plus statins versus ezetimibe plus statins in primary hypercholesterolaemia LDL-C>2.5mmol/L secondary prevention population	102
Figure 11	Tornado diagram for evolocumab plus statins versus ezetimibe plus statins in HeFH primary and secondary prevention population	102

LIST OF BOXES

		Page
Box 1	Inclusion and exclusion criteria for company's review of cost-effectiveness studies	58
Box 2	Summary of main issues identified within the critical appraisal of the company's model	109

ABBREVIATIONS

AAC	American College of Cardiology
ACS	Acute coronary syndrome
AE	Adverse event
AF	Atrial fibrillation
AHA	American Heart Association
AIC	Academic-in-confidence
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AWMSG	All Wales Medical Strategy Group
CAD	Coronary artery disease
CEAC	Cost-effectiveness acceptability curve
CHD	Coronary heart disease
CI	Confidence interval
CIC	Commercial-in-confidence
CG	Clinical guideline
CHD	Chronic Heart Disease
CHMP	Committee for Medicinal Products for Human Use
CMU	Commercial Medicines Unit
CPRD	Clinical Practice Research Datalink
CS	Company's submission
CTT	Cholesterol Treatment Trialists collaboration
CVD	Cardiovascular disease
DLCN	Dutch Lipid Clinic Network
EAS	European Atherosclerosis Society
ECVD	Established CVD
EQ-5D	EuroQol-5D
EMBASE	Excerpta Medica database
eMIT	Electronic market information tool
ERG	Evidence Review Group
ESC	European Society of Cardiology
FAS	Full analysis set
FH	Familial hypercholesterolaemia
GDG	Guideline Development Group
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HES	Hospital Episode Statistics
HF	Heart failure
HoFH	Homozygous familial hypercholesterolaemia
HRQoL	Health-related quality of life
HSE	Health Survey for England
HSSS	Highly Sensitive Search Strategy
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IC	Intermittent claudication
IPD	Individual patient data

IS	Ischaemic stroke
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
Lp(a)	Lipoprotein(a)
MEDLINE	Medical Literature Analysis and Retrieval System Online
MI	Myocardial infarction
mmol/L	millimole per litre
NCEP	National Cholesterol Education Program
NHS	National Health Service
NHS EED	National Health Service Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OD	Once daily
ONS	Office of National Statistics
PCSK9	Proprotein convertase subtilisin/kexintype 9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
Q2W	Every 2 weeks
QM	Monthly
RCT	Randomised controlled trial
REACH	REduction of Atherothrombosis for Continued Health
SAE	Serious adverse event
SBP	Systolic blood pressure
SmPC	Summary of product characteristics
SI	Statin intolerant
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SMR	Standardised mortality ratio
ST	Statin tolerant
TA	Technology Appraisal
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
TTO	Time trade-off
UA	Unstable angina
UKPDS	UK Prospective Diabetes Study
VLDL-C	Very low-density lipoprotein cholesterol
WTP	Willingness to pay

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

Cardiovascular disease (CVD) can have major health and economic implications for people and health services: it remains the most common cause of mortality in women in England and the second most common cause of mortality in men in England. Elevated cholesterol is predictive of CVD risk. Lipid-lowering therapies are recognised as being effective for reducing hypercholesterolaemia and also for reducing risk of CVD. Recent years have seen consistent increases in prescription rates for lipid-lowering therapies in England.

Hypercholesterolaemia, a type of hyperlipidaemia, specifically refers to the presence of high levels of cholesterol, including low-density lipoprotein cholesterol (LDL-C), in the blood. Primary hypercholesterolaemia can be familial or non-familial. Heterozygous familial hypercholesterolaemia (HeFH) is monogenic, i.e. related to a single genetic locus; the LDL-cholesterol is elevated from birth and can lead to life-long elevated LDL-C levels. LDL-C levels in people with HeFH are typically two to three times higher than normal. Homozygous familial hypercholesterolaemia (HoFH) is a more severe and rare form of hyperlipidaemia with defects in LDL-receptor genes inherited from both parents rather than one. Non-familial primary hypercholesterolaemia is polygenic: elevated LDL-C is produced by a combination of various genes and nutritional and lifestyle factors. However, the exact role of polygenic inheritance in producing LDL-C levels is unclear. This is the most common form of primary hypercholesterolaemia in the UK; approximately 70% of people with primary hypercholesterolaemia have this non-familial polygenic type. Mixed dyslipidaemia or “combined hyperlipidaemia” is characterised by elevated LDL-C and high triglycerides and/or reduced or elevated high-density lipoprotein cholesterol (HDL-C). It is a type of primary hypercholesterolaemia. Like primary non-familial hypercholesterolaemia, it is also relatively common; approximately 10% of people with primary hypercholesterolaemia in the UK have this type of “mixed dyslipidaemia.”

The decision problem required an assessment of the clinical effectiveness and cost-effectiveness of evolocumab compared to ezetimibe in treating primary hypercholesterolaemia (familial and non-familial) in patients with inadequately-controlled LDL-C levels despite being on a maximum-tolerated dose of statins, or in patients for whom statins are inappropriate (due to intolerance or contraindication).

Evolocumab is a fully human monoclonal antibody that binds selectively to proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that regulates the recycling of LDL-receptors on the surface of liver cells and decreases the ability of the liver to clear LDL from the blood. By binding to PCSK9, evolocumab increases liver levels of LDL receptors, thereby reducing serum LDL-cholesterol levels.

It is indicated in adults aged 18 years or older with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, for those who have reached a maximum-tolerated dose on statins, or who are contraindicated for statins. It is also indicated for use in populations with homozygous familial hypercholesterolaemia (HoFH), although this population is not part of the final scope issued by the National Institute for Health and Care Excellence (NICE). Evolocumab is given as either one dose (140mg) every 2 weeks (Q2W) or three doses (420mg) every month (QM), administered by subcutaneous injection (s.c.) via a prefilled pen or syringe. The intervention is designed to be self-administered by the patient after proper training. The cost of evolocumab is £170.10 per 140 mg prefilled pen or syringe.

The population described in the clinical trial evidence was adult patients with primary hypercholesterolaemia (which includes mixed dyslipidaemia), for whom statins do not provide optimal control of their LDL-C levels and/or for whom statins are contraindicated or not tolerated. This was consistent with the decision problem. There was a single trial of evolocumab within a diagnosed HeFH subgroup population (RUTHERFORD-2). The populations in the clinical trial evidence and the scope are in keeping with the wording of the marketing authorisation for ezetimibe, which is the comparator specified within the decision problem. Clinical evidence was presented for each of the subgroups listed for consideration in the final NICE scope: presence of CVD or known risk factors for CVD; adults with HeFH; adults in whom two or more statins cannot be tolerated, or only the lowest dose can be tolerated; and groups with differing levels of severity of hypercholesterolaemia, which is defined by the company according to baseline LDL-C level. The trial populations were generally consistent with the decision problem, although it is unclear whether some of the populations in some of the included trials were currently receiving the maximum-tolerated dose of statins.

The decision problem required the consideration of evolocumab as monotherapy or in combination with a statin with or without ezetimibe, or in combination with ezetimibe (without statin therapy). The clinical evidence presented satisfied the majority of these principal combinations of interventions, although evidence was absent for certain subgroups that were to be considered: in particular, there were no trials of evolocumab in combination with ezetimibe in populations (both non-familial and HeFH) in whom statins could not be tolerated or were contraindicated.

The principal efficacy outcomes for consideration were plasma lipid and lipoprotein levels, including LDL-cholesterol, non-HDL-cholesterol, HDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB) and lipoprotein(a) (Lp(a)). These were reported in all randomised controlled trials (RCTs) included in the review of clinical efficacy (LAPLACE-2, GAUSS-2, DESCARTES and RUTHERFORD-2). The majority of the clinical evidence reported the required minimum 12-week

follow-up, with the exception of the DESCARTES trial (52 weeks). The use of LDL-C as a potential surrogate for CVD is generally accepted and the company provided evidence for the relationship between LDL-C reduction, due to statin therapy, and the reduction of CV events based on a meta-analysis of 26 trials by the Cholesterol Treatment Trialists' collaboration (CTT). CV events include myocardial infarction (MI) and unstable angina (collectively referred to as coronary heart disease [CHD]), stroke, transient ischaemic attacks (TIAs) and peripheral artery disease. However, this meta-analysis concerned statin therapies only.

The principal safety outcomes were all also considered and reported in the company's submission (CS). The short follow-up of most trials (12 weeks) prevented the reporting of meaningful numbers of fatal and non-fatal cardiovascular events, mortality data, apheresis (a type of 'extracorporeal' procedure to remove low density lipoprotein (LDL) cholesterol from the blood) or revascularisations. However, all available data were reported and additional safety data were also provided. Health-related quality of life (HRQoL) was not assessed or reported in any of the included trials. There were no reported equity issues, end of life criteria were not relevant to the submission and no PAS application was submitted. The Evidence Review Group (ERG) considers that the evidence presented in the submission was therefore generally consistent with the decision problem, with only minor discrepancies between the submission and the available evidence.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company submission (CS) consisted of three separate reviews: (i) a review of the clinical efficacy evidence from RCTs of evolocumab; (ii) a review of the evidence from non-randomised and non-controlled studies, and; (iii) a review of safety evidence from randomised and a non-randomised studies. The principal clinical efficacy review included four relevant RCTs: two trials comparing evolocumab with ezetimibe in adults with primary non-familial hypercholesterolaemia who were able to take statins (LAPLACE-2) or who were statin-intolerant (GAUSS-2); and two placebo-controlled trials, one in adults with primary non-familial hypercholesterolaemia (DESCARTES) and one in adults with HeFH (RUTHERFORD-2). Three RCTs evaluated both licensed doses of evolocumab (Q2W and QM) and one trial (DESCARTES) evaluated only the QM dose. All RCTs were found to be at a low risk of bias following quality assessment using a standard critical appraisal tool. The following results were presented for the primary efficacy outcome of LDL-C: mean percentage change from baseline, and mean percentage treatment difference, for a range of follow-ups: both the mean of the values at 10 and 12 weeks; and for 12 weeks alone (LAPLACE-2, GAUSS-2, RUTHERFORD-2) and for 12 and 52 weeks (DESCARTES). Detailed results were presented for all trial arms (based on the two licensed evolocumab doses and different background statins and comparator treatments). Detailed results were also provided in the main submission and appendices

for other lipid parameters and pre-specified and *post hoc* subgroup analyses based on key covariates. The submission reported that evolocumab provided consistent and intensive reductions in LDL-C compared to ezetimibe and placebo, regardless of patient population, dosing regimen, CVD risk, and presence and type of background lipid-lowering therapy. The results presented within the company's submission were based on the full analysis set (FAS) of the trials rather than the published data reported in the original publications.

The CS supplemented the main clinical efficacy review with additional efficacy evidence from two open-label extension trials, which included some slightly different populations in terms of baseline LDL-C and ethnicity (OSLER 1 and 2), and a single non-RCT (TAUSSIG) undertaken within the HeFH subgroup. The reported findings from these studies were consistent with the four key RCTs in terms of LDL-C reduction.

The review of the safety evidence included the four key RCTs, the supplementary studies from the efficacy review, and an integrated analysis set, which included a total of 14 RCTs. It was unclear how some of the evidence was identified and selected. The company's submission included extensive safety data on all adverse events (AEs), serious adverse events (SAEs), events leading to discontinuation, fatal and common AEs, as well as all-cause mortality and adjudicated cardiovascular events and non-coronary revascularisations, where such evidence was available. The submission concluded that the AEs were overall balanced between groups in all three periods of the integrated safety data set (12 weeks, year 1 and year 2), as well as across populations and therapeutic settings, and that most AEs were mild to moderate in severity, and SAEs and AEs leading to discontinuation of the intervention were infrequently reported and generally similar across treatment groups. A number of relevant ongoing trials were also listed.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The principal efficacy review represents a good quality systematic review of four relevant, good quality RCTs. The trials were generally consistent with the NICE scope. The primary efficacy outcome was mean percentage change in LDL-C from baseline, and mean treatment difference across trial arms, at follow-ups of 12 weeks (LAPLACE-2, GAUSS-2, DESCARTES and RUTHERFORD-2) and 52 weeks (DESCARTES).

In the LAPLACE-2 trial, at 12 weeks, patients with primary hypercholesterolaemia on background atorvastatin therapy (intensive and non-intensive doses) had a treatment difference in mean percentage change in LDL-C from baseline of -46.9 (95% CI, -53.0 to -40.7, $p < 0.001$) and -42.5 (95%

confidence interval [CI], -47.9 to -37.0, $p<0.001$) for the Q2W and QM doses of evolocumab respectively, compared with ezetimibe (fixed effects model).

In the GAUSS-2 trial, at 12 weeks, patients with primary hypercholesterolaemia who were statin intolerant had a treatment difference in mean percentage change in LDL-C from baseline of -39.3 (95% CI, -45.0 to -33.5, $p<0.001$) and -38.1 (95% CI, -42.9 to -33.4, $p<0.001$) for the Q2W and QM doses of evolocumab compared with ezetimibe.

In the placebo-controlled RUTHERFORD-2 trial, at 12 weeks, patients with HeFH on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -62.7 (95% CI, -66.3 to -59.1) and -56.6 (95% CI, -60.9 to -52.3) for the Q2W and QM doses of evolocumab. The treatment difference in mean percentage change compared with placebo was -60.6 (95% CI, -66.7 to -54.5, $p<0.001$) and -60.3 (95% CI, -67.8, -52.9, $p<0.001$) for the Q2W and QM doses of evolocumab, respectively. The ERG received clinical advice that the HeFH population of the RUTHERFORD trial with a confirmed genetic mutation was higher than might be found in usual clinical practice in the UK, but the implications of this are unclear. The ERG also noted, following clinical advice, that the proportion of patients with Chronic Heart Disease (CHD) was higher in the intervention arms of the RUTHERFORD-2 trial (i.e. 30-36%) than would be expected in clinical practice in a HeFH population, and was higher than the prevalence reported for the other three trials (e.g. LAPLACE-2 trial arm populations ranged from 17% to 24% with CHD characteristics).

In the placebo-controlled DESCARTES trial, patients with primary hypercholesterolaemia on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -50.6 (95% CI, -53.2 to -48.0) for the QM dose of evolocumab at 52 weeks. The treatment difference in mean percentage change compared with placebo was -59.3 (95% CI, -63.8 to -54.9, $p<0.001$) at 52 weeks.

The results for other lipid parameters, such as non-HDL-cholesterol, HDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB) and lipoprotein(a) (Lp(a)), were consistent with the results for LDL-C, and pre-specified subgroup analyses demonstrated that these results were not sensitive to the different doses of evolocumab, or other key variables such as LDL-C baseline levels, severity of hypercholesterolaemia or CVD risk factors. The ERG noted that only 12-week evidence was available for the efficacy of the Q2W dose, whilst the QM dose had some data for 52 weeks. Additional clinical efficacy evidence was provided from a non-RCT study (TAUSSIG) and two open-label, extension studies (OSLER1 and 2). However, the extension studies included some trials with populations and/or comparators that were excluded from the principal review of the four RCTs and it is unclear how these trials and the non-RCT study were identified for inclusion in the company's review. The

inclusion of these studies was justified by the company on account of the longer-term evidence both from the extension studies and from TAUSSIG on the HeFH subgroup (36 weeks). A network meta-analysis (NMA) was not performed, although this might have been possible using particular trial evidence from both the primary non-familial hypercholesterolaemia population and the HeFH subgroup.

The clinical effectiveness review found that evolocumab is efficacious at lowering LDL-C, but in itself this is not a clinically important outcome: its importance is derived from it being a surrogate for CVD. Although there is an established relationship between statin-generated LDL-C reduction and reduced CV events, the impact of evolocumab on CVD has not been demonstrated: there is little or no direct evidence on this relationship. The ongoing FOURIER trial (clinicaltrials.gov identifier NCT02207634) aims to evaluate the impact of evolocumab on CVD outcomes, but only in people who have already had a CV event. The ERG also noted that there was no evidence on the relative efficacy of evolocumab versus ezetimibe in the familial hypercholesterolaemia subgroup, or for evolocumab in combination with ezetimibe in any population, and there was little or no direct trial evidence for evolocumab in terms of HRQoL or apheresis.

The submission of safety evidence was a non-systematic review of good quality RCTs, providing evidence for up to two years. There were no obvious safety concerns, with most AEs being balanced across evolocumab and comparator trial arms, and very small numbers of SAEs. However, the ERG noted that relatively higher 12-week AE rates were reported in patients who had HeFH or who had primary non-familial hypercholesterolaemia and were statin-intolerant. Similarly, these rates were also relatively higher for trials with a longer follow-up duration. This suggests that some patient subgroups might experience more frequent events and that all patients are at risk of AEs over time, though the rates are generally similar to comparators. The ERG noted also that the longer-term evidence presented was derived from some trials with populations who would not be eligible to receive evolocumab in clinical practice in the NHS (e.g. people who were not on maximum-tolerated doses of statins). Further long-term data are therefore needed in relevant UK populations, although it is not clear whether ongoing trials will address this.

1.4 Summary of cost effectiveness submitted evidence by the company

The CS includes a systematic review of economic evaluations of lipid lowering therapies together with a *de novo* model-based economic evaluation to assess the incremental cost-effectiveness of evolocumab versus ezetimibe (both with or without statins) for the treatment of patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia.

The company's systematic review included 108 previously published economic evaluations. One of the included studies is the model developed to inform NICE Clinical Guideline (CG) 181. None of these studies assessed the cost-effectiveness of evolocumab.

The company developed a *de novo* health economic model to assess evolocumab versus ezetimibe (both with and without statins) in three populations:

- (i) Patients with non-familial primary hypercholesterolaemia who have no history of CVD (primary prevention);
- (ii) Patients with non-familial primary hypercholesterolaemia who have existing CVD (secondary prevention), and;
- (iii) Patients with HeFH, comprising a mix of patients who have no history of CVD and patients who have existing CVD (primary and secondary prevention).

For all three populations, separate analyses are presented for patients who are able to take statins (denoted ST) and for patients for whom statins are contraindicated or not tolerated (denoted SI). The company's base case analysis assesses evolocumab with/without statins; additional scenario analyses are presented in which evolocumab is used in combination with ezetimibe.

The company's base case model adopts a Markov approach and evaluates costs and health outcomes from the perspective of the NHS over a lifetime horizon. The model includes 24 mutually exclusive health states which include three individual "acute" event states (where patients remain for a maximum duration of one year unless they experience the same event during the next cycle), five individual "chronic" event states (including three "post-event" health states - post-acute coronary syndrome (ACS), post-ischaemic stroke (IS) and post-heart failure (HF), as well as no CVD and "established" CVD (ECVD), and thirteen composite CVD health states (including "acute" and "post-event" health states, which contain either two or three individual health states), and three death states (CHD death, stroke death and death due to other causes). The model is evaluated using an annual cycle length. Baseline characteristics for the non-familial primary prevention and secondary prevention populations were based on individual patient data (IPD) for a subset of patients from the LAPLACE-2 trial (those with LDL-C > 2.5 mmol/L), whilst baseline characteristics for the HeFH population were based on IPD from the modified intention-to-treat (ITT) population of the RUTHERFORD-2 trial. The model uses risk equations from the Framingham Heart Study and Reduction of Atherothrombosis for Continued Health (REACH) Registry to predict CV risk and then adjusts these using calibration factors derived from an analysis of data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES), or using literature. For patients who are able to take statins, LDL-C treatment effects were based on the LAPLACE-2 trial. For patients for whom statins are contraindicated or not tolerated, treatment effects were based on the

GAUSS-2 trial. The impact of lowering lipid levels was modelled based on an assumed relationship between LDL-C reduction and CV event reduction. Health utilities were based on Euroqol 5-D (EQ-5D) and time trade-off (TTO) studies used in the NICE CG181 model. Costs were drawn from the NHS Drugs Tariff, NHS Reference Costs, the Personal Social Services Research Unit (PSSRU) and a CPRD/HES costing analysis.

The company's original base case model indicates the following results. Within the non-familial primary prevention statin tolerant (ST) population, the company's threshold analyses indicate that in patients with a baseline LDL-C of 3.5mmol/L, the incremental cost-effectiveness ratio (ICER) for evolocumab plus statins versus ezetimibe plus statins would be below £30,000 per QALY gained in patients with a 10-year CVD risk of 79% (or higher). The corresponding 10-year risk thresholds for patients with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 73% and 70%, respectively. Within the non-familial primary prevention statin intolerant (SI) population with a baseline LDL-C of 3.5mmol/L, the ICER for evolocumab versus ezetimibe would be below £30,000 per QALY gained in patients with a 10-year CVD risk of 81% (or higher). The corresponding 10-year risk thresholds for patients with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 75% and 71%, respectively. Within the non-familial secondary prevention ST population, the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.44 QALYs at an additional cost of £51,407 compared with ezetimibe plus statins; the resulting ICER is estimated to be £116,713 per QALY gained (probabilistic ICER=£119,012 per QALY gained). Within the non-familial secondary prevention SI population, the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.42 QALYs at an additional cost of £50,542 compared with ezetimibe monotherapy; the resulting ICER is estimated to be £119,971 per QALY gained (probabilistic ICER=£123,780 per QALY gained). Within the HeFH primary/secondary prevention ST population, the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.20 QALYs at an additional cost of £53,565 compared with ezetimibe plus statins; the resulting ICER is estimated to be £44,741 per QALY gained (probabilistic ICER=£46,412 per QALY gained). Within the HeFH primary/secondary prevention SI population, evolocumab monotherapy is expected to produce an additional 1.10 QALYs at an additional cost of £51,749 compared with ezetimibe monotherapy; the resulting ICER is estimated to be £47,193 per QALY gained (probabilistic ICER=£48,362 per QALY gained).

The ERG critically appraised the company's economic analysis and partially double-programmed the company's health economic model using transition probabilities taken directly from the company's model. Whilst the ERG's rebuild of the Markov component of the model did not identify any major problems, serious logic errors were identified in the transition probabilities used in the company's model whereby under certain combinations of parameter inputs, some of the model's transition

probabilities and hence health state populations became negative. The ERG requested that the company submit an amended model in which this problem was rectified. In response, the company acknowledged the problem and noted that their results for the non-familial primary prevention population were “invalid.” The company also submitted an amended model and accompanying addendum which included an additional assumption which affects the risk predictions in the HeFH primary/secondary prevention population. The results for the non-familial secondary prevention population were unaffected by the company’s amendments to the model.

The amendment to the company’s model indicates the following results. Within the HeFH primary/secondary prevention ST population, the company’s amended base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.15 QALYs at an additional cost of £73,620 compared with ezetimibe plus statins; the resulting ICER is estimated to be £47,195 per QALY gained (probabilistic ICER=£48,664 per QALY gained). Within the HeFH primary/secondary prevention SI population, evolocumab monotherapy is expected to produce an additional 1.05 QALYs at an additional cost of £52,486 compared with ezetimibe monotherapy; the resulting ICER is expected to be £49,900 per QALY gained (probabilistic ICER=£51,061 per QALY gained).

1.5 Summary of the ERG’s critique of cost effectiveness evidence submitted

The ERG’s critique of the company’s model identified a number of matters of concern. These include: (i) deviations from the NICE Reference Case; (ii) concerns regarding the conceptualisation and implementation of the company’s model structure and logic; (iii) concerns regarding the populations and baseline characteristics included in the company’s analyses; (iv) issues regarding the use of CVD risk equations and the need for subsequent calibration; (v) concerns regarding the derivation of calibration factors to adjust the baseline risk of CVD for the raised LDL-C analysis; (vi) issues surrounding the derivation of the calibration factor to adjust the baseline risk of CVD for patients with HeFH; (vii) concerns regarding the appropriateness of treatment effects; (viii) issues regarding the relationship between LDL-C reduction and CVD events; (ix) the limited relevance of health utility estimates; (x) discrepancies in the cost parameters used in the company’s model, and; (xi) errors in the interpretation and reporting of health economic results.

Whilst some of these issues reflect matters of subjective opinion, others reflect serious underlying problems regarding the conceptualisation and implementation of the model and the use of evidence to inform the model’s parameters. These issues impact upon the credibility of the results presented within the CS and the subsequent addendum. The ERG notes that the amendments made to the company’s model during the clarification process do not address the underlying issue, but merely

makes it less visible. Consequently, the ERG considers that all results presented by the company should be interpreted with caution.

1.6 ERG commentary on the robustness of evidence submitted by the company

The ERG considered the RCT evidence submitted by the company to be robust: it generally satisfied the requirements of the decision problem, with some minor exceptions, and should be considered to be good quality. The results were consistent across trials for both efficacy and safety outcomes.

1.6.1 Strengths

The ERG recognises that the submission included a good quality systematic review of the efficacy evidence and the four key RCTs were all good quality and at low risk of bias. The trials address most of the issues raised in the decision problem, their findings were generally consistent and appear to be unaffected by moderating variables.

The CS includes large reviews of existing economic evaluations, previous health utility studies, costing studies and CV risk equations. However, the relationship between these reviews and the structure and parameters used within the company's *de novo* health economic model are unclear.

1.6.2 Weaknesses and areas of uncertainty

The ERG noted that the principal areas of uncertainty in the clinical evidence concerned the absence of any direct evidence of the effectiveness of evolocumab compared with ezetimibe in HeFH populations and for evolocumab in combination with ezetimibe in any population. The ERG also noted uncertainty regarding the impact of evolocumab on CVD, apheresis and HRQoL because there was little or no direct evidence on these key outcomes. The safety evidence, though extensive, was derived in part from trial populations which do not reflect the patients likely to present in UK clinical practice, and AE rates appear to be higher in some subgroups: the provision of more long-term safety evidence in these populations would therefore be helpful. The ERG also notes that the longer-term efficacy and safety evidence from the placebo controlled trial DESCARTES relates only to the QM evolocumab dose: there are no equivalent data for the Q2W dose. Finally, it should be noted that, whilst LDL-C is an accepted surrogate outcome for CVD for statins, there is little or no direct evidence for the relationship between evolocumab and CV events. This is the reason for the current ongoing FOURIER trial, although this trial includes only people who have already had a CV event.

Serious logic errors were identified in the derivation of the transition probabilities within the company's model. Consequently, the ERG has serious doubts regarding the validity of the results presented within the CS and would advise considerable caution in their interpretation and use in

informing decision-making. Given the problems identified within the company's health economic model, the cost-effectiveness of evolocumab in any population remains unclear.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

As a consequence of multiple problems identified within the company's model, the ERG did not consider it appropriate or valuable to undertake additional exploratory analyses.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

Based on 2006 survey data, one third of adults aged 40-79 years in England are estimated to have high total serum cholesterol.¹ Elevated LDL-C is one of a number of factors that is predictive of the risk of CVD.^{1,2} Estimates of the number of people in the UK in 2012/2013 who have CVD are based on around 2.3 million people suffering from CHD, 1.2 million people suffering from stroke, around one million from atrial fibrillation (AF) and just over 480,000 from HF.³ There is variation in prevalence rates by gender, age and region.³ The current management of elevated cholesterol levels includes dietary and lifestyle changes, such as smoking cessation, weight loss and increased physical activity. For individuals who still have elevated LDL-C, lipid-lowering therapies are recognised as being effective as first-line treatment for reducing LDL-C and also for reducing risk of CVD.¹ CVD can have major health and economic implications for people and health services: it remains the most common cause of mortality in women and the second most common cause of mortality in men in England.³ Recent years have also seen consistent increases in prescription rates for lipid-lowering therapies in England.³

The populations referred to in the final NICE scope are people with primary hypercholesterolaemia and mixed dyslipidaemia.⁴ Hypercholesterolaemia, a type of hyperlipidaemia, specifically refers to an excessive total plasma cholesterol concentration, especially LDL-C, in the blood. Hypercholesterolaemia has been defined as an elevated LDL-cholesterol of approximately $\geq 3\text{mmol/l}$.² Hypercholesterolaemia might be secondary to a number of recognised conditions or factors, such as: nephrotic syndrome; type 2 diabetes mellitus; obesity; excessive alcohol consumption; and renal dialysis.² However, if these causes are excluded following clinical examination, then the hypercholesterolaemia is considered to be primary. Primary hypercholesterolaemia can be familial or non-familial. The former is defined as monogenic, i.e. related to a single genetic locus, in which the LDL-cholesterol is elevated from birth; it is characterised by a “dominant pattern of inheritance of premature coronary disease and/or tendon xanthomata.”⁵ In this population, one of the pair of LDL-receptor genes is defective or mutated and impairs the LDL cholesterol receptor activity leading to life-long elevated LDL-C levels.^{2,5,6} This population is principally composed of the heterozygous familial hypercholesterolaemia (HeFH) subgroup specified in the final NICE scope and is most commonly diagnosed in the UK using the Simon Broome criteria,^{7,8} although more novel molecular diagnosis tests are being developed.⁹ The LDL-C levels in people with HeFH are typically two to three times higher than normal.^{10,11} The prevalence of HeFH within primary hypercholesterolaemia in the UK is 0.2%,² with up to one in every 300 people affected worldwide.¹² Homozygous familial hypercholesterolaemia (HoFH) is a more severe and rare form of hyperlipidaemia with defects in LDL-receptor genes inherited from both parents rather than one.

Non-familial primary hypercholesterolaemia is elevated LDL-C produced by a combination of various genes and nutritional and lifestyle factors.² However, the exact role of genetic inheritance in producing LDL-C levels is unclear.⁵ Non-familial hypercholesterolaemia is the most common form of primary hypercholesterolaemia in the UK: approximately 70% of people with primary hypercholesterolaemia have this non-familial type.²

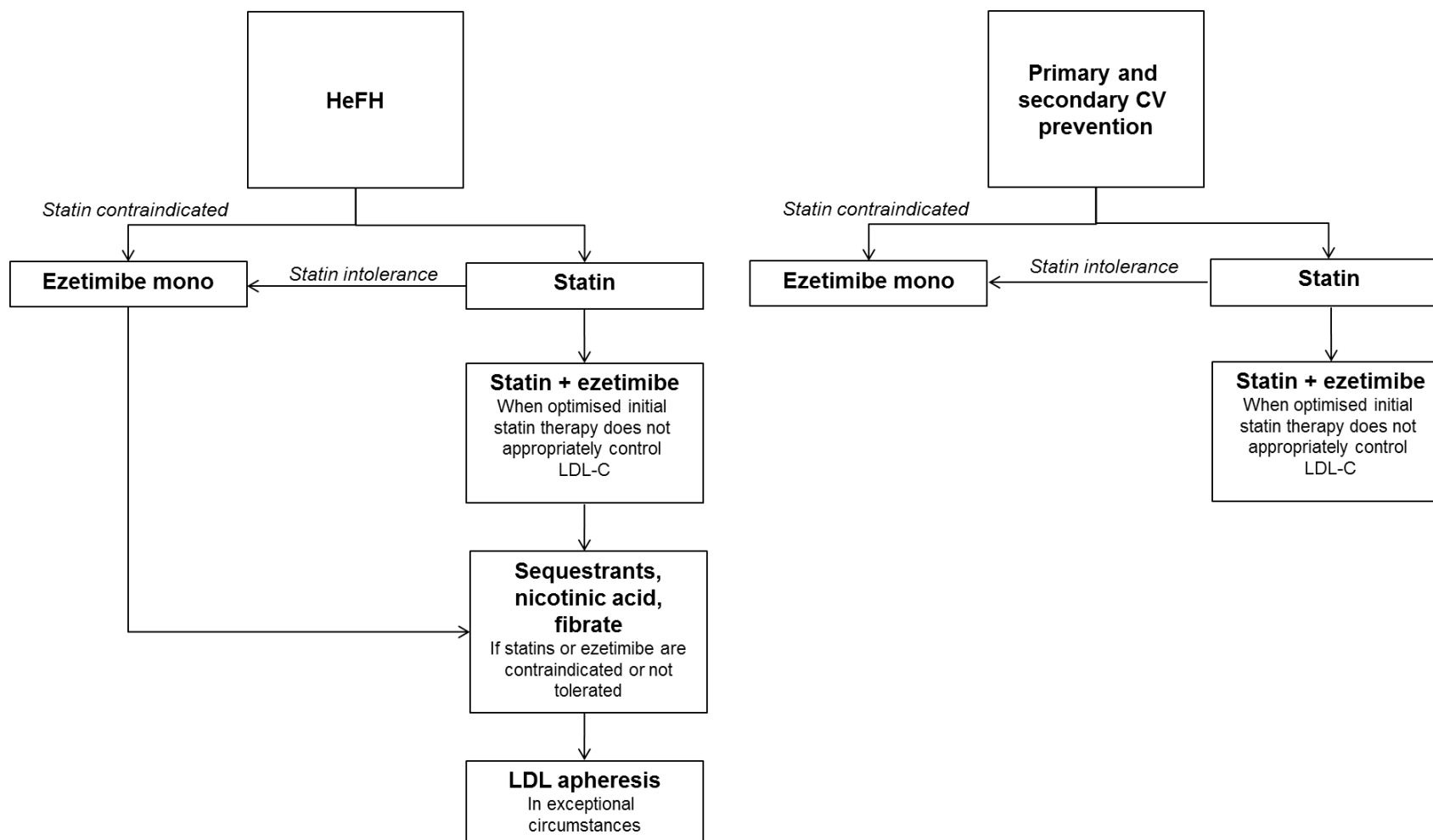
The second principal population referred to in the final NICE scope is people with “mixed dyslipidaemia.” This is described in the literature also as “combined hyperlipidaemia”, a disorder which is characterised by elevated LDL-C and high triglycerides and/or reduced or elevated HDL-C. It is a type of primary hypercholesterolaemia. Like primary non-familial hypercholesterolaemia, it is also relatively common: approximately 10% of people with primary hypercholesterolaemia in the UK have this type of “mixed dyslipidaemia”.²

The CS provides a brief description of primary hypercholesterolaemia and mixed dyslipidaemia in accordance with the terminology used in the scope. The principal focus of the submission was a description of the relationship between elevated LDL-C and the risk of CVD and CV events (see CS,¹³ pages 38-41).

2.2 Critique of manufacturer’s overview of current service provision

The ERG and clinical advisors consider that the company’s description of current service provision for the treatment of populations with primary hypercholesterolaemia and mixed dyslipidaemia (see CS,¹³ pages 43-54) is mostly appropriate and relevant to the decision problem and that the recommendations of all relevant clinical guidelines have been taken into account. Figure 1 presents the company’s view of the current UK clinical pathway of care for lipid-lowering therapy for primary hypercholesterolaemia, derived from relevant NICE guidelines and technology appraisals (TAs). The principal therapies prescribed for these populations are statins and, where relevant, ezetimibe and/or bile acid sequestrants, fibrates or high dose omega-3 fatty acids, which might be used if statins and/or ezetimibe are not appropriate.^{14,15}

Figure 1: Summary of current UK clinical pathway of care for lipid-lowering therapy for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia based on NICE clinical guidelines and technology appraisal guidance (reproduced from CS,¹³ Figure 3-2, page 49)



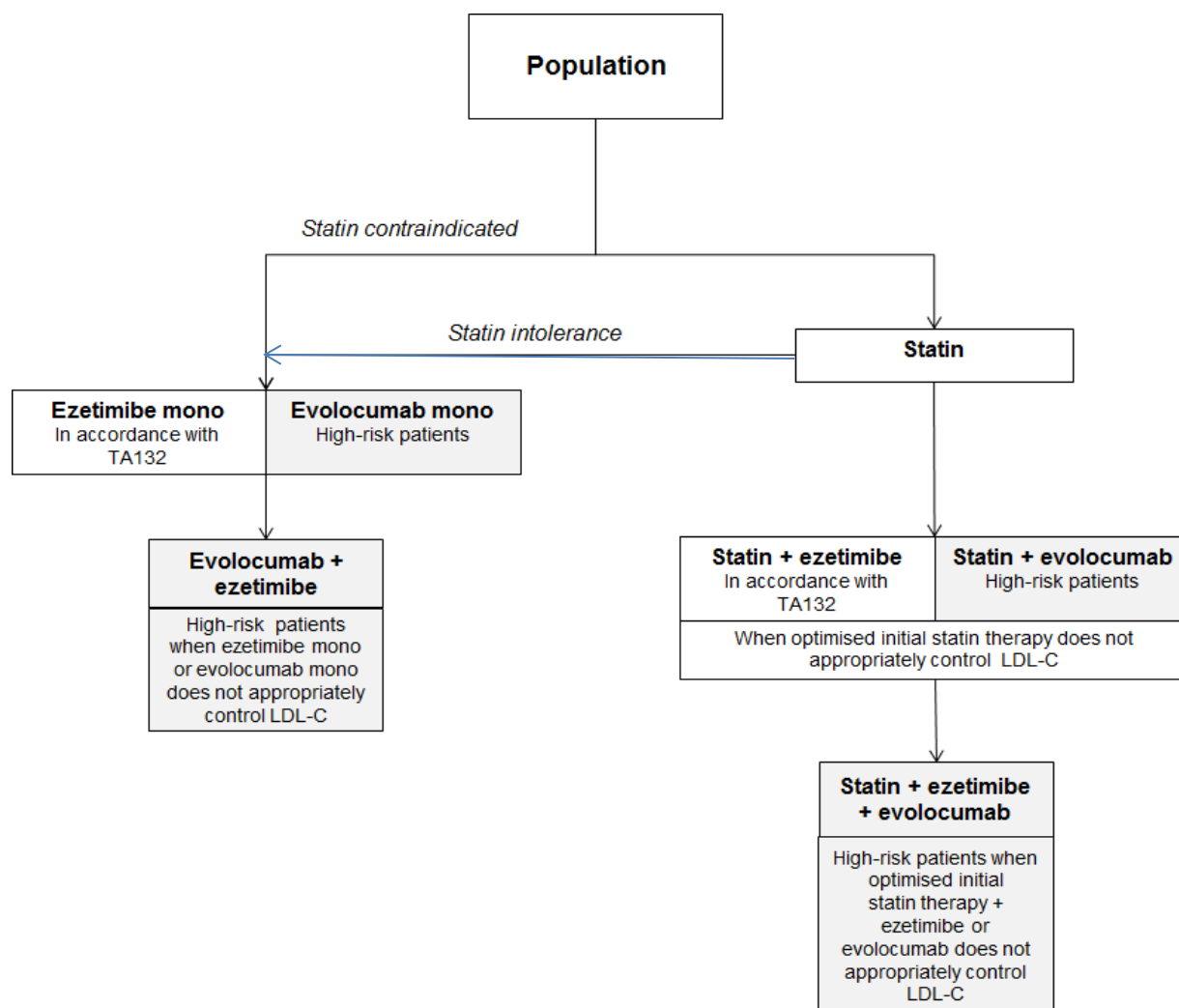
CV - cardiovascular; HeFH - heterozygous familial hypercholesterolaemia; LDL-C - low-density lipoprotein cholesterol; mono - monotherapy; NICE - National Institute for Health and Care Excellence

Figure 2 presents the company's view of the possible place of evolocumab in the pathway, with the different populations of Figure 1 possibly represented within the "high-risk patients" groups listed in Figure 2. As with ezetimibe, the company anticipates that evolocumab would only be prescribed in secondary care clinics. It would only be used after referral to specialist lipid clinics when initial statin therapy was considered to offer inadequate control of LDL-C or when patients were identified as being unable to take statins due to intolerance or contraindications. Statins are accepted as the first-line therapy for reducing LDL-C levels;¹⁵ statin intolerance due to side effects, such as muscle-related symptoms (e.g. myalgia), might be encountered in between 5%¹⁶ and 10%-20% of hypercholesterolemia patients.¹⁷

Clinical advisors to the ERG confirmed that the prescription of evolocumab only in secondary care clinics was appropriate. Advice from one clinician suggested that evolocumab might be used only when ezetimibe is inappropriate or ineffective rather than as an alternative to ezetimibe; this is because ezetimibe has longer-term safety data and evidence relating to its impact on CVD outcomes (e.g. the IMPROVE-IT trial¹⁸). The pathway fails to take account of the role of evolocumab relative to bile acid sequestrants, fibrates or high dose omega-3 fatty acids, which might be used if statins and/or ezetimibe are not appropriate.

Clinical advice received by the ERG confirmed that it was unlikely that there would be any requirement for additional tests or investigations for selection of patients appropriate for evolocumab, or any additional monitoring, over and above those which are part of routine clinical practice. The CS recommends using the Simon Broome criteria for diagnosing HeFH in accordance with NICE guidance.¹⁹ However, the ERG noted, following clinical advice, that the accurate diagnosis of HeFH is potentially problematic in practice, especially in the absence of appropriate genetic testing.^{9,20} It is worthy of note that in the trial of HeFH patients included in the submission (RUTHERFORD-2), between 17% and 24% of patients in any arm had a "possible" rather than a "definite" diagnosis of HeFH (CS, Table 4-8), and also that the proportion of participants who were tested and had a genetic mutation was much higher than in most studies.²¹

Figure 2: Proposed place of evolocumab in the treatment pathway (reproduced from CS,¹³ Figure 3-3, page 55)



LDL-C - low-density lipoprotein cholesterol; mono - monotherapy; TA - technology appraisal

Currently available recommended therapies and their efficacy and safety are described in some detail in the CS, principally atorvastatin (dose based on risk of CVD, with a maximum dose of 80mg)¹⁵ and ezetimibe (based on inadequate LDL-C control by statins or statin intolerance or contraindication).¹⁴

The CS proposes evolocumab as an alternative to ezetimibe as monotherapy for people in whom statins are contraindicated or are not tolerated, or in combination with statins if optimised statin therapy does not adequately control LDL-C levels. It is also proposed as a treatment, in combination with ezetimibe, when response to monotherapy is considered inadequate. Eligible patients are considered to be at high-risk of a CV event on account of inadequately-controlled LDL-C levels, one of a number of risk factors for CV events, due to the inappropriateness of statin therapy or the failure of a maximum-tolerated dose of statins to control LDL-C levels. This includes people with HeFH.

The CS claims that there is unmet need in these groups, who are at high risk of CV events. These high risk populations are defined in the CS (page 58) as:

- adults with primary non-familial hypercholesterolaemia who have not had a CVD event but have a greater than 10% 10-year risk of an event based on QRISK2,²²
- adults with primary non-familial hypercholesterolaemia who have had a CVD event;
- adults with heterozygous familial hypercholesterolaemia (HeFH).

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The evidence presented within the CS was generally consistent with the decision problem, with only minor discrepancies between the submission and the available evidence. These are described in Sections 3.1-3.4 below. Table 1 summarises the populations, interventions and comparators specified within the company's decision problem.

Table 1: Decision problem in final NICE scope

Population	Intervention	Comparator
Primary hypercholesterolaemia and mixed dyslipidaemia	Evolocumab with statin	Ezetimibe with statin
Primary hypercholesterolaemia and mixed dyslipidaemia	Evolocumab with statin and ezetimibe	Ezetimibe with statin
Subgroups in NICE scope		
Primary hypercholesterolaemia, Statin intolerant	Evolocumab alone	Ezetimibe alone
Primary hypercholesterolaemia, Statin intolerant	Evolocumab with ezetimibe	Ezetimibe alone
HeFH	Evolocumab with statin	Ezetimibe with statin
HeFH	Evolocumab with statin and ezetimibe	Ezetimibe with statin
HeFH, statin intolerant	Evolocumab alone	Ezetimibe alone
HeFH, statin intolerant	Evolocumab with ezetimibe	Ezetimibe alone

HeFH - heterozygous familial hypercholesterolaemia

The clinical evidence focused on four RCTs: LAPLACE-2²³, GAUSS-2²⁴, RUTHERFORD-2²¹ and DESCARTES.²⁵ Table 2 summarises the clinical trial evidence available for evolocumab in the treatment of hypercholesterolaemia.

Table 2: Clinical evidence presented within the CS

Population	Intervention	Comparator	Trial evidence (Acronym)
Primary hypercholesterolaemia	Evolocumab with statin	Ezetimibe with statin	LAPLACE-2, DESCARTES
Primary hypercholesterolaemia	Evolocumab with statin and ezetimibe	Ezetimibe with statin	DESCARTES (trial subgroup)
Subgroups in NICE scope			
Primary hypercholesterolaemia, Statin intolerant	Evolocumab alone	Ezetimibe alone	GAUSS-2
Primary hypercholesterolaemia, Statin intolerant	Evolocumab with ezetimibe	Ezetimibe alone	None
HeFH	Evolocumab with statin	Ezetimibe with statin	None
HeFH	Evolocumab with statin and ezetimibe	Ezetimibe with statin	RUTHERFORD-2
HeFH, statin intolerant	Evolocumab alone	Ezetimibe alone	None
HeFH, statin intolerant	Evolocumab with ezetimibe	Ezetimibe alone	None

HeFH - heterozygous familial hypercholesterolaemia

3.1 Population

Evolocumab is indicated for the treatment of adults aged 18 years or older with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, for those who have reached a maximum-tolerated dose on statins, or who are contraindicated for statins.²⁶

It is also indicated for use in populations with homozygous familial hypercholesterolaemia (HoFH); this population is not covered by this appraisal.

The population described in the available clinical evidence is adult patients with primary hypercholesterolaemia (which includes mixed dyslipidaemia). This is consistent with the decision problem specified in the final NICE scope.⁴ There is a single trial of evolocumab undertaken within a HeFH subgroup population.²¹ The populations in the clinical evidence and the scope are largely consistent with the wording of the marketing authorisation for ezetimibe, which is the comparator required by the final NICE scope. Clinical evidence is presented for each of the subgroups listed for consideration in the scope: presence or risk of CVD (LAPLACE-2, DESCARTES); adults with HeFH (RUTHERFORD-2); adults in whom two or more statins cannot be tolerated, or only the lowest dose can be tolerated (GAUSS-2); and groups with differing levels of severity of hypercholesterolaemia (LAPLACE-2). The trial populations are generally consistent with the final NICE scope. One issue

concerns whether the populations in the trials where statin intolerance is not an issue were actually receiving the maximum-tolerated dose of statins, as required by the licence. For example, the LAPLACE-2 trial included patients on both moderate-intensity and high-intensity statin therapy; however, although data on the different statin groups were presented separately, the main comparison between evolocumab and ezetimibe did involve patients taking a higher dose of statin (atorvastatin 80 mg daily). DESCARTES also involved patients taking different doses of statin, including some on no statin or low-dose statin.

3.2 Intervention

The technology described is evolocumab (brand name: Repatha; AMG145) produced by Amgen. Evolocumab is a fully human monoclonal antibody that binds selectively to proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that affects the recycling of LDL-receptors on the surface of liver cells and decreases the ability of the liver to clear LDL from the blood.²⁶ By binding to PCSK9, evolocumab increases liver levels of LDL receptors, thereby reducing serum LDL-cholesterol levels. The benefits of evolocumab are its ability to reduce the level of serum LDL-cholesterol in patients who are unable to control their cholesterol despite taking a maximum tolerated dose of statins, or in patients who cannot take statins. The most common side effects are: nasopharyngitis, upper respiratory tract infection, headache and back pain. Evolocumab received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) regarding marketing authorisation within the EU on 22nd May 2015. Full marketing authorisation was granted in July 2015. The marketing authorisation states that evolocumab “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.”

Evolocumab is given as either one dose (140mg) every two weeks (Q2W) or three doses (420mg) every month (QM), administered by subcutaneous injection (s.c.) via a prefilled pen or syringe. The intervention is designed to be self-administered by the patient after proper training.

The final NICE scope required the consideration of evolocumab as monotherapy or in combination with a statin with or without ezetimibe, or in combination with ezetimibe (without statin). The clinical evidence presented satisfied the majority of these principal combinations of interventions, although data on the combination of evolocumab with statin therapy and ezetimibe in primary non-familial

(DESCARTES trial subgroup) and familial (RUTHERFORD-2) hypercholesterolaemia populations were from trial subgroups only, and then only with ezetimibe as background therapy. Evidence was also absent for certain subgroups that were to be considered, in particular there were no head-to-head trials of evolocumab in combination with ezetimibe in populations in whom statins could not be tolerated or were contraindicated in either the non-familial or HeFH populations.

3.3 Comparators

The decision problem required the consideration of evolocumab (with or without statins and with or without ezetimibe) versus ezetimibe (with or without statins). The clinical evidence presented satisfied the majority of these principal combinations of interventions and comparators. The appraisal focused on evolocumab and ezetimibe and does not consider other lipid-lowering therapies, such as bile acid sequestrants, fibrates and nicotinic acid.²⁷

3.4 Outcomes

The principal efficacy outcomes for consideration were plasma lipid and lipoprotein levels, including LDL-cholesterol, non-HDL-cholesterol, HDL-cholesterol, TG, triglycerides (TG), apolipoprotein B (ApoB) and lipoprotein(a) (Lp(a)). These were reported in all RCTs included in the company's review of clinical efficacy. The majority of the clinical evidence reported follow-up for 12-weeks. The exception was the DESCARTES trial, which reported data for 12 weeks and 52 weeks. The use of LDL-C as a surrogate for CVD is generally accepted for statin therapies and the company provided evidence for the relationship between LDL-C reduction and the reduction of CV events, citing the meta-analyses of the CTTC, which have recently found that a reduction of 1mmol/L might lead to 22% reduced risk of CV events.^{18,28-30} CV events include MI and unstable angina (collectively referred to as CHD) stroke, TIAs and peripheral artery disease.³¹ However, the optimal LDL-C level to minimise risk of CVD is not known and only long-term data can provide robust evidence of the efficacy of evolocumab on CVD outcomes, as well as its long-term safety. These issues are being addressed in part in ongoing trials, such as the FOURIER trial (NCT01764633) for CV events in a hypercholesterolaemia population with existing CVD³² and the long-term, open-label extension studies OSLER 1 and OSLER-2.³³

The principal safety outcomes were all also considered and reported in the submission. However, the short follow-up of most trials (12 weeks) prevented the reporting of meaningful numbers of fatal and non-fatal cardiovascular events, all-cause mortality data, apheresis or revascularisations. However, all available data were reported and additional safety data were also provided. For example, coronary and non-coronary revascularisations were not reported from the four clinical efficacy trials, but were reported from other sources (see CS,¹³ Table 4-27, pages 145-146). In order to address the required outcome of apheresis, the results of a non-RCT assessing efficacy in LDL-C reduction at 36 weeks in

people with familial hypercholesterolaemia currently receiving apheresis were also reported (see CS,¹³ Section 4.11).

Health-related quality of life (HRQoL) was not assessed or reported in any of the included trials. The company's *de novo* model used other published evidence for HRQoL based on studies used to inform NICE CG181.¹⁵

3.5 Other relevant factors

There were no reported equity issues, end of life criteria were not relevant to the submission and no PAS application was submitted.

4. CLINICAL EFFECTIVENES

This section presents a summary and critique of the reviews submitted by the company on the efficacy and safety of evolocumab in the relevant populations. The critique was performed following the principles of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and checklist.³⁴

4.1 Critique of the methods of review(s)

The CS reports three separate reviews:

- a review of the efficacy evidence from RCTs (see CS,¹³ Sections 4.1-4.10);
- a review of the efficacy and safety evidence from non-randomised and non-controlled studies (see CS,¹³ Section 4.11), and;
- a review of safety evidence from RCTs and a non-randomised study (see CS, Section 4.12).¹³

Each review appears to have applied different inclusion criteria. However, only the criteria for the first review of clinical efficacy evidence from RCTs were described within the CS. Following a request for clarification regarding certain process elements (the searching, study selection, data extraction and quality assessment processes and descriptive synthesis), this efficacy review of RCT evidence was considered by the ERG to be generally robust (see clarification response,³⁵ questions A1, A9 and A12). The review of the efficacy and safety evidence from non-randomised and non-controlled studies was limited to a single two-arm Phase II/III trial of a severe familial hypercholesterolaemia (FH) population (TAUSSIG). This was not considered to be a systematic review because it was unclear how the evidence was identified, selected and extracted, no inclusion or exclusion criteria were provided, no list of excluded studies was provided, and no quality assessment of the included study was performed by the company. The review of the safety evidence is also not considered to be a systematic review because it was unclear from the original submission how some of the evidence was identified and selected; no detailed inclusion or exclusion criteria were provided, no list of excluded studies was provided, and no quality assessment was performed on the majority of included studies. However, in response to a request for clarification by the ERG (see clarification response,³⁵ question A12), the company conducted a quality assessment of the studies included in the safety evidence review.

4.1.1 Searches

Searches to identify evidence of clinical effectiveness and safety were conducted in March 2015 and were reproduced in full in the appendices to the CS. The searches were well structured, based on an appropriate PICO analysis of the key concepts specified in the review question and, by searching for a

range of comparators in addition to evolocumab, allowed for the possibility of identifying relevant studies for indirect as well as direct comparisons of effectiveness. Subject headings and free text terms (including a range of synonyms) have been used appropriately. The search terms used are consistent with the topic of the appraisal. Terms for “mixed dyslipidaemia” were not included among the indications in the search strategy, but this was corrected in a supplementary search conducted by the company at the request of the ERG (see clarification response,³⁵ question A1) and no additional relevant studies were identified. There were also some minor errors in the company’s searches, including redundant repetition (e.g. fluvastatin or fluvastatin sodium) and some minor typographical errors (e.g. “.tn.” is not a valid index in MEDLINE). There was also some inconsistency in the use of field tags, with some terms only being searched for in specific fields, whilst others were searched for in all fields.

Searches were conducted across a range of relevant databases (including MEDLINE, EMBASE and the Cochrane Library) and were accurately translated to the different requirements of these platforms (for example, choosing the correct subject headings available in each database). PubMed was not among the sources searched; had it been included, there would have been an additional opportunity to find recent studies not yet indexed in MEDLINE or MEDLINE In-Process. No limits were applied to these searches, except for an RCT filter, based on Cochrane’s Highly Sensitive Search Strategy (HSSS) for identifying randomised controlled trials.³⁶ The ERG notes that the company’s searches made several minor alterations to this filter without explanation; these were later clarified by the company and the search was not adversely affected (see clarification response,³⁵ question A2). The ERG also questioned how non-RCT evidence was identified, given that this was explicitly excluded by the use of an RCT filter; the company responded that non-RCT evidence was not identified using systematic review methods (see clarification response,³⁵ question A3).

Additional searches of several relevant trials registers and conference proceedings were also conducted, and there is some mention of hand-searching of reference lists, which did not include forward tracking of citations. On re-running a sample of searches, the numbers of results were consistent with those reported in the PRISMA diagram and search histories (see CS, p.66 and Appendix 3). Despite the caveats noted above, the ERG is broadly satisfied with the comprehensiveness of the company’s search strategy.

4.1.2 Inclusion criteria

The inclusion criteria for the reviews are described in Table 4-1 of the CS (see Table 3). However, these criteria can only relate to the reviews of RCT evidence assessing clinical efficacy and safety because non-randomised studies are explicitly excluded (and an RCT study filter is applied in the reported searches). The criteria also specifically include populations with HoFH, although these

studies, as well as studies of Japanese populations,³⁷ are then correctly excluded using additional inclusion/exclusion criteria described later in the CS. The intervention should have also included evolocumab in combination with ezetimibe in accordance with the decision problem specified in the final NICE scope.

The review of RCT evidence of clinical efficacy also included evidence from a non-RCT study, TAUSSIG,³⁸ which should have been excluded based on the reported inclusion criteria, and the OSLER 1 and 2 trials,³³ which included participants from trials excluded from the principal clinical efficacy review because the populations and comparators did not satisfy the criteria outlined in the company submission (see CS, Table 4-1¹³ and Table 3), for example, the studies involving Japanese patients and varying standards of care. This was acknowledged in the CS, but the trials were all retained with the justification that they provided longer-term evaluation data.

The review of the efficacy and safety evidence from non-randomised and non-controlled studies did not specify any inclusion criteria. This review reported a single study of severe FH patients who were allocated to a trial arm depending on whether or not they were also receiving apheresis (TAUSSIG). The inclusion of this study was justified in the submission on account of having included populations (FH and apheresis) which were relevant to the decision problem and on account of having longer-term efficacy evidence than RUTHERFORD-2 (36 weeks versus 12 weeks).

The inclusion criteria for the review of safety evidence from both RCTs and non-randomised studies were not specified. This review initially included the four RCTs from the clinical efficacy review, as well as the OSLER 1 and 2 trials, and the TAUSSIG study from the review of non-randomised and non-controlled studies. However, as noted above, the methods by which these additional studies were identified and the criteria by which they were selected, and others were excluded, are not clear. A set of integrated analyses of safety data were then presented that contained additional randomised and non-randomised studies which were excluded from the clinical efficacy review (see CS, Section 4.12).¹³

Table 3: Inclusion and exclusion criteria for the broad clinical efficacy/safety systematic literature review (reproduced from CS,¹³ Table 4-1, page 63)

	Inclusion criteria	Exclusion criteria
Population	•Studies in adults (≥ 18 years old) with primary hypercholesterolaemia (including familial and non-familial) who are candidates for treatment of elevated lipid levels (hyperlipidaemia) and consequent reduction in CV events. For patients with HoFH, studies including patients ≥ 12 years old were also included •Where available, data were identified and reported for two specific groups of patients: ▪Patients whose condition is not adequately controlled or is unlikely to be adequately controlled (according to European lipid targets) with a statin alone ▪Patients in whom a statin is considered inappropriate or is only tolerated at low dose/intensity. •Data relevant to the following subgroups were identified: ▪Patients with HeFH; patients with HoFH; patients with IHD, CVD, or PAD; and patients with diabetes mellitus type 2 •Data were also recorded for subgroups defined by gender, age (< 65, ≥ 65 years), and race (white, non-white) where reported	•Studies including patients with organ transplantations and infectious diseases (e.g. HIV) were excluded. In addition, studies including patients with significant heart failure (NYHA grade III-IV) or significant renal dysfunction (Stage 4-5), which are considered to be major confounding comorbidities, were also excluded
Intervention	•Evolocumab used in combination with moderate- or high-dose statins where cholesterol is insufficiently controlled with statin therapy alone and as monotherapy (in for example statin-intolerant patients). The following doses of evolocumab evaluated will be eligible for inclusion: ▪140 mg SC Q2W (1 prefilled AI/pen injection) ▪420 mg SC QM (3 prefilled AI/pen injections or 1 personal injector injection)	•Studies that do not include either the included intervention or comparator agents as one of their treatment arms
Comparators ^a	<u>Patients whose condition is not adequately controlled with a statin alone</u> •Alternative moderate- to high-intensity statin monotherapies (daily dose lowers LDL-C on average, by approximately $\geq 30\%$): atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin •Or alternatively, statins in combination with any of the following alternative lipid-lowering therapies such as: other alternative PCSK9 inhibitor monotherapies; cholesterol absorption inhibitors; nicotinic acids; fibrates; cholesteryl ester transfer proteins; and lomitapide, mipomersen, and apheresis (for HoFH) <u>Patients in whom a statin is considered inappropriate or is not tolerated</u>	

	Inclusion criteria	Exclusion criteria
	•No treatment/placebo; other alternative PCSK9 inhibitor monotherapies; cholesterol absorption inhibitors; bile acid resins; fibrates; cholesteryl ester transfer proteins; and lomitapide, mipomersen, and apheresis (for HoFH)	
Outcomes	<u>Clinical outcomes</u> •Overall survival; incidence of CV death; incidence of non-CV death; incidence of fatal and non-fatal CV events (composite and individual outcomes) e.g. CV death, MI, ischaemic stroke, TIA, hospitalisation for unstable angina, hospitalisation for worsening heart failure, symptomatic PAD, CHD and coronary revascularisation; time to fatal or non-fatal CV events (composite and individual outcomes) <u>Lipid-related outcomes (absolute values and change from baseline):</u> •LDL-C; triglycerides; HDL-C; VLDL-C; total cholesterol; total cholesterol/ HDL-C ratio; non-HDL-C; ApoB; ApoB/ApoA1 ratio; Lp(a); and incidence of apheresis (HoFH only). <u>Safety outcomes</u> •Incidence of treatment-related adverse events (any event, serious events, and specific individual events such as hepatic events, gastrointestinal events, headaches, muscle-related events, etc.) <u>Patient-reported outcomes (absolute values and change from baseline)</u> •HRQoL	•RCTs that do not assess one of the included outcomes
Study design	RCTs (including randomised dose finding and formulation studies with either a control or active control arm) were eligible for inclusion, if they were of ≥ 12 weeks' duration. This reflects regulatory guidance on the minimum duration of studies to demonstrate the lipid-lowering effects of investigational agents. It is also in line with previous recommendations included in NICE TA132 (ezetimibe for the treatment of hypercholesterolaemia). This STA reported that trials of shorter duration were considered 'unlikely to inform on survival, CVD events, adverse events or HRQoL' and were also 'excluded to allow for the tachyphylaxis effects'.	•Non-randomised studies •Studies < 12 weeks' duration or with < 10 participants per arm •Pre-clinical, phase 1, and animal studies
Language	Searches were not limited by language.	N/A

^aA more detailed list of specific comparator agents was provided in CS, Appendix 3.AI, autoinjector; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; HIV, human immunodeficiency virus; HoFH, homozygous familial hypercholesterolaemia; HRQoL, health-related quality of life; IHD, ischaemic heart disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); MI, myocardial infarction; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; QM, monthly; RCT, randomised controlled trial; SC, subcutaneous; STA, single technology appraisal; TIA, transient ischaemic attack; VLDL-C, very low-density lipoprotein cholesterol

4.1.3 Critique of study selection and data extraction

No information was given in any of the reviews regarding the data extraction process (for example, the number of reviewers involved, actions taken to minimise error), but this was addressed in response to clarification requests (see clarification response,³⁵ question A9). Following standard systematic review processes, trials were independently selected for inclusion by two reviewers, with any discrepancies between reviewers resolved through discussion or the intervention of a third reviewer. Data extraction was performed by one reviewer and independently checked for errors against the original trial report by a second reviewer. Any discrepancies were resolved through discussion or through the intervention of a third reviewer. An error in the PRISMA flowchart was acknowledged and addressed by the company in response to a clarification request from the ERG (see clarification response,³⁵ question A10).

4.1.4 Quality assessment

For the review of clinical efficacy, the company undertook a thorough critical appraisal of the four included trials using a standard risk of bias assessment tool (see CS,¹³ Section 4.6). The submission reported that the trials were at low risk of bias across all domains. Critical appraisal of the four trials was also conducted by the ERG and the assessments reported by the company were found to be generally reasonable based on data presented in the trial protocols, published journal articles and clinical study reports. It should be noted that the 52-week DESCARTES trial had greater scope for bias in the potential moderating effects of co-interventions regarding maintenance of diet, exercise and other lipid-lowering regimens, but the principal caveat is that the data in all trials were analysed using a ‘modified intention-to-treat (ITT)’ approach (all patients who received at least one dose of study drug included in the analysis) rather than a true ITT analysis (including all randomised patients in the groups to which they were assigned). This approach can result in bias: trials using a modified ITT analysis tend to report larger treatment effects than those that use a true ITT approach.³⁹ Numbers of patients who were excluded from the analysis after randomisation were as follows: 3/1899 in LAPLACE-2; 1/307 in GAUSS-2; 4/905 in DESCARTES; and 2/331 in RUTHERFORD-2. These data suggest that bias introduced by deviation from a true ITT analysis is unlikely to have had a major impact on the results of these trials.

For the non-randomised evidence, a single additional, non-RCT study was identified and its findings were presented, but a quality assessment was not performed for this study. The risk of bias affecting this study is therefore uncertain.

For the review of the safety evidence (see CS,¹³ Section 4.12), data from fourteen studies, RCTs and one non-RCT were presented, but other than the four trials also included in the clinical effectiveness

review, no quality assessment of these studies was performed within the CS. However, this was addressed by the company in response to a clarification request from the ERG (see clarification response,³⁵ question A12). The ERG accepts that the included studies are likely to be at low risk of bias.

4.1.5 Evidence synthesis

The synthesis for the review of clinical efficacy was a basic descriptive summary of the evidence from the four included trials. A meta-analysis was not performed and there was no discussion of heterogeneity in treatment effects between studies.

Following a request from the ERG, the company provided a justification for not conducting a network meta-analysis (NMA); the company argued that such an analysis was not necessary due to the availability of relevant head-to-head trials for the principal population: *“Given the availability of robust RCTs that provide head-to-head efficacy data for the intervention versus relevant comparators for patients with primary hypercholesterolaemia and mixed dyslipidaemia, a network meta-analysis was not considered to be necessary”* (clarification response,³⁵ question A14). The submission justified not undertaking an NMA within the HeFH subgroup on account of baseline differences between the identified studies in terms of background lipid-lowering therapy; the ERG considered this to be reasonable.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Review of clinical efficacy (RCT evidence)

The submission provides a very detailed, extensive description of four included trials (see Table 4). Two RCTs were presented as relevant interventions versus relevant comparators for the decision problem: LAPLACE-2 and GAUSS-2. These two trials compared evolocumab with ezetimibe in people with primary hypercholesterolaemia whose LDL-C was uncontrolled on statins (LAPLACE-2) or who were statin intolerant (GAUSS-2). Two further trials included in the CS were placebo-controlled, but were included because: they provided longer-term data (DESCARTES, 52 weeks); because pre-specified stratification factor and covariate subgroup analyses provided relevant comparative data (DESCARTES); or because they provided comparative data on a recognised subgroup of interest (HeFH) (RUTHERFORD-2).

Table 4: Included RCTs: Basic characteristics

Study (Acronym)	Population	Intervention	Comparator
LAPLACE-2	Primary hypercholesterolaemia	Evolocumab with statin	Ezetimibe with statin
GAUSS-2	Primary hypercholesterolaemia, intolerant to at least 2 statins or able to tolerate only the smallest dose because of muscle-related side-effects	Evolocumab alone	Ezetimibe alone
DESCARTES	Primary hypercholesterolaemia	Evolocumab with statin and ezetimibe	Ezetimibe with statin
RUTHERFORD-2	HeFH	Evolocumab with statin	Placebo and statin

HeFH - heterozygous familial hypercholesterolaemia

The LAPLACE-2 trial recruited people who have non-familial primary hypercholesterolaemia. The trial directly compared evolocumab in its two licensed doses with ezetimibe (10mg once daily (OD)) in people also taking a statin. The trial directly compared evolocumab in combination with three statins at five doses: an intensive statin dose (atorvastatin 80mg and rosvastatin 40mg) and a non-intensive dose (atorvastatin 10mg, simvastatin 40mg and rosvastatin 5mg). The trial measured change in LDL-C from baseline to 12 weeks.

The GAUSS-2 trial recruited people who have non-familial primary hypercholesterolaemia but in whom two or more statins could not be tolerated, or only the smallest dose could be tolerated. The trial directly compared evolocumab in its two licensed doses with ezetimibe (10mg OD) in the absence of statin therapy. The trial measured change in LDL-C from baseline to 12 weeks.

The DESCARTES trial recruited people who have non-familial primary hypercholesterolaemia. The trial directly compared evolocumab, at the QM dose only, with placebo in the presence of background lipid-lowering therapy. The trial measured change in LDL-C from baseline to both 12 weeks and 52 weeks. The trial was included on account of its longer-term data. However, the trial did not compare evolocumab with ezetimibe, and included people who did not receive statins or received only low intensity statins (10mg atorvastatin), who were neither statin intolerant nor on a maximum-tolerated dose of a statin. It was therefore not wholly consistent with the decision problem specified in the final NICE scope.⁴ The trial also had a subgroup of patients who received ezetimibe as background therapy.

The RUTHERFORD-2 trial recruited patients with HeFH. The trial directly compared evolocumab in its two licensed doses with placebo in patients receiving stable lipid-lowering therapy at baseline. The trial measured change in LDL-C from baseline to 12 weeks. The ERG received clinical advice that the HeFH population of the RUTHERFORD trial with a confirmed genetic mutation was higher than might be found in usual clinical practice in the UK,⁴⁰ but the implications of this are unclear. The ERG also noted, following clinical advice, that the proportion of patients with CHD was higher in the intervention arms of the RUTHERFORD-2 trial (i.e. 30-36%) than would be expected in clinical practice in a HeFH population, and was higher than the prevalence reported for the other three trials (e.g. LAPLACE-2 trial arm populations ranged from 17% to 24% with CHD characteristics).

A list of excluded studies, with reasons, was provided by the company (see CS,¹³ Section 4.1 and Appendix 3). The principal reasons for excluding studies that otherwise satisfied the inclusion criteria for the review (for example, a number of relevant Phase II trials) were the publication of an identical, subsequent, larger Phase III trial (e.g. LAPLACE-1, GAUSS-1, RUTHERFORD-1), the absence of statins in a cohort who were eligible for statins, as required by the marketing authorisation for evolocumab,^{41,42} or the absence of a relevant comparator.^{43,44}

All four included trials were international and multicentre. The populations of three of the included trials are reported in the submission as having “primary hypercholesterolaemia and mixed dyslipidaemia” (LAPLACE-2, GAUSS-2, DESCARTES, see Table 5). The final selection of four included trials for the clinical effectiveness review was therefore considered by the ERG to be reasonable. However, the appearance of two new, open-label extension trials, OSLER 1 and OSLER 2,³³ within the results section of the CS (see CS,¹³ Section 4.10, Table 4-10) was neither justified nor appropriate. Efficacy results are provided from these “Supplementary ongoing, randomised, controlled, open-label LTE studies” (see CS, pages 120-121), but these trials contain mixed populations from Phase II and other RCTs that were otherwise explicitly excluded from the clinical effectiveness review, as described above. It was acknowledged in the CS that this population might not reflect the population that would receive evolocumab in clinical practice in England. This evidence is therefore arguably not relevant to this appraisal.

Patient characteristics were generally well-balanced across arms in all trials. It should also be noted that people with type 1 diabetes mellitus or newly-diagnosed or poorly-controlled type 2 diabetes mellitus were excluded from the four key trials. This group represent a cohort of patients who are highly likely to present with hypercholesterolaemia⁴⁵ and who are at a high risk of CVD events.

Table 5: Included RCTs: Populations

Study (Acronym)	Design	Population	Inclusion criteria	Exclusion criteria
Non-familial primary hypercholesterolaemia				
LAPLACE-2	International, multi-centre, Phase III, parallel-group, double-blind RCT	Patients with “primary hypercholesterolaemia and mixed dyslipidaemia” treated with background moderate- to high-intensity statin therapy	• Informed consent • Male or female ≥ 18 to ≤ 80 years of age • Fasting LDL-C ≥ 2.1 mmol/L (taking an intensive statin at screening), ≥ 2.6 mmol/L (taking a non-intensive statin at screening), or ≥ 4.5 mmol/L (not taking a statin at screening) at screening • Fasting TG ≤ 4.5 mmol/L at screening • Negative pregnancy test, AST and ALT ≤ 2 times ULN, CK $\leq 3 \times$ ULN as determined by central laboratory at the end of the lipid stabilisation period	• Use of other lipid-lowering therapy other than statin or ezetimibe in previous 6 weeks • NYHA class III/IV HF or LVEF $< 30\%$ • Uncontrolled cardiac arrhythmia within 3 months • MI, UA, PCI, CABG, or stroke within 6 months • Planned cardiac surgery or revascularisation • Type 1 diabetes or newly diagnosed or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction
GAUSS-2	International, multi-centre, Phase III, parallel-group, double-blind RCT	Patients with “primary hypercholesterolaemia and mixed dyslipidaemia” with statin intolerance	• Informed consent • Male or female ≥ 18 to ≤ 80 years of age • No or low-dose statin at baseline • Fasting LDL-C at screening based on NCEP ATP III risk category goals ▪ LDL-C ≥ 2.6 mmol/L for those with CHD or CHD risk equivalents ▪ LDL-C ≥ 3.4 mmol/L for patients without diagnosed	• NYHA class III/IV HF or LVEF $< 30\%$ • Uncontrolled cardiac arrhythmia in the prior 3 months • MI, UA, PCI, CABG, or stroke within 3 months • Planned cardiac surgery or revascularisation • Type 1 or 2 diabetes or newly diagnosed

Study (Acronym)	Design	Population	Inclusion criteria	Exclusion criteria
Non-familial primary hypercholesterolaemia				
			CHD or risk equivalent but with ≥ 2 risk factors ▪ LDL-C ≥ 4.1 mmol/L for patients without diagnosed CHD or risk equivalent but with 1 risk factor ▪ LDL-C ≥ 4.9 mmol/L for patients without diagnosed CHD or risk equivalent and no risk factors • Statin intolerant (history of intolerance to ≥ 2 statins) ▪ Inability to tolerate any dose or increase above a maximum dose^b because of intolerable muscle-related side effects; AND ▪ Symptoms resolved or improved when statin dose was decreased or discontinued • Stable lipid-lowering therapy for ≥ 4 weeks before screening if on statin and/or bile acid sequestrant and/or stanol; if on ezetimibe at screening, ezetimibe must be discontinued for ≥ 4 weeks before LDL-C screening • Fasting TG ≤ 4.5 mmol/L at screening	or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction
DESCART ES	International, multi-centre, Phase III, parallel-group, double-blind RCT	Patients with “primary hypercholesterolaemia and mixed dyslipidaemia” treated with background lipid-lowering therapy	• Informed consent • Male or female ≥ 18 to ≤ 75 years of age • Fasting LDL-C ≥ 2.0 mmol/L and fasting TG ≤ 4.5 mmol/L at screening • Fasting LDL-C after 4-week lipid stabilisation period with one of four background lipid-lowering therapy regimens based on NCEP ATP III risk category goals	• CHD or CHD risk equivalent and not receiving statin with LDL-C at screening ≤ 2.6 mmol/L • NYHA class II/III/IV HF or LVEF $< 30\%$ • Uncontrolled cardiac arrhythmia within 3 months prior to randomisation

Study (Acronym)	Design	Population	Inclusion criteria	Exclusion criteria
Non-familial primary hypercholesterolaemia				
			▪ LDL-C ≥ 2.0 mmol/L and < 2.6 mmol/L for those with CHD or CHD risk equivalents; ▪ LDL-C ≥ 2.0 mmol/L and < 3.4 mmol/L in patients without CHD or risk equivalent; ▪ OR for patients on maximal background lipid-lowering therapy (diet + atorvastatin 80 mg + ezetimibe), LDL-C ≥ 2.0 mmol/L	• MI, UA, PCI, CABG, or stroke within 3 months prior to randomisation • Planned cardiac surgery or revascularisation • Type 1 diabetes or newly diagnosed or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction
Familial primary hypercholesterolaemia: HeFH				
RUTHER-FORD-2	International, multi-centre, Phase III, parallel-group, double-blind RCT	Patients with HeFH treated with stable background lipid-lowering therapy (statin $\pm$ other lipid-lowering therapy)	• Informed consent • Male or female ≥ 18 to ≤ 80 years of age • Diagnosis of HeFH by Simon Broome criteria • On a stable dose of an approved statin $\pm$ other allowed lipid-lowering therapy (e.g. ezetimibe, resins, stanols, or niacin) for ≥ 4 weeks before screening and, in the opinion of the investigator, not requiring up titration • Fasting LDL-C ≥ 2.6 mmol/L at screening • Fasting TG ≤ 4.5 mmol/L at screening	• HoFH • LDL or plasma apheresis within 4 months • NYHA class III/IV HF or LVEF $< 30\%$ • Uncontrolled cardiac arrhythmia within 3 months • MI, UA, PCI, CABG, or stroke within 3 months • Planned cardiac surgery or revascularisation • Type 1 diabetes or newly diagnosed or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction

The three RCTs that assessed a general primary non-familial hypercholesterolaemia population included more than 3,000 participants. Three of the RCTs had a follow-up of 12 weeks; one trial reported data for 12 and 52 weeks (DESCARTES, see Table 6). The intervention was administered using both licensed doses of evolocumab in separate arms in all trials, with the exception of the 52-week DESCARTES trial, which only used the QM regime of 3 doses per month (420mg). The doses of ezetimibe (10mg OD) and background statin therapy were generally in accordance with NICE guidance.^{14,15} The ERG noted that there is a lack of evidence on the effectiveness of evolocumab in combination with ezetimibe (all populations). This was provided in subgroups for the RUTHERFORD and DESCARTES trials, but with ezetimibe only as part of the background therapy (in a comparison with placebo).

Table 6: Included RCTs: Interventions and comparators

Study (Acronym)	Numbers randomised	Follow-up	Intervention	Comparator
Non-familial primary hypercholesterolaemia				
LAPLACE-2	n=1899	12 weeks	•Evolocumab 420 mg QM + Placebo OD oral (n = 562) •Evolocumab 140 mg Q2W + Placebo OD oral (n = 557)	•Placebo QM + Placebo OD oral (n = 278) •Ezetimibe 10 mg OD oral + Placebo QM (n = 109) •Ezetimibe 10 mg OD oral + Placebo Q2W (n = 112) •Placebo Q2W + Placebo OD oral (n = 281)
GAUSS-2	n=307	12 weeks	•Evolocumab 140 mg Q2W + Placebo OD oral (n = 103) •Evolocumab 420 mg QM + Placebo OD oral (n = 102)	• Ezetimibe 10 mg OD oral + Placebo Q2W (n = 51) •Ezetimibe 10 mg OD oral + Placebo QM (n = 51)
DESCARTES	n=905	52 weeks	•Evolocumab 420 mg QM (n = 602)	•Placebo QM (n = 303)
Familial primary hypercholesterolaemia: HeFH				
RUTHERFORD-2	n=331	12 weeks	•Evolocumab 420 mg QM (n = 110) •Evolocumab 140 mg Q2W (n = 111)	•Placebo QM (n = 55) •Placebo Q2W (n = 55)

HeFH - heterozygous familial hypercholesterolaemia; OD – once daily; Q2W - every 2 weeks; QM - monthly

The majority of the clinical evidence reported 12-week follow-up (the minimum required duration to demonstrate lipid-lowering effects of investigational agents¹⁵), with the exception of the DESCARTES trial (52 weeks). The principal efficacy outcomes for consideration were plasma lipid

and lipoprotein levels, including LDL-cholesterol, non-HDL-cholesterol, apolipoprotein B and lipoprotein(a). These were reported in all RCTs. Only the mean percentage change from baseline in calculated LDL-C and treatment differences are reported here. The results for non-HDL-cholesterol, apolipoprotein B and lipoprotein(a) were detailed in Appendix 5 of the CS.¹³ Separate, pre-specified subgroup analyses were reported that assessed whether there was any difference in treatment effect based on trial stratification factors, such as background lipid-lowering therapy and severity of hypercholesterolaemia, as well as other covariates, such as evolocumab dose (Q2W versus QM), age, gender, baseline LDL-C level, and CHD risk factors (see Table 7).

Table 7: Included RCTs: Outcomes

Study (Acronym)	LAPLACE-2	GAUSS-2	DESCARTES	RUTHERFORD-2
Primary efficacy outcome	•Percent change from baseline in LDL-C at week 12 •Percent change from baseline in LDL-C at the mean of weeks 10/12	•Percent change from baseline in LDL-C at week 12 •Percent change from baseline in LDL-C at the mean of weeks 10/12	•Percent change from baseline in LDL-C at week 52	•Percent change from baseline in LDL-C at week 12 •Percent change from baseline in LDL-C at the mean of weeks 10/12
Pre-specified subgroups	<u>Stratification factors</u> •Entry statin therapy •Simvastatin contraindicated therapy usage for first randomisation <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2 , region, family history of premature CHD, baseline PCSK9, baseline TG, and NCEP high risk	<u>Stratification factors</u> •Screening LDL-C < 4.7 mmol/L vs. ≥ 4.7 mmol/L •Baseline statin use <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2 , region, family history of premature CHD, baseline PCSK9, baseline TG, NCEP high risk, intolerance to statin, and background lipid-modifying therapy	<u>Stratification factors</u> •Background lipid-lowering therapy <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2 , region, family history of premature CHD, baseline PCSK9, baseline TG, and NCEP high risk	<u>Stratification factors</u> •Screening LDL-C < 4.2 mmol/L vs. ≥ 4.2 mmol/L •Ezetimibe use at baseline <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2 , region, family history of premature CHD, baseline PCSK9, baseline TG, NCEP high risk, HeFH status, and background lipid-modifying therapy

4.2.2 Results

Results for the primary outcome - the mean percentage change in calculated LDL-C from baseline to follow-up – for all four trials were reported in the CS. In within-trial pooled analyses, data were reported for all trial arms, all follow-ups, and for all pre-specified and *post hoc* subgroups. For LAPLACE-2, within-trial pooled analyses for evolocumab trial arms were reported using both fixed and random effects models.

Across all four trials, evolocumab at both licensed doses (Q2W and QM) in primary hypercholesterolaemia populations (for whom statins were and were not appropriate) was associated with reductions, and statistically significant treatment differences ($p < 0.001$), compared with ezetimibe or placebo in mean percentage change in LDL-C from baseline at the mean follow-ups of weeks 10/12 and week 12 (LAPLACE-2, GAUSS-2) and at weeks 12 and 52 (DESCARTES). Similar results were found versus placebo for the HeFH population (RUTHERFORD-2).

Tables 8 to 16 summarise the main results of the four key evolocumab trials included in the CS for the outcome of LDL-C. The results presented here are those considered most relevant to the decision problem specified in the final NICE scope,⁴ particularly those comparing treatment regimens involving evolocumab with regimens involving ezetimibe. All the results are expressed as the least-squares mean percentage change from baseline in LDL-C, with associated 95% Confidence Intervals (CIs). Most results are reported at two time points: a mean of the values for weeks 10 and 12, and the mean value for the results for week 12; the exception is the DESCARTES trial, which measured outcomes at 12 and 52 weeks. *P*-values with associated 95% CIs are only reported for treatment difference in mean percentage change from baseline in calculated LDL-C.

LAPLACE-2

This trial allows a comparison to be made between evolocumab and ezetimibe (10mg OD) in patients also taking a statin. The trial compared both doses of evolocumab in combination with three statins at five doses: an intensive statin dose (atorvastatin 80mg and rosvastatin 40mg) and a non-intensive dose (atorvastatin 10mg, simvastatin 40mg and rosvastatin 5mg). For the purposes of this appraisal, the results for atorvastatin (both doses versus ezetimibe) and all statins (combined) are reported here: these are the focus of the appraisal and were used in the company's health economic model (see Section 5.2).

The results for mean percentage change (and 95% CIs) in LDL-C from baseline to week 12 in the atorvastatin groups are reported in Table 8. In the atorvastatin (10mg) groups, the mean percentage change in LDL-C from baseline to week 12 was -20.9 (95% CI, -26.4 to -15.5) and -17.1 (95% CI, -22.7 to -11.4) for ezetimibe, compared with -64.6 (95% CI, -68.3 to -60.8) for evolocumab Q2W and

-60.1 (95% CI, -64.1 to -56.0) for evolocumab QM. For the atorvastatin (80mg) groups, the mean percentage change in LDL-C from baseline to week 12 was -15.0 (95% CI, -24.3 to -5.8) and -21.1 (95% CI, -28.7 to -13.4) for ezetimibe compared with -64.9 (95% CI, -71.5 to -59.5) for evolocumab Q2W and -62.4 (95% CI, -67.9 to -57.0) for evolocumab QM.

Table 8: Mean percentage change from baseline (and 95% CIs) in calculated LDL-C in LAPLACE-2: evolocumab versus ezetimibe arms

Timepoint	Ezetimibe 10 mg OD + placebo Q2W	Evolocumab 140 mg Q2W + placebo OD	Ezetimibe 10 mg OD + placebo QM	Evolocumab 420 mg QM + placebo OD
Atorvastatin 10 mg cohort				
Mean of weeks 10/12	-23.4 (-28.3 to -18.5)	-64.1 (-67.5 to -60.8)	-18.8 (-24.0 to -13.6)	-64.1 (-67.7 to -60.4)
Week 12	-20.9 (-26.4 to -15.5)	-64.6 (-68.3 to -60.8)	-17.1 (-22.7 to -11.4)	-60.1 (-64.1 to -56.0)
Atorvastatin 80 mg cohort				
Mean of weeks 10/12	-17.3 (-25.3 to -9.3)	-65.3 (-71.0 to -59.5)	-22.1 (-29.0 to -15.2)	-68.1 (-72.9 to -63.2)
Week 12	-15.0 (-24.3 to -5.8)	-64.9 (-71.5 to -58.4)	-21.1 (-28.7 to -13.4)	-62.4 (-67.9 to -57.0)

OD - once daily, LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

The results for the treatment difference in mean percentage change (and 95% CIs) in LDL-C from baseline to week 12 in the atorvastatin groups are reported in Table 9. For the atorvastatin (10mg) groups, the treatment difference in the mean percentage change in LDL-C from baseline to week 12 was -43.6 (95% CI, -50.2 to -37.1) for evolocumab Q2W compared to ezetimibe, and -43.0 (95% CI, -49.9 to -36.1, $p<0.001$) for evolocumab QM compared with ezetimibe. For the atorvastatin (80mg) groups, the treatment difference in the mean percentage change in LDL-C from baseline to week 12 was -49.9 (95% CI, -61.2 to -38.7) for evolocumab Q2W compared with ezetimibe, and -41.4 (95% CI, -50.8 to -31.9, $p<0.001$) for evolocumab QM compared with ezetimibe.

Table 9: Treatment difference in mean percentage change (and 95% CIs) in calculated LDL-C from baseline in LAPLACE-2: evolocumab versus ezetimibe arms

Timepoint	Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg OD		Evolocumab 420 mg QM vs. Ezetimibe 10 mg OD	
	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort
Mean of weeks 10/12	-40.8 (-46.7 to -34.9)	-48.0 (-57.8 to -38.1)	-45.2 (-51.6 to -38.9)	-46.0 (-54.4 to -37.5)
Week 12	-43.6 (-50.2 to -37.1)	-49.9 (-61.2 to -38.7)	-43.0 (-49.9 to -36.1)	-41.4 (-50.8 to -31.9)

OD - once daily; LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

The results for the mean percentage change from baseline, and treatment difference, in LDL-C from baseline to week 12 across all of the statin groups are reported in Table 10. In the pooled analysis across all statin groups, both doses of evolocumab were significantly superior to placebo at 12 weeks both in terms of mean change from baseline and treatment difference ($p < 0.001$), regardless of whether fixed or random effects models were used.

Table 10: Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C in LAPLACE-2: pooled analysis across all statin cohorts

Timepoint	Outcome	Placebo Q2W (N = 281)	Evolocumab 140 mg Q2W (N = 555)	Placebo QM (N = 277)	Evolocumab 420 mg QM (N = 562)
Mean of weeks 10/12	Mean percentage change from baseline (95% CI)	7.9 (5.4 to 10.5)	-64.3 (-66.1 to -62.5)	4.6 (1.7 to 7.4)	-65.1 (-67.0 to -63.1)
	Fixed effect treatment difference (95% CI)		-72.3 (-75.4 to -69.1)		-69.6 (-73.1 to -66.1)
	Random effects treatment difference (95% CI)		-71.8 (-74.7 to -68.9)		-69.1 (-73.5 to -64.8)
Week 12	Mean percentage change from baseline (95% CI)	9.5 (6.6 to 12.4)	-64.3 (-66.4 to -62.3)	5.6 (2.4, 8.7)	-59.1 (-61.3 to -56.8)
	Fixed effect treatment difference (95% CI)		-73.8 (-77.4 to -70.3)		-64.6 (-68.5 to -60.8)
	Random effects treatment difference (95% CI)		-73.3 (-76.6 to -70.0)		-64.4 (-69.2 to -59.6)

OD - once daily; LDL-C, low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

The results for the mean percentage change from baseline, and treatment difference, in LDL-C from baseline to week 12 across all of the atorvastatin groups are reported in Table 11. For this pooled

analysis of the atorvastatin (10mg and 80mg) groups, the findings were similar to and consistent with the findings for separate atorvastatin cohorts, both in terms of mean percentage change from baseline and statistically significant treatment difference ($p < 0.001$), regardless of whether fixed or random effects models were used.

Table 11: Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C in LAPLACE-2: pooled analysis across atorvastatin cohorts

Timepoint	Outcome	Placebo Q2W + ezetimibe 10 mg OD (N = 112)	Evolocumab 140 mg Q2W (N = 219)	Placebo QM + ezetimibe 10 mg OD (N = 109)	Evolocumab 420 mg QM (N = 220)
Mean of weeks 10/12	Mean percentage change from baseline (95% CI)	-20.2 (-24.6 to -15.8)	-64.7 (-67.8 to -61.6)	-20.4 (-24.5 to [-]16.3)	-66.2 (-69.1 to -63.3)
	Fixed effect treatment difference (95% CI)		-44.5 (-49.9 to -39.2)		-45.8 (-50.8 to -40.8)
	Random effects treatment difference (95% CI)		-43.3 (-50.0 to -36.5)		-45.5 (-50.5 to -40.5)
Week 12	Mean percentage change from baseline (95% CI)	-17.9 (-23.0 to -12.8)	-64.8 (-68.3 to -61.2)	-18.9 (-23.4 to -14.5)	-61.4 (-64.6 to -58.2)
	Fixed effect treatment difference (95% CI)		-46.9 (-53.0 to -40.7)		-42.5 (-47.9 to -37.0)
	Random effects treatment difference (95% CI)		-45.2 (-50.8 to -39.6)		-42.4 (-48.0 to -36.9)

OD - once daily; LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

GAUSS-2

The GAUSS-2 trial recruited people in whom two or more statins could not be tolerated or only the smallest dose could be tolerated, and so directly compared evolocumab and ezetimibe in the absence of statin therapy. The main results are summarised in Table 12. At week 12, a mean percentage change in LDL-C from baseline of -18.2 (95% CI, -23.2 to -13.1) and -14.9 (95% CI, -19.2 to -10.5) was reported for ezetimibe across the two cohorts, compared with -57.4 (95% CI, -61.3 to -51.6) and -53.0 (95% CI, -56.2 to -49.8) for evolocumab Q2W and QM, respectively. At week 12, the treatment

difference for mean percentage change in LDL-C from baseline was -39.3 (95% CI, -45.0 to -33.5, $p<0.001$) and -38.1 (95% CI, -42.9 to -33.4, $p<0.001$) for evolocumab Q2W and QM, respectively, compared with the two ezetimibe cohorts.

The ERG noted that the results presented in the CS are for the Full analysis Set (FAS) and report greater efficacy than the results reported in the original publication.²⁴ At week 12, the treatment difference for mean percentage change in LDL-C from baseline was -38.1 (95% CI, -43.7 to -32.4) and -37.6 (95% CI, -42.2 to -32.9) in the original publication for evolocumab Q2W and QM versus the two ezetimibe cohorts, compared with -39.3 (95% CI, -45.0 to -33.5) and -38.1 (95% CI, -42.9 to -33.4) in the CS. The p -value for these comparisons in both the CS and journal publications was the same ($p<0.001$). All of the Week 12 results were consistent with the findings for Weeks 10/12.

Table 12: Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C from baseline in GAUSS-2

Outcome	Placebo Q2W + ezetimibe 10 mg OD (N = 51)	Evolocumab 140 mg Q2W + placebo OD (N = 103)	Placebo QM + ezetimibe 10 mg OD (N = 51)	Evolocumab 420 mg QM + placebo OD (N = 102)
Mean of weeks 10/12 mean percentage change from baseline	-19.0 (-23.9 to -14.1)	-57.1 (-60.8 to -53.4)	-16.6 (-20.7 to -12.5)	-55.8 (-58.9 to -52.8)
Mean of weeks 10/12 treatment difference		-38.1 (-43.6 to -32.6)		-39.2 (-43.7 to -34.8)
Week 12 mean percentage change from baseline	-18.2 (-23.2 to -13.1)	-57.4 (-61.3 to -53.6)	-14.9 (-19.2 to -10.5)	-53.0 (-56.2 to -49.8)
Week 12 treatment difference		-39.3 (-45.0 to -33.5)		-38.1 (-42.9 to -33.4)

OD - once daily; LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

DESCARTES

The DESCARTES trial measured change in LDL-C from baseline to both 12 weeks and 52 weeks in people with primary hypercholesterolaemia. The main results comparing evolocumab, at the QM dose only, with placebo in the presence of background lipid-lowering therapy are summarised in Table 13. The comparison with placebo is not in line with the final NICE scope (although this is used in the model), partly because ezetimibe is not a comparator, but also because the trial included people who did not receive statins or received only low intensity statins (10mg atorvastatin), who were therefore neither statin intolerant nor on a maximum-tolerated dose of a statin, as required by the decision problem specified in the final NICE scope⁴ and the marketing authorisation for evolocumab. The results are reproduced here briefly only for comparison with the 12 week results of the LAPLACE-2 and GAUSS-2 trials, and for comparison with the 52-week results, which represent the longest relevant follow-up of efficacy data for evolocumab.

At week 52, the mean percentage change in LDL-C from baseline was -50.6 (95% CI, -53.2 to -48.0) for evolocumab at the QM dose compared with 8.7 (95% CI, 5.1 to 12.4) for the placebo group, producing a treatment difference of -59.3 (-95% CI, -63.8 to -54.9) ($p<0.001$).

Table 13: Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C from baseline in DESCARTES

Outcome	Placebo QM (N = 302)	Evolocumab 420 mg QM (N = 599)
Week 12 mean percentage change from baseline	4.4 (1.7 to 7.0)	-56.7 (-58.7 to -57.8)†
Week 12 treatment difference		-61.1 (-64.3 to -57.9)†
Week 52 mean percentage change from baseline	8.7 (5.1 to 12.4)	-50.6 (-53.2 to -48.0)
Week 52 treatment difference		-59.3 (-63.8 to -54.9)

LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

† It should be noted that the CS reported erroneous data for mean change from baseline at week 12, which also affect the treatment difference. These data are clearly in error because the mean is outside of the 95% CI: -56.7 (-58.7 to -57.8). Alternative data for this outcome measurement were not available.

However, this trial also had a subgroup of people on high-dose statins (atorvastatin 80mg) plus ezetimibe. The results for this subgroup are presented in Table 14. This analysis compares placebo plus diet plus statin plus ezetimibe with evolocumab plus diet plus statin plus ezetimibe (described in the CS¹³ [page 152] as a “relevant intervention and comparator”).

At week 52, the mean percentage change in LDL-C from baseline was -47.1 (95% CI, -52.9 to -41.2) for evolocumab QM compared with 2.3 (95% CI, -6.1 to 10.6) for the placebo group, producing a treatment difference of -49.3 (95% CI, -59.5 to -39.1, $p<0.001$).

Table 14: Subgroup analysis of mean percentage change and treatment difference in ultracentrifugation LDL-C from baseline in DESCARTES for patients using ezetimibe at baseline (from DESCARTES study report Table 14-4.7.1)

Outcome	Placebo QM	Evolocumab 420 mg QM
Number in subgroup	55	115
Week 52 mean percentage change from baseline	2.3 (-6.1 to 10.6)	-47.1 (-52.9 to -41.2)
Week 52 treatment difference		-49.3 (-59.5 to -39.1)

OD - once daily; LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

RUTHERFORD-2

RUTHERFORD-2 recruited patients with HeFH. This was a placebo-controlled trial in patients receiving stable lipid-lowering therapy at baseline. Table 15 presents the results of the main analysis. A subgroup analysis of patients receiving ezetimibe at baseline allows a comparison of statin plus ezetimibe versus evolocumab plus statin plus ezetimibe (see Table 15). The ERG received clinical advice that the HeFH population of the RUTHERFORD trial with a confirmed genetic mutation was higher than might be found in usual clinical practice in the UK, but the implications of this are unclear. The ERG also noted, following clinical advice, that the proportion of patients with CHD was higher in the intervention arms of the RUTHERFORD-2 trial (i.e. 30-36%) than would be expected in clinical practice in a HeFH population, and were higher than the prevalence reported for the other three trials (e.g. LAPLACE-2 trial arm populations ranged from 17% to 24% with CHD characteristics).

At week 12, the mean percentage change in LDL-C from baseline was -62.7 (95% CI, -66.3 to -59.1) for evolocumab Q2W compared with -2.1 (95% CI, -7.2 to 3.0) for the placebo group, producing a treatment difference of -60.6 (95% CI, -66.7 to -54.5, $p<0.001$). At week 12, the mean percentage change in LDL-C from baseline was -56.6 (95% CI, -60.9 to -52.3) for evolocumab QM compared with 3.8 (95% CI, -2.5 to 10.0) for the placebo group, resulting in a treatment difference of -60.3 (95% CI, -67.8 to -52.9, $p<0.001$).

The ERG noted that the data presented in the submission are from the FAS and report greater treatment differences than in the original publication.²¹ For example, for the mean of the results for weeks 10/12, the mean percentage change in LDL-C from baseline for the evolocumab Q2W dose was -61.2 (95% CI, -64.6 to -57.9) in the original publication, rather than -62.7 (95% CI, -66.3 to -59.1) in the CS and, for placebo, it was -1.1 (95% CI, -5.8 to 3.7) rather than -1.4 (95% CI, -6.3 to 3.6), resulting in a treatment difference of -60.2 (95% CI, -65.8 to -54.5) rather than the -61.3 (95% CI, -67.2 to -55.4) in the company submission. For weeks 10/12, the mean percentage change in LDL-C from baseline for the evolocumab QM dose was -63.3 (95% CI, -66.6 to -59.9) in the original publication, rather than -64.7 (95% CI, -68.1 to -61.4) in the CS and, for placebo, was 2.3 (95% CI, -2.5 to 7.1) rather than 1.5 (95% CI, -3.2 to 6.2), resulting in a treatment difference of -65.6 (95% CI, -71.3 to -59.8) rather than -66.2 (95% CI, -71.9 to -60.6). However, the p -values for treatment differences between both evolocumab doses and placebo in both the company submission and the journal publications all remain the same ($p<0.001$).

Table 15: Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C from baseline in RUTHERFORD-2 (patients with heterozygous familial hypercholesterolaemia, based on CS,¹³ Table 4.15 and Figure 4-8*)

Outcome	Placebo Q2W	Evolocumab 140 mg Q2W	Placebo QM	Evolocumab 420 mg QM
Mean of weeks 10/12 mean percentage change from baseline	-1.4 (-6.3 to 3.6)	-62.7 (-66.2 to -59.2)	1.5 (-3.2 to 6.2)	-64.7 (-68.1 to -61.4)
Mean of weeks 10/12 treatment difference		-61.3 (-67.2 to -55.4)		-66.2 (-71.9 to -60.6)
Week 12 mean percentage change from baseline	-2.1 (-7.2 to 3.0**)	-62.7 (-66.3 to -59.1)	3.8 (-2.5 to 10.0)	-56.6 (-60.9 to -52.3)
Week 12 treatment difference		-60.6 (-66.7 to -54.5)		-60.3 (-67.8, -52.9)

LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

*Minor discrepancies between figure and table; data from table have been extracted **-3.0 in submission seems incorrect. Comparison is stable LLT vs. evolocumab + LLT, OD:

As with the ezetimibe subgroup in DESCARTES, at week 12, the mean percentage change in LDL-C from baseline was -58.6 (95% CI, -63.6 to -53.6) for background ezetimibe and evolocumab at the Q2W dose compared with -0.2 (95% CI, -7.3 to 6.9) for the background ezetimibe and placebo group, producing a treatment difference of -58.4 (95% CI, -67.1 to -49.7, $p < 0.001$). At week 12, the mean percentage change in LDL-C from baseline was -56.2 (95% CI, -62.1 to -50.4) for ezetimibe and evolocumab at the QM dose compared with 4.6 (95% CI, -3.6 to 12.9) for the ezetimibe and placebo group, producing a treatment difference of -60.9 (95% CI, -71.0 to -50.8, $p < 0.001$).

Table 16: Subgroup analysis of mean percentage change and treatment difference (and 95% CIs) in calculated LDL-C from baseline in RUTHERFORD-2 for patients using ezetimibe at baseline (from study report Table 14-4.4.2)

Outcome	Placebo Q2W	Evolocumab 140 mg Q2W	Placebo QM	Evolocumab 420 mg QM
Number in subgroup	33	67	35	67
Mean of weeks 10/12 mean percentage change from baseline*	0.2 (-6.7 to 7.1)	-59.0 (-63.8 to -54.1)	0.6 (-5.5 to 6.7)	-64.6 (-68.9 to -60.2)
Mean of weeks 10/12 treatment difference		-59.2 (-67.6 to -50.8)		-65.2 (-72.7 to -57.7)
Number in subgroup	32	64	32	65
Week 12 mean percentage change from baseline*	-0.2 (-7.3 to 6.9)	-58.6 (-63.6 to -53.6)	4.6 (-3.6 to 12.9)	-56.2 (-62.1 to -50.4)
Week 12 treatment difference		-58.4 (-67.1 to -49.7)		-60.9 (-71.0 to -50.8)

LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

*Least squares mean as in other tables.

Other lipid parameters

Across all four trials, statistically significant reductions were also reported for evolocumab versus placebo or ezetimibe for all other lipid parameters for weeks 10/12, week 12 and, in DESCARTES, for week 52: HDL-C, non-HDL-C, ApoB and Lp(a), triglycerides (TG) and very low-density lipoprotein cholesterol (VLDL-C). These results are not reported here but were provided in Appendix 5 of the CS. The p -values were between $p < 0.001$ and $p < 0.05$ depending on the parameter.

Pre-specified subgroups

The subgroup analyses were extensive and were presented in detail, with forest plots provided in Appendix 6 of the CS for all stratification factors and relevant covariates for each trial.¹³ The conclusion that there were no significant differences between the two evolocumab dose regimens (which appear to be clinically equivalent), baseline lipid-lowering therapies, severity of hypercholesterolaemia, LDL-C level, statin use, CHD risk factors etc. appears sound, based on the results submitted for these trials. Analyses were also conducted on the following pre-specified high-risk subgroups, with no notable differences between groups:

From LAPLACE-2 and DESCARTES:

- CHD or CHD-risk equivalent with baseline LDL-C > 2.6 mmol/L, treated with statin;
- Statin-treated subjects with a history of MI or ischaemic stroke and baseline LDL-C > 1.8 mmol/L, > 2.6 mmol/L, or > 3.4 mmol/L

From RUTHERFORD and GAUSS-2:

- CHD risk equivalent

From RUTHERFORD:

- High risk HeFH (defined as any of the following: history of CV event; presence of xanthomas or premature arcus cornea; LDL-C > 4.1 mmol/L; ≥ 1 CV risk factors (e.g. smoking, diabetes): Lp(a) > 125 nmol/L, with subgroups (LDL-C > 3.4 mmol/L and > 5.2 mmol/L)

From all trials:

- Very high risk according to ESC/EAS guidelines.

Evolocumab at both licensed doses, and in patients who could and who could not have statins, was therefore consistently effective relative to placebo and to ezetimibe in lowering LDL-C (mean percentage change from baseline at the mean of weeks 10/12 and at week 12 [RUTHERFORD-2, LAPLACE-2, GAUSS-2] or at week 52 [DESCARTES]) in all stratification factor and baseline covariate subgroups in each study.

4.2.3 *Review of clinical efficacy and safety (non-randomised and non-controlled evidence)*

The CS presents findings from a single non-randomised study: TAUSSIG (see CS,¹³ Section 4.11). This is an ongoing long-term, open-label Phase II/III study, which recruited patients with severe familial hypercholesterolaemia. The study reported findings for up to 36 weeks. As noted above, however, it is not clear how this study was identified. It should also be noted that the study is unpublished (and cannot be appraised for risk of bias) and the population includes people with HeFH and HoFH; the latter group are excluded from the final scope for this appraisal. The ERG assumes, though this is not specified, that the interim FAS results presented are for the HeFH group alone. The study was considered relevant by the company because of the relative lack of data on evolocumab in the HeFH subgroup and in patients receiving apheresis, an outcome of relevance to the decision problem. However, the 16 patients receiving apheresis also received an unlicensed dose of evolocumab (420mg Q2W). For these reasons, the full results data are not reproduced here. The results reported that mean percentage change of LDL-C from baseline for evolocumab QM by week 36 in the severe FH, non-apheresis group (n=126) was -50.5 (standard error [SE]=3.6).

4.2.4 *Review of safety (randomised and non-randomised trial evidence)*

The submitted review of the safety evidence was extensive with all key adverse events covered and particular events addressed in detail. The principal omission was the failure to provide discrete data for each of the two licensed doses. The submission stated that there was no difference between doses, but the data were not clearly presented. Given that the two doses appear to be equivalent in terms of efficacy, the ERG considered that it therefore made sense to assess whether they are also equivalent in terms of safety. For this reason, the ERG has provided these data, where available from the original trial publications and submission appendices, in addition to the combined evidence for both doses, which was provided in the CS (see Tables 17-24). These data are not provided for all safety outcomes, but only for the principal outcomes of interest, as articulated in the literature and the CS: all AEs; SAEs; events leading to discontinuation of the study drug; nasopharyngitis; headache; back pain; neurocognitive events and upper respiratory tract infection.

Whilst the company's review appears to be sound, the ERG notes that it is not a systematic review of the safety evidence. The inclusion criteria for this review were not specified. CS Section 4.12 initially summarised the evidence from the four principal RCTs included in the efficacy review, as well as the OSLER 1 and 2 trials, and the TAUSSIG trial from the review of non-randomised and non-controlled studies (see CS,¹³ Table 4-23, page 136). A set of integrated analyses of safety data from 14 randomised studies (11 studies of approximately 12 weeks in duration and three longer-term studies (one 52-week completed study and two ongoing extension studies, with unpublished data) are also presented. This is the "integrated parent analysis set", which includes the four principal RCTs but also many studies that were excluded from the clinical efficacy review. Reasons for exclusion from the

efficacy review included the level and appropriateness of the background lipid-lowering therapy used/not used, the inclusion of certain population groups, and the comparison being assessed. Consequently, the ERG notes that this population might not reflect the population that would receive evolocumab in clinical practice in England. Further, as noted above, the methods by which all of these studies were identified, in addition to the four trials included in the efficacy review, and the criteria by which they were selected, and others excluded, are not reported. However, in response to a request for clarification from the ERG (see clarification response,³⁵ question A12), the company provided a complete quality assessment of the included studies, all of which appear to be at low risk of bias. The data presented here are for the four principal RCTs, the integrated parent analysis set, and separate integrated data for year 1 and year 2 of the long-term, open-label extension studies, which include cumulative data to a 1st July 2014 cut-off date.

Table 17: Percentage rates of all AEs (from submission FAS, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338	12	36.3	36.3	36.3	40.3	
GAUSS-2	307	12	61	71	66	73	
DESCARTES	901	52		74.8			74.2
RUTHERFORD-2	329	12	55	57			49
OSLER 1, 2: Yr 1	4465				65.4 (69.2)†		61.1 (64.8) †
OSLER 1, 2: Yr 2	1675				■		
Integrated parent analysis set	6026	12, 52*			51.1	■	■

Evo = evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks; FAS - full analysis set

11 RCTs have 12 weeks, 1 RCT has 52 weeks. †Sabatine et al³³

Table 18: Percentage rates of SAEs (from submission FAS, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338 555/562	12	2.3	1.7	2.1	0.9	
GAUSS-2	307	12	5	1	3	4	
DESCARTES	901	52		5.5			4.3
RUTHERFORD-2	329	12	3	4			4
OSLER 1, 2: Yr 1	4465				6.6 (7.5)†		6.7 (7.5)†
OSLER 1, 2: Yr 2	1675				■		
Integrated parent analysis set	6026	12, 52*			2.8	■	■

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks. †Sabatine et al³³

Table 19: Percentage rates of AEs leading to discontinuation (from submission FAS, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338 555/562	12	2.3	1.7	1.9	1.8	
GAUSS-2	307	12	6	11	8	13	
DESCARTES	901	52		2.2			1.0
RUTHERFORD-2	329	12	0	0			0
OSLER 1, 2: Yr 1	4465				2.1 (2.4) †		NA
OSLER 1, 2: Yr 2	1675						
Integrated analysis set	6026	12, 52*			1.9		

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks. † Sabatine et al³³

Table 20: Percentage rates of nasopharyngitis (from submission FAS, Appendix 7, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	881	12			0.7	1.8	2.3
GAUSS-2	307	12	4.9	2.0	3.2	2.9	
DESCARTES	901	52		10.5			9.6
RUTHERFORD-2	329	12	7	10			4.8
Integrated analysis set	6026	12, 52*			5.9		

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks.

Table 21: Percentage rates of headache (from submission FAS, Appendix 7, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338 555/562	12	1.3	2.1	1.7	2.3	
GAUSS-2	307	12	3.9	11.2	7.8	8.8	
DESCARTES	901	52		4.0			3.6
RUTHERFORD-2	329	12	4	5			3.6
OSLER 1, 2†	4465	52			3.6		2.1
Integrated analysis set	6026	12, 52*			3.0		

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks. † Sabatine et al³³

Table 22: Percentage rates of back pain (from submission FAS, Appendix 7, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338 555/562	12	2.5	1.1	1.8	3.2	
GAUSS-2	307	12					
DESCARTES	901	52		6.2			5.6
RUTHERFORD-2	329	12	2	5			0.9
Integrated analysis set	6026	12, 52*			3.0	■	■

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks.

Table 23: Percentage rates of neurocognition AEs (from submission FAS, Appendix 7, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338 555/562	12			0.1	1.4	
GAUSS-2	307	12					
DESCARTES	901	52					
RUTHERFORD-2	329	12	0	0			0
OSLER 1, 2†	4465				0.9		0.3
Integrated analysis set	6026	12, 52*					

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks. † Sabatine et al³³

Table 24: Percentage rates of upper respiratory tract infection (from submission FAS, Appendix 7, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	881	12			1.4	1.4	0.9
GAUSS-2	307	12					
DESCARTES	901	52		9.3			6.3
RUTHERFORD-2	329	12			3.2		2.8
Integrated analysis set	6026	12, 52*			3.2	■	■

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks.

The incidence of overall AEs appears to be quite high for evolocumab with a range of 36% to 74%, depending on the trial population, with the higher rates in the statin-intolerant and HeFH trial cohorts. However, the rates of SAEs are relatively low, at around 1-2%, and neither the overall nor serious event rates appear to be dissimilar to ezetimibe. There do not appear to be any AEs for evolocumab that are substantially higher than those found for ezetimibe.

[REDACTED]

[REDACTED]

[REDACTED] The higher incidence of neurocognitive events (delirium, confusion, cognitive and attention disorders and disturbances, dementia, amnesia, disturbances in thinking and perception) in the evolocumab arms relative to the comparator arms (0.9 vs 0.3) reported in the OSLER 1 and 2 open-label extension studies appears to be associated with people who were at high risk of such events.³³ The ERG notes that a sub-study of the ongoing FOURIER outcomes study, EBBINGHAUS, includes an assessment of cognitive function in this group.⁴⁶

There is also no consistent trend in relative frequency of AEs for the higher QM dose compared with the Q2W dose of evolocumab. For example, for the higher dose, the data from GAUSS-2 indicate much higher incidence rates of AEs leading to discontinuation, and a higher reported frequency of headache, but this is not reflected across other trials and the comparisons with ezetimibe are generally favourable. Across both doses of evolocumab, there also appears to be a slightly higher incidence of events at 12 weeks in the GAUSS and RUTHERFORD trials compared to ezetimibe or placebo, respectively. This might suggest that the statin intolerant and HeFH subgroups are at a slightly higher risk. The key finding is that AE rates are clearly higher for the DESCARTES trial across all of the safety outcomes reported here. The DESCARTES trial included only the higher QM dose of evolocumab. Given that the definition of AEs does not appear to differ between trials, the higher incidence of these events in the DESCARTES trial is almost certainly due to the longer follow-up (52 weeks compared with 12 weeks across most trials), as noted in the CS. This is also suggested by the data from the OSLER 1 and 2 open-label extension studies, which also report relatively higher rates of overall AEs and SAEs. In DESCARTES, event rates were, unsurprisingly, always higher for the evolocumab group than for the placebo group, with some rates as much as twice those found in the placebo group (e.g. events leading to discontinuation, 2.2% vs 1.0%). This suggests that long-term safety might be an issue. Greater clarity needs to be provided on the relative safety of both licensed doses compared to therapies such as ezetimibe in the long-term. None of the highlighted differences in safety outcomes have been assessed for statistical significance.

The CS reported that the number of deaths and positively adjudicated CV events (including revascularisation procedures) was small and similar between evolocumab and controls as reported from the larger integrated safety analysis and extension studies (see CS,¹³ Table 4-27, page 145). It also noted that the preliminary empirical evidence from safety analyses suggested that long-term use of evolocumab to lower LDL-C may be associated with reduced risk of CV events (including revascularisation procedures). However, the CS acknowledged that these data are preliminary, the trials are not powered to detect a difference in major CV events, and the incidence is typically 0.5% or less for most positively adjudicated cardiovascular events and outcomes. The ongoing, longer-term

FOURIER trial is seeking to test this potential relationship in people who have had a CV event, with CVD as an efficacy rather than a safety outcome (clinicaltrials.gov identifier NCT01764633). This is an area of uncertainty in the evidence base.

The following additional safety outcomes are reported in the CS: injection site reactions; muscle and creatine kinase levels; incidence of liver function test abnormalities; Hepatitis C; immunogenicity and diabetes events. Frequency of hypersensitivity and injection site reactions was between 2% and 4% for evolocumab, with a higher incidence over time. Across these outcomes, events were infrequent and generally balanced between arms and between the parent and extension studies. Event rates also appear to be unaffected by baseline level of LDL-C. The presence of diabetes events was considered infrequent, but it should be noted that type 1 and newly-diagnosed or poorly-controlled type 2 diabetes mellitus was an exclusion criterion of the four key trials: LAPLACE-2; GAUSS-2; DESCARTES and RUTHERFORD-2 (see Table 4).

Evolocumab therefore appears to have an acceptable safety profile. However, longer-term data are required to determine whether reported frequency rates are maintained, whether or not certain subgroups of patients are at higher risk of certain events, and to confirm whether or not there are any differences between the two licensed doses of evolocumab.

4.2.5 Ongoing studies

The submission detailed a number of ongoing studies of evolocumab. The most relevant of these studies are listed in Table 25. For key efficacy outcomes, the most important trials are the Phase III RCTs FOURIER and GAUSS-3. FOURIER seeks to evaluate the effectiveness of evolocumab (both doses) on CVD outcomes in a population with CVD; GAUSS-3 is seeking to assess mean percentage change from baseline LDL-C at weeks 22 and 24 for people who are statin-intolerant (after a statin re-challenge). For safety outcomes, the most important trials are the ongoing OSLER 1 and 2 trials, and the EBBINGHAUS⁴⁶ subset from the FOURIER trial,³² which has a particular focus on neurocognitive events (cognitive function).

These trials will provide important direct evidence of the relationship between evolocumab and CV events for people with CVD, longer-term efficacy evidence for people who are statin-intolerant, and some longer-term safety evidence, albeit with the caveats expressed above regarding the OLSER 1 and 2 trial populations. The FOURIER trial will therefore test the assumption that LDL-C is a viable surrogate for CV events for evolocumab for one subset of the relevant population; this is a key area of uncertainty in the current evidence base.

Table 25: Relevant ongoing studies of evolocumab (as of 1st July 2015, adapted from CS, Table 0-1)

Study	Description	Interventions	No. of patients	Primary outcome measure	Estimated completion dates
Efficacy outcomes					
FOURIER	Multicentre, international, Phase 3, RCT	•Placebo Q2W •Evolocumab 140 mg Q2W •Placebo QM •Evolocumab 420 mg QM	27,564	Time to CV death, MI, stroke, hospitalisation for UA, or coronary revascularisation, whichever occurs first	Completion date: February 2018 Primary completion date ^a : October 2017
GAUSS-3	Multicentre, international, Phase 3, RCT	<u>Part A – Cross-over statin rechallenge</u> •Placebo OD •Atorvastatin 20 mg OD <u>Part B – Comparison of evolocumab and ezetimibe</u> •Placebo QM + ezetimibe OD •Evolocumab 420 mg QM + Placebo OD <u>Part C – open-label extension</u> •Evolocumab 420 mg QM or 140 mg Q2W	519	Mean percent change from baseline in LDL-C at weeks 22 and 24 and mean percent change from baseline in LDL-C at week 24 in part B	Completion date: November 2017 Primary completion date ^a : October 2015
Safety outcomes					
OSLER-1	Phase 2, open-label extension	•SoC^b •Evolocumab 420 mg QM + SoC^b	1,324	Patient incidence of treatment emergent AEs (timeframe: approximately 1 year)	Completion date: July 2016 Primary completion date ^a : July 2016
OSLER-2	Phase 3, open-label extension	•SoC^b •Evolocumab 140 mg Q2W or 420 mg QM + SoC^b	4,428 (estimated)	Patient incidence of AEs (timeframe: 156 weeks)	Completion date: May 2018 Primary completion date ^a : May 2018

Study	Description	Interventions	No. of patients	Primary outcome measure	Estimated completion dates
EBBINGHAUS ^c	Multicentre, international, Phase 3, RCT	•Evolocumab Q2W or QM + effective statin dose •Placebo Q2W or QM + effective statin dose	4,000 (estimated)	Mean change from baseline over time in spatial working memory index of executive function	Completion date: February 2018 Primary completion date ^a : October 2017

^aFinal data collection date for primary outcome measure. ^bSoC (standard of care) therapy as per local practices. This could include prescribed therapies and/or dietary/exercise regimens. ^cEBBINGHAUS evaluates the effect of evolocumab on cognitive function in a subset of patients enrolled in FOURIER.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Two studies were identified as being potentially useful for synthesising comparative efficacy data for evolocumab plus statins compared with ezetimibe plus statins in patients with HeFH. One of the two included studies was the previously identified RUTHERFORD-2 study which assessed evolocumab Q2W plus lipid-lowering therapy and evolocumab QM plus lipid-lowering therapy (interventions) versus lipid-lowering therapy alone (comparator). Patients were receiving lipid lowering therapy prior to baseline measurement.

The additional identified study was ENHANCE,⁴⁷ which assessed ezetimibe plus statin (intervention) versus statin alone (comparator). In ENHANCE, patients were washed out of prior lipid-lowering therapy before the randomisation and then randomised to either statins and placebo, or statins and ezetimibe. The percentage change from baseline therefore reflects the treatment effect against a baseline of no lipid lowering therapy. This is different from the RUTHERFORD-2 study, which assesses the percentage change against a baseline of lipid-lowering therapy. The CS (page 130) therefore states that the percentage change from baseline within each patient is not comparable between ENHANCE and RUTHERFORD-2. For this reason, an indirect comparison was not performed.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The CS considered the use of an NMA only for the HeFH population. In this population, the CS asserts (page 130) that since the percentage change from baseline within each patient was not comparable between ENHANCE and RUTHERFORD-2, an NMA was “neither appropriate nor feasible.” The ERG considers this conclusion to be appropriate.

Although an NMA was deemed inappropriate for the HeFH population, the ERG considers that it may have been useful for the company to consider undertaking an NMA for the primary non-familial hypercholesterolaemia population (LAPLACE-2, DESCARTES) and generate the joint posterior distribution of treatment effect for these studies. The treatment effect in LDL-C for evolocumab QM versus placebo was: -69.1 (95% CI, -73.5,-64.8) in LAPLACE-2 and -61.1 (95% CI, -64.3,-57.9) in DESCARTES, with the non-overlapping 95% confidence intervals suggesting heterogeneity in the treatment effects between studies ($p=0.004$ for difference between means).

The purpose of an NMA is primarily to estimate relative efficacy. However, it is also used to quantify uncertainty associated with the treatment effects as required for subsequent health economic analyses. In the presence of heterogeneity, the predictive distribution, rather than the distribution of the mean treatment effect, would better represent uncertainty about the treatment effect in a future study.

In the absence of head-to-head data in HeFH for evolocumab plus statins versus ezetimibe plus statins, the CS states (page 193) that treatment effects from the primary non-familial hypercholesterolaemia population are generalisable to the HeFH population. If this assertion is indeed true, the ERG considers that it would have been useful to perform an NMA over both populations: the hypercholesterolaemia population (LAPLACE-2, DESCARTES) and the HeFH population (RUTHERFORD-2) so that the clinical evidence from the HeFH population contributes to the utilised treatment effect, rather than simply replacing the required measure with that from the primary non-familial hypercholesterolaemia population. The treatment effect for evolocumab Q2M versus placebo was -71.8 (95% CI, -74.7,-68.9) in LAPLACE-2 and -61.3 (95% CI, -67.2,-55.4) in RUTHERFORD-2 ($p=0.002$ for difference between means). The use of only LAPLACE-2 to inform the treatment effect for the HeFH population therefore under-represents the true uncertainty in this treatment effect, and potentially over-estimates the magnitude of the treatment effect also.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG did not undertake any additional analyses for the clinical effectiveness review.

4.6 Conclusions of the clinical effectiveness section

The principal efficacy review represents a good quality systematic review of four relevant, good quality RCTs. The trials were generally consistent with the final NICE scope. The primary efficacy outcome was mean percentage change in LDL-C from baseline, and mean treatment difference across trial arms, at follow-ups of 12 weeks (LAPLACE-2, GAUSS-2, DESCARTES and RUTHERFORD-2) and 52 weeks (DESCARTES).

In the LAPLACE-2 trial, at 12 weeks, patients with primary hypercholesterolaemia on background atorvastatin therapy (intensive and non-intensive doses) had a treatment difference in mean percentage change in LDL-C from baseline of -46.9 (95% CI, -53.0 to -40.7, $p<0.001$) and -42.5 (95% CI, -47.9 to -37.0, $p<0.001$) for the Q2W and QM doses of evolocumab respectively, compared with ezetimibe (fixed effects model).

In the GAUSS-2 trial, at 12 weeks, patients with primary hypercholesterolaemia who were statin intolerant had a treatment difference in mean percentage change in LDL-C from baseline of -39.3 (95% CI, -45.0 to -33.5, $p<0.001$) and -38.1 (95% CI, -42.9 to -33.4, $p<0.001$) for the Q2W and QM doses of evolocumab compared with ezetimibe.

In the placebo-controlled RUTHERFORD-2 trial, at 12 weeks, patients with HeFH on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -62.7 (95% CI, -66.3 to -59.1) and -56.6 (95% CI, -60.9 to -52.3) for the Q2W and QM doses of evolocumab. The treatment difference in mean percentage change compared with placebo was -60.6 (95% CI, -66.7 to -54.5, $p<0.001$) and -60.3 (95% CI, -67.8, -52.9, $p<0.001$) for the Q2W and QM doses of evolocumab respectively. The ERG received clinical advice that the HeFH population of the RUTHERFORD trial with a confirmed genetic mutation was higher than might be found in usual clinical practice in the UK, but the implications of this are unclear. The ERG also noted, following clinical advice, that the proportion of patients with CHD was higher in the intervention arms of the RUTHERFORD-2 trial (i.e. 30-36%) than would be expected in clinical practice in a HeFH population, and was higher than the prevalence reported for the other three trials (e.g. LAPLACE-2 trial arm populations ranged from 17% to 24% with CHD characteristics).

In the placebo-controlled DESCARTES trial, patients with primary hypercholesterolaemia on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -50.6 (95% CI, -53.2 to -48.0) for the QM dose of evolocumab at 52 weeks. The treatment difference in mean percentage change compared with placebo was -59.3 (95% CI, -63.8 to -54.9, $p<0.001$) at 52 weeks.

The results for other lipid parameters, such as non-HDL-cholesterol, HDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB) and lipoprotein(a) (Lp(a)), were consistent with the results for LDL-C, and pre-specified subgroup analyses demonstrated that these results were not sensitive to the different doses of evolocumab, or other key variables, such as LDL-C baseline levels, severity of hypercholesterolaemia or CVD risk factors. The ERG noted that only 12-week evidence was available for the efficacy of the Q2W dose, whilst the QM dose had some data for 52 weeks. Additional clinical efficacy evidence was provided from a non-RCT study (TAUSSIG) and two open-label, extension

trials (OSLER 1 and 2). However, the extension studies included some trials with populations and/or comparators that were excluded from the principal review of four RCTs and it is unclear how these trials and the non-RCT study were identified for inclusion in the company's review. The inclusion of these studies was justified by the company on account of the longer-term evidence both from the extension studies and from TAUSSIG on the HeFH subgroup (36 weeks). An NMA was not performed, although this might have been possible using particular trial evidence from both the primary non-familial hypercholesterolaemia population and the HeFH subgroup.

The clinical effectiveness review found that evolocumab is efficacious at lowering LDL-C, but in itself this is not a clinically important outcome: its importance is derived from it being a surrogate for CVD. Although there is an established relationship between statin-generated LDL-C reduction and reduced CV events, the impact of evolocumab on CVD has not been demonstrated: there is little or no direct evidence on this relationship. The ongoing FOURIER trial ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02207634) identifier NCT02207634) aims to evaluate the impact of evolocumab on CVD outcomes, but only in people who have already had a CV event. The ERG also noted that there was no evidence on the relative efficacy of evolocumab versus ezetimibe in the familial hypercholesterolaemia subgroup, or for evolocumab in combination with ezetimibe in any population, and there was little or no direct trial evidence for evolocumab in terms of HRQoL or apheresis.

The submission of safety evidence was a non-systematic review of good quality RCTs, providing evidence for up to two years. There were no obvious safety concerns, with most AEs being balanced across evolocumab and comparator trial arms, and very small numbers of SAEs were reported. However, the ERG noted that relatively higher 12-week AE rates were reported in patients who had HeFH or who had primary non-familial hypercholesterolaemia and were statin-intolerant. Similarly, these rates were also relatively higher for trials with a longer follow-up duration. This suggests that some patient subgroups might experience more frequent events and that all patients are at risk of AEs over time, though the rates are generally similar to comparators. The ERG noted also that the longer-term evidence presented was derived from some trials with populations who would not be eligible to receive evolocumab in clinical practice in the NHS (e.g. people who were not on maximum-tolerated doses of statins). More long-term data are therefore needed in relevant UK populations, although it is not clear whether ongoing trials will address this.

5 COST EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the company's review of published economic evaluations and the *de novo* health economic analysis presented within the CS.¹³

5.1 ERG comment on the company's systematic review of cost-effectiveness evidence

5.1.1 Description of company's systematic review of cost-effectiveness evidence

The CS¹³ presents the methods and results of a systematic review of existing health economic evaluations of lipid-lowering drug therapies for the treatment of hypercholesterolaemia. According to the CS, the purpose of the review was *"to systematically identify, critically review, and summarise studies evaluating the cost-effectiveness of evolocumab, statins, and ezetimibe for LDL-C reduction in adults with hypercholesterolaemia"* (see CS,¹³ page 161). The CS states that the review was undertaken to inform the *de novo* model developed as part of the submission.

Search strategy

The company undertook electronic searches within the following electronic databases:

- MEDLINE
- EMBASE
- Econlit
- National Health Service Economic Evaluations Database (NHS EED).

Searches were limited to articles with abstracts written in English and published during the period 2000 to 2014.

In addition to the electronic searches, conference abstracts published between 2013 and 2014 from the following congresses were reviewed:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- American College of Cardiology (ACC)
- American Heart Association (AHA)
- European Society of Cardiology (ESC)
- European Atherosclerosis Society (EAS).

The CS states that the conference abstract search used the same strategy as the EMBASE search. The websites of the conferences not indexed by EMBASE (ESC 2014 and EAS 2014) were searched manually for relevant abstracts.

In addition, HTA documents assessing economic evaluations of lipid-lowering drug therapies were identified through a manual search of the health technology assessment (HTA) websites in a variety of countries including the UK (NICE, the All Wales Medical Strategy Group [AWMSG], and the Scottish Medicines Consortium [SMC]), Spain, Sweden, France, Australia, Canada, Netherlands, Belgium, Austria, Ireland, Portugal, Poland, Hungary, Slovenia, Mexico, and Brazil. As with the electronic searches, HTA websites were searched for studies reported during the period 2000-2014.

The reference sections of review articles identified in search results were hand-searched for original relevant articles which met the review inclusion criteria.

Inclusion and exclusion criteria

The inclusion and exclusion criteria adopted within the company's review are summarised in Box 1.

Box 1: Inclusion and exclusion criteria for company's review of cost-effectiveness studies

Inclusion criteria

- Full economic evaluations undertaken in adults with LDL hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies would be considered
- Studies assessing evolocumab, ezetimibe and/or statins
- Studies reporting on: cardiovascular event reduction; treatment costs; QALYs / quality of life measures; cost-effectiveness and/or cost-utility results for the interventions of interest (i.e. ICERs)

Exclusion criteria

- Studies undertaken in children only (<18 years of age)
- Studies undertaken in non-humans
- Studies evaluating surgical procedures, lifestyle interventions and/or dietary modification
- Models which do not involve economic evaluations
- Studies that assess only cost, utilisation or efficacy
- Studies that do not present cost-effectiveness measures
- Studies in which no abstract is available
- Studies not reported in English
- Studies published before the year 2000

Study selection and quality assessment

The CS¹³ (page 164) states that study selection followed a 3-stage process involving the assessment of titles and abstracts of potentially relevant studies against the inclusion/exclusion criteria, followed by re-assessment of full texts of potentially includable studies against the criteria. Included studies were

assessed using the checklist reported by Drummond and Jefferson.⁴⁸ The CS notes that studies were not selected or excluded from the review based on quality assessment.

Results of the company's review of cost-effectiveness evidence

The company's electronic searches yielded 775 potentially relevant unique citations. Of these, 645 studies were excluded at the title/abstract stage. One additional study was identified through hand-searching, leading to 131 potentially includable studies. Following a review of the full texts of these studies, 35 were excluded. The conference proceedings search in EMBASE yielded 33 potentially includable studies; all but one of these was excluded as they did not evaluate at least one intervention of interest. The conference proceedings search for studies not yet indexed in EMBASE yielded 184 potentially includable abstracts, however all of these were excluded. The company's manual search of HTA websites identified 11 HTA reports that contained details of cost-effectiveness models that were deemed relevant to the decision problem.

A total of 108 studies were included in the review. The CS notes that 28 of these studies were UK-focussed, 66 adopted a Markov approach and 53 adopted a lifetime horizon. None of the identified studies evaluated evolocumab. The CS¹³ (Table 5-2, page 176) presents a summary of 14 UK-based studies which presented a Markov model with a lifetime time horizon.

5.1.2 ERG critique of company's systematic review of cost-effectiveness evidence

The searches undertaken by the company were of a reasonable quality. Search terms were drawn from NICE CG181¹⁵ and appropriate subject headings and syntax were used for each database. The ERG did however identify some problems. In particular, there is a risk of missing relevant foreign language studies by imposing a restriction to include only English language studies. Furthermore, the company appears to have developed their own filter for identifying economic evaluations; this was tailored to each database searched, but includes some minor syntax errors (for example, "pharmaco?economic*" – the "?" character cannot be used to find hyphens or spaces in Ovid). The ERG considers that the use of a validated filter e.g. the Scottish Intercollegiate Guidelines Network (SIGN) economic evaluation filter, would have minimised the risk of missing potentially relevant economic studies. In addition, the ERG notes that the process of study selection and review described in the CS is not entirely clear. The PRISMA diagram presented in Figure 5-1 of the CS¹³ (page 165) includes only those studies identified through the electronic searches; this should have also included studies identified through searching of conferences and HTA websites. There is also some ambiguity regarding the study selection process which is described as a three stage process but only appears to include two stages (sifting by title and abstract followed by full text review).

The results of the review are partially summarised in Table 5-2 of the CS.¹³ Data extraction tables and quality assessment tables are presented in CS Appendix 9. The reasons for including only the 14 studies which adopted a Markov structure and a lifetime horizon (see CS¹³, Table 5-2), rather than the broader set of 28 included UK studies, are unclear from the CS. Perhaps more importantly, neither the main submission document nor the accompanying appendix offers any interpretation of results of the review of cost-effectiveness evidence, and these contain only very abbreviated information regarding the structures and data sources adopted in previous models. Neither the CS nor the accompanying appendix includes any discussion of key structural issues arising from previous models, for example, methods for modelling compound health states which incorporate prior events, approaches to modelling CV event risk using surrogate measures, or alternative methods for quantifying baseline event risk. Consequently, the extent to which the company's review has been used to inform the company's *de novo* model is unclear; this issue is discussed in more detail in Section 5.3.

Despite the limitations of the review, the ERG is satisfied that the company's searches are unlikely to have missed any relevant economic evaluation studies of evolocumab. The ERG notes that in September 2015, the US Institute for Clinical and Economic Review published a draft report assessing the cost-effectiveness of PCSK9 inhibitors for the treatment of hypercholesterolaemia.⁴⁹ Given the publication date, this study was not identified by the company's searches. The analysis was based on the previously published CVD Policy Model,^{50,51} this is a Markov model of CHD and stroke incidence, prevalence, mortality, and costs in the US population over the age of 35 years. Within the analysis, the authors evaluate the comparative clinical effectiveness and cost-effectiveness of two PCSK9 inhibitors, evolocumab and alirocumab as a class, for people with elevated LDL-C. The health economic analysis was undertaken from a healthcare perspective over a time horizon of 20 years. The results of the analyses indicate that within the HeFH population, the ICER for PCSK9 inhibitors plus statins versus ezetimibe plus statins is approximately \$681,000 per QALY gained. For people with non-familial primary hypercholesterolaemia with a prior history of CVD who are able to take statins, the ICER for the PCSK9 inhibitors plus statins versus ezetimibe plus statins was reported to be approximately \$557,000 per QALY gained. For people with non-familial primary hypercholesterolaemia with a prior history of CVD who are unable to take statins, the ICER for PCSK9 inhibitors versus ezetimibe was reported to be about \$506,000 per QALY gained.

5.2 Description of the company's model

5.2.1 Health economic evaluation scope

As part of their submission, the company submitted a fully executable health economic model programmed in Microsoft Excel. The company's model assesses the cost-effectiveness of evolocumab versus ezetimibe, each in combination with atorvastatin in patients who are able to take statins, or as monotherapy (without concomitant atorvastatin) in patients for whom statins are contraindicated or not tolerated. The company's model assesses the cost-effectiveness of evolocumab over a lifetime horizon from the perspective of the UK NHS; costs borne by Personal Social Services (PSS) were not included in the company's analysis. All costs and health outcomes were discounted at a rate of 3.5% per annum.

Table 26: Scope of the company's health economic analysis

Population	(i) People with non-familial primary hypercholesterolaemia and LDL-C >2.5mmol/L without a history of CVD, based on the subset of patients enrolled within the LAPLACE-2 trial²³ who had these characteristics. (ii) People with non-familial primary hypercholesterolaemia LDL-C >2.5mmol/L with a history of CVD, based on the subset of patients enrolled within the LAPLACE-2 trial²³ who had these characteristics. (iii) People with or without a history of CVD and a diagnosis of HeFH, based on the modified ITT population of the RUTHERFORD-2 trial.²¹ These populations are further subdivided in terms of those patients who are able to take statins (denoted ST) and those for whom statins are contraindicated or not tolerated (denoted SI). Subgroup analyses are also presented for patients with additional risk factors in people with a history of CVD.
Interventions and comparators	For patients who are able to take statins, the base case analysis compares: • Evolocumab plus statins versus ezetimibe plus statins. For patients for whom statins are contraindicated or not tolerated, the base case analysis compares: • Evolocumab monotherapy versus ezetimibe monotherapy Additional scenario analyses are presented for evolocumab in combination with ezetimibe (with or without concomitant statins).
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS
Time horizon	Lifetime
Discount rate	3.5% per year

LDL-C – low density lipoprotein cholesterol; CVD – cardiovascular disease, ST – statin-tolerant; SI – statin intolerant; QALY – quality-adjusted life year; HeFH - Heterozygous familial hypercholesterolaemia

Population

The company's model assesses the cost-effectiveness of evolocumab in three main populations, based on the baseline characteristics of people enrolled in the LAPLACE-2 trial²³ and the RUTHERFORD-2 trial.²¹

- (i) People with non-familial primary hypercholesterolaemia and LDL-C > 2.5 mmol/L without a history of CVD, based on the subset of patients enrolled into the LAPLACE-2 trial²³ who had these characteristics. Throughout the remainder of this chapter, this population is referred to as the non-familial primary prevention population. It should be noted that results for this population were deemed “invalid” by the company following the identification of problems in the model (the presence of negative probabilities) by the ERG during the clarification stage.
- (ii) People with non-familial primary hypercholesterolaemia and LDL-C > 2.5 mmol/L with a history of CVD, based on the subset of patients enrolled into the LAPLACE-2 trial²³ who had these characteristics. Throughout the remainder of this chapter, this population is referred to as the non-familial secondary prevention population. The mathematical inconsistency described above is also applicable to this population however the company did not comment on the validity of results for this population.
- (iii) People with a diagnosis of HeFH with or without a history of CVD, based on the modified ITT population of the RUTHERFORD-2 trial.²¹ Throughout the remainder of this chapter, this population is referred to as the HeFH primary/secondary prevention population. The mathematical inconsistencies described above also apply to this population, however the company did not consider the analyses in the population to be invalid, but instead introduced adjustments to some transition probabilities to avoid the occurrence of negative transition probabilities under the base case assumptions; these issues are described in Section 5.3.

For all three populations described above, separate analyses are presented for: (a) patients who are able to take statins (ST), and; (b) patients for whom statins are contraindicated or not tolerated (SI). These subgroups are hereafter therefore denoted “ST” and “SI”, respectively.

In addition, the model includes subgroup analyses based on the LAPLACE-2 trial in which further individual or combinations of risk factors are included (increased baseline LDL-C, presence of diabetes, presence of AF and number of vascular beds) in patients with a history of CVD. It should be noted that these are not within-trial subgroup analyses *per se* as they are evaluated within the model by manipulating the baseline characteristics of patients in the LAPLACE-2 primary hypercholesterolaemia LDL-C > 2.5 mmol/L secondary prevention population to reflect the scenario under consideration. For example, in order to evaluate evolocumab versus ezetimibe in patients with diabetes, all patients are assumed to have diabetes whilst their other characteristics are left unchanged at their observed baseline values.

It should be noted that the GAUSS-2 trial²⁴ was not used by the company to inform baseline population characteristics despite including a population of patients for whom statin therapies are contraindicated or not tolerated. The CS¹³ (page 174) justifies this exclusion on the basis that patients for whom statins are contraindicated or not tolerated are a subgroup of the primary hypercholesterolaemia and mixed dyslipidaemia and HeFH populations, there are no RCTs assessing evolocumab in a HeFH statin-intolerant population, and patients for whom statin therapies are contraindicated or not tolerated are anticipated to have comparatively higher cholesterol levels.

Interventions

The intervention under consideration is evolocumab 140mg pre-filled syringe in 1mL solution. The company's base case analysis focusses only on the 140mg 2-weekly (Q2W) dose; the 420mg monthly (QM) dose is considered only within the company's scenario analysis (see CS,¹³ Section 5.12). Patients receiving evolocumab are assumed to require training to administer subcutaneous treatment. Patients are assumed to receive evolocumab indefinitely for the remainder of their lifetime.

Comparators

The main comparator included in the company's model is ezetimibe 10mg once daily (OD) (oral tablet). Patients receiving ezetimibe are assumed to receive treatment for the remainder of their lifetime.

Within the non-familial primary prevention ST population, background statin therapy is assumed to be atorvastatin 20mg OD. Within the non-familial secondary prevention ST population, the background statin therapy is assumed to be atorvastatin 80mg OD. Page 229 of the CS¹³ justifies this with respect to current NICE recommendations.¹⁵ It should be noted that the LAPLACE-2 trial²³ also included other background statin therapies. Within the HeFH primary/secondary prevention population, background statin therapy was assumed to be atorvastatin 80mg OD irrespective of patients' history of prior CVD events. Patients for whom statin therapies are contraindicated or not tolerated are assumed to receive no background lipid-lowering therapy.

It should be noted that whilst the comparator specified in the final NICE scope⁴ is ezetimibe (in combination with a statin or as monotherapy), the company's model also includes statins alone as a comparator in its own right. This is beyond the remit of the appraisal and is therefore not considered in detail in this ERG report.

5.2.2 Description of the company's health economic model structure and logic

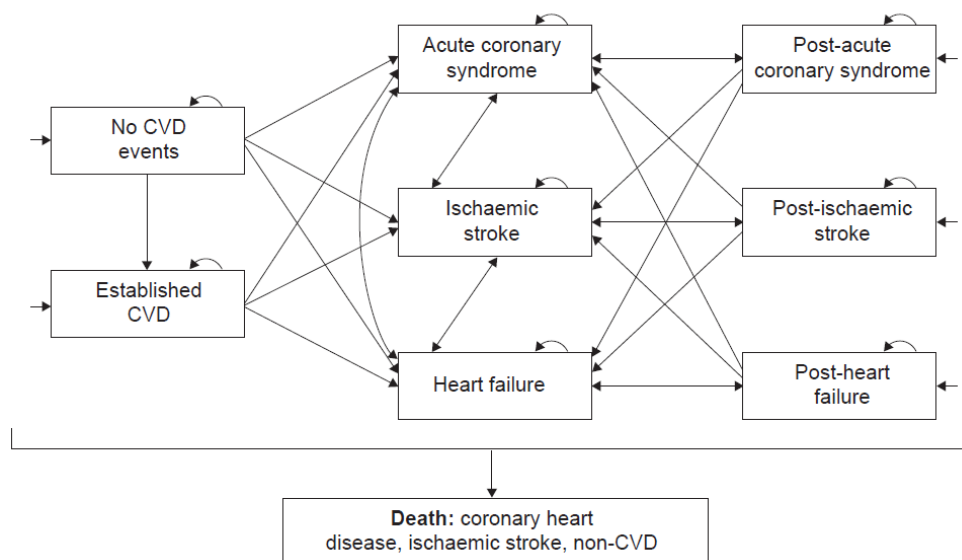
The description of the model's logic and input parameters contained within the CS is on some occasions brief and on others inaccurate.¹³ The description of the economic model submitted by the

company presented here is largely based on information contained within the CS,¹³ although in the instance of discrepancies between the CS and the model, the model is used as the basis of the description. It should also be noted from the outset that following the detection by the ERG of a serious programming error (the presence of negative transition probabilities) in the company's original model, the company submitted an amended model and an addendum outlining the revised results produced using this model.⁵² The principal amendments made by the company relate to: (i) the removal of the functionality to conduct threshold analyses according to baseline LDL-C levels in the non-familial primary prevention population (base case analyses A and B), and; (ii) arbitrary adjustments to some transition probabilities for the analyses undertaken in the HeFH primary/secondary prevention population (base case analyses G and H). The analyses of the non-familial secondary prevention population (base case analyses C and D) are unaffected by the company's model amendments.

A simplified representation of the company's model structure is presented in Figure 3. The model adopts a Markov approach and simulates the experience of an average cohort of people with or without a history of CVD. Patients who are able to take statins are assumed to continue to do so indefinitely for the remainder of their lives; these patients are assumed to experience no change in LDL-C or CVD events above their current risk levels. Within the statin-tolerant populations, patients in the evolocumab and ezetimibe groups are assumed to receive these treatments in addition to statin therapy. In the analyses of patients for whom statins are contraindicated or not tolerated, patients are assumed to receive evolocumab and ezetimibe as monotherapy. Within the model, patients receiving these therapies benefit from reduced LDL-C, which is in turn, translated into benefits in terms of reduced CV events. The CS¹³ (page 174) states that a Markov approach was adopted: (a) because it adequately reflects the scope of the disease and clinical practice and; (b) because it is commonly used in economic evaluations of drugs for reducing LDL-C in patients with hypercholesterolaemia.

The model is comprised of 24 mutually exclusive health states (see Table 27) and is evaluated using an annual cycle length. The model health states include three individual "acute" event states (where patients remain for a maximum duration of one year unless they experience the same event during the next cycle), five individual "chronic" event states (including three "post-event" health states - post-Acute Coronary Syndrome (ACS), post-ischaemic stroke (IS) and post-heart failure (HF), as well as no CVD and established CVD [ECVD]), and thirteen composite CVD health states (including "acute" and "post-event" health states, which contain either two or three individual health states), and three death states (CHD death, stroke death and death due to other causes).

Figure 3: Simplified representation of the company’s model structure (reproduced from CS,¹³ Figure 5-2, page 175)



CVD, cardiovascular disease

Table 27: Health states used in the company’s model

Health state types	Health states included in model
Individual “acute” health states	- acute coronary syndrome (ACS) including myocardial infarction (MI) and unstable angina (UA) - ischemic stroke (IS) - heart failure (HF)
Individual “chronic” health states	- no CVD - established CVD (ECVD) including stable angina, transient ischemic attack (TIA), carotid stenosis, revascularisation without history of myocardial infarction (MI), abdominal aortic aneurism, peripheral vascular disease. - post-ACS - post-IS - post-HF
Composite health states (combination of “acute” and “chronic” health states)	- combined 2-level health states (IS+post-ACS, post-IS+ACS, post-IS+post-ACS, HF+post-ACS, post-HF+ACS, post-HF+post-ACS, HF+post-IS, post-HF+post-IS) - combined 3-level health states (HF+post-IS+post-ACS, post-HF+post-IS+ACS, post-HF+post-ACS+IS, post-HF+post-IS+post-ACS)
Death states	- CVD death – coronary heart disease (CHD) death - CVD death - stroke death - non-CVD death.

The rationale for selecting ECVD, IS, ACS and HF to reflect the range of CVD events in the model described in the CS is rather limited.¹³ The CS (page 176) states that ECVD events were separated from other CVD events (IS, ACS and HF) as they are less severe and are associated with lower

baseline risks of experiencing further CVD events, as well as lower management costs and higher utility values. The CS further states that ACS, IS and HF are separated into “acute” and “chronic” health states to account for the differences in risks, costs and HRQoL between the first and subsequent years.

For analyses undertaken within the non-familial primary prevention population, all patients enter the model in the “no CVD” health state. For analyses undertaken within the non-familial secondary prevention population, patients enter the model in one of the three post-CVD event health states (“post-ACS”, “post-IS” or “post-HF”) or the “ECVD” health state. Subgroup analyses are presented according to the type of previous CVD event experienced. For analyses undertaken within the HeFH primary/secondary prevention population, patients enter the model in the one of the three post-CVD event health states (“post-ACS”, “post-IS” or “post-HF”), the “ECVD” health state or the “No CVD events” health state.

During a given cycle, patients in the “No CVD events” health state remain in this state until they experience:

- an acute non-fatal CVD event (ECVD, ACS, IS or HF);
- a fatal CVD event (CHD or stroke death), or;
- death due to causes other than CVD.

During any cycle following the first acute CVD event, patients are assumed to experience:

- no further CVD events (hence patients transit to the corresponding “post-event” health state);
- the same acute event (hence patients remain in the same acute event health state);
- a different acute event (hence patients transit to a composite health state incorporating the post-event state for previous events and the new acute event);
- a fatal CVD event, or;
- death due to causes other than CVD.

During any cycle following transition to a “post-event” health state, patients are assumed to experience:

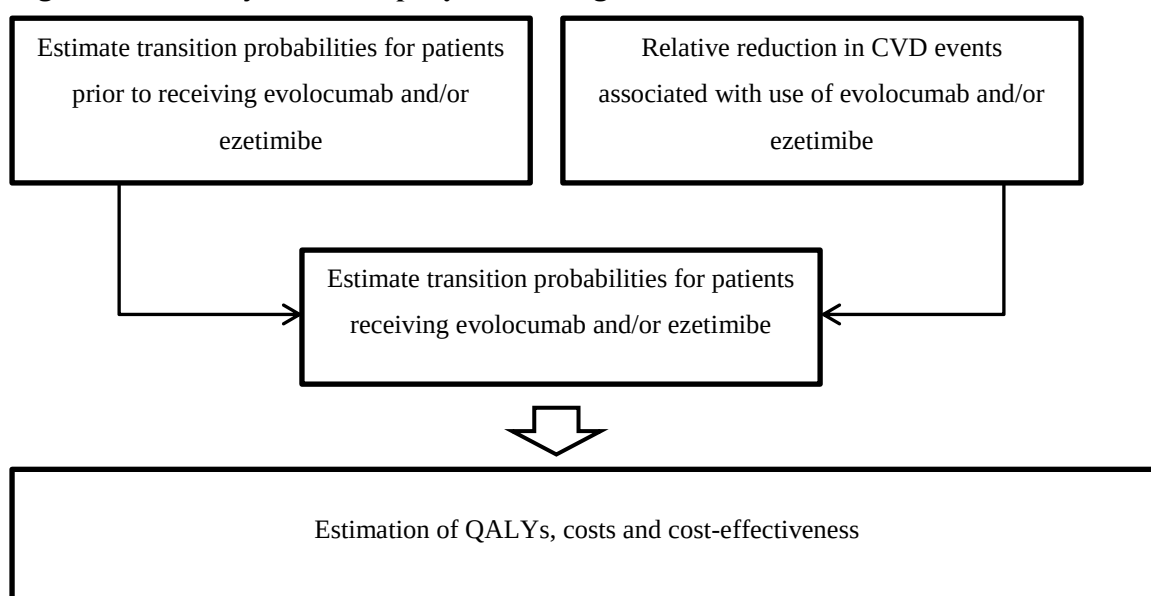
- the same acute event (hence patients transit to the corresponding acute health state or the relevant composite state if the individual has a history of other CVD events);
- a different acute event (hence patients transit to a composite health state incorporating the post-event state for the previous event and the new acute event);
- a fatal CVD event, or;
- death due to causes other than CVD.

The company's model also employs the following key structural assumptions:

- Upon experiencing a CVD event, patients cannot transit back to a less severe health state (e.g. patients cannot transit to ECVD once they have experienced a CVD event);
- For patients in a composite health state, the model assumes the highest probability, highest management cost and lowest utility for the relevant individual health states.
- Revascularisation procedures are not included as health states. Instead, only the costs of revascularisation procedures are included, based on a proportion of patients requiring revascularisation procedures in the "ACS" and "post-ACS" health states.

The logic adopted by the company's model is summarised in Figure 4. The company's model uses absolute reduction in LDL-C associated with the use of evolocumab and/or ezetimibe as a surrogate to predict a corresponding reduction in CVD events. The need to model this surrogate to final endpoint relationship is justified by the company based on the absence of data on the impact of evolocumab on CVD events from an RCT (see CS,¹³ page 192, and as mentioned in Section 4.6 of this report). As noted in the CS, a double-blind, randomised, placebo-controlled, multicentre trial (the FOURIER study³², clinicaltrials.gov identifier NCT01764633), which is assessing the impact of evolocumab when used in combination with a statin therapy in people with clinically evident CVD, is currently ongoing and is due to report in 2018.

Figure 4: Summary of the company's model logic



CVD – cardiovascular disease; QALYs – quality-adjusted life year

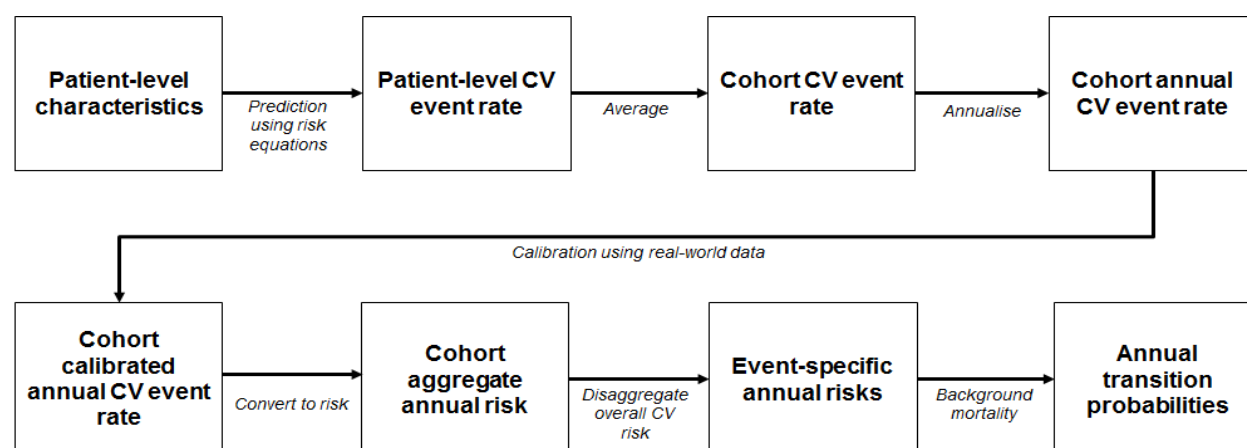
The logic employed within the company's model can be described in terms of four sequential components:

- (i) Estimation of transition probabilities for people prior to receiving evolocumab and/or ezetimibe.
- (ii) Estimation of the relative reduction in CVD events associated with the use of evolocumab and/or ezetimibe based on reductions in LDL-C observed in RCTs.^{23,24}
- (iii) Estimation of transition probabilities in patients receiving evolocumab, ezetimibe or evolocumab plus ezetimibe.
- (iv) Estimation of QALYs, costs and cost-effectiveness.

(i) *Estimation of transition probabilities for people prior to receiving evolocumab and/or ezetimibe*

The steps used by the company to estimate transition probabilities in the absence of evolocumab and/or ezetimibe (referred to as “population CV event rates” in the CS) are described in Figure 5.

Figure 5: Step-wise sequence of estimating event-specific transition probabilities from patient-level characteristics (reproduced from CS,¹³ Figure 5-4 page 182)



CV - cardiovascular

Published risk equations^{53,54} are applied to individual patient data (IPD) from the subgroup of patients enrolled in the LAPLACE-2 trial²³ who had a baseline LDL-C>2.5mmol/L and from the modified ITT population of the RUTHERFORD-2 trial²¹ to estimate the average aggregate risk of the next CVD event for males and females separately. The Framingham equations for males and females⁵³ are used to estimate the risk of a first CVD event in people who do not have a history of CVD. The REDuction of Atherothrombosis for Continued Health (REACH) Registry equations⁵⁴ are used to predict the risk of experiencing a fatal or any CVD event (assumed incorrectly to be non-fatal by the company) in people who have a history of CVD. The company assumes (incorrectly) that the risk predicted for “cardiovascular death” and “next cardiovascular event” from the REACH equations are independent of each other and can be added (effectively producing a total CVD risk). It should also be noted that the predicted risks from both the Framingham and REACH equations are actually probabilities which are bounded between 0 to 1, but are not treated as such within the company’s model; these are instead

assumed to be “event rates” (see Figure 5, box 2 “patient-level CV event rate”). This error in logic is discussed in more detail in Section 5.3.

The calculated average aggregate risks of CVD events (10-year risk from Framingham⁵³ and 20-month risk from REACH⁵⁴) are then transformed into annualised rates; these are calculated separately for males and females (using a sex-specific equation from Framingham and a covariate for sex within the REACH equation). Limited details are provided within the CS¹³ regarding this step in the process. From the company’s model, the age coefficients (for males and females separately) from the risk equations are used to obtain annual age- and sex-specific rates under the assumption that the event rate follows an exponential distribution such that the sum of the CVD event risks is equal to the average aggregate 10-year risk of CVD using the following formula:

$$risk(t) = \hat{\phi} \times \exp(\phi)^{\ln(\frac{age(t)}{\rho})} \quad [i]$$

Where:

$risk(t)$ = annual risk at a given age

$\hat{\phi}$ = risk prediction by risk equation

ϕ = age coefficient in the risk equation

$age(t)$ = current age

ρ = mean age

The annual age-specific risks obtained for males and females are then averaged to obtain an average annual age-specific risk; these are capped at a maximum age of 86 years (i.e. the risk is assumed to remain constant after age 85 years) and are subsequently multiplied by either: (a) state-specific calibration factors to reflect the performance of the risk equations in the UK for the non-familial primary hypercholesterolaemia populations (based on the LAPLACE-2 trial²³), or (b) an overall calibration factor to reflect the differences in the risk of CVD events between HeFH and non-HeFH patients (HeFH analyses only). Following this process, the company transform the resulting risks onto the probability scale using the following formula:

$$probability = 1 - \exp(-rate) \quad [ii]$$

The average aggregate annual age-specific probabilities of CVD events are then apportioned according to specific CVD events based on multinomial logistic regression models (see Section 5.2.2). The average aggregate risks for first CVD events derived from the Framingham equations⁵³ after calibration are apportioned into ECVD, ACS, IS, HF, CHD death and stroke death events. The risks for subsequent CVD events derived from the REACH Registry equations⁵⁴ after calibration are

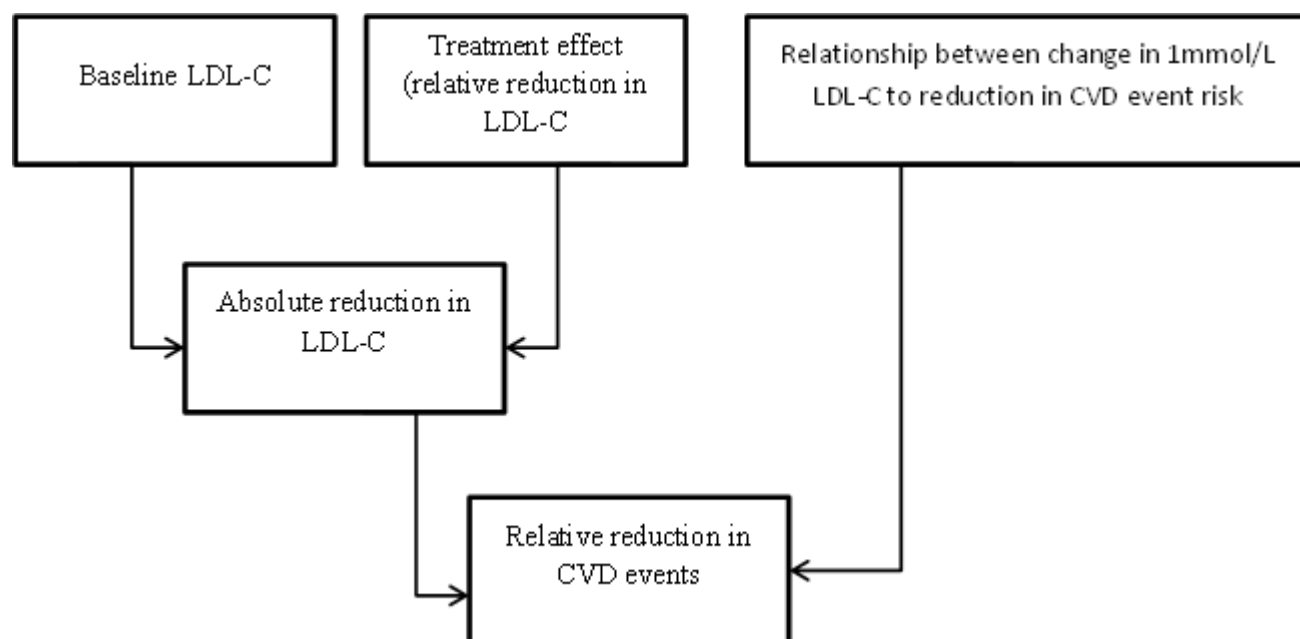
separated into ACS, HF and IS. The risks for cardiovascular death derived from the REACH Registry equation⁵⁴ after calibration are apportioned to either stroke death or CHD death.

(ii) Estimation of the relative reduction in CVD events associated with the use of evolocumab and/or ezetimibe based on reductions in LDL-C observed in RCTs

Separate to the derivation of the transition probabilities for patients receiving background statin therapies (for patients who are able to take statins) or no treatment (for patients for whom statins are contraindicated or not tolerated), the company's model calculates the relative reduction in CVD events associated with adding evolocumab and/or ezetimibe to statin therapy in people who are able to take statins, or with using evolocumab and/or ezetimibe as monotherapy for patients for whom statins are contraindicated or not tolerated.

The process by which the company derives the relative reduction in CVD events associated with the use of evolocumab and ezetimibe is described in Figure 6. This involves three stages: (a) defining baseline LDL-C; (b) applying a treatment effect (as a percentage reduction in LDL-C) associated with the use of evolocumab and/or ezetimibe to calculate the absolute reduction in LDL-C associated with additional lipid-lowering therapy, and; (c) applying a relationship which translates the reduction in 1mmol/L in LDL-C into a relative reduction in specific CVD events (non-fatal MI, any coronary revascularisation, IS, CHD death and IS death).

Figure 6: Company's approach to modelling the effects of LDL-C reduction on reductions in CV events



It should be noted that the company's model assumes that the minimum LDL-C is 40mg/dL (equivalent to 1.03mmol/L), thus it is assumed that evolocumab and ezetimibe cannot reduce LDL-C to a level lower than this threshold. To illustrate, assuming a baseline LDL-C of 2mmol/L and assuming that evolocumab reduces LDL-C by 1.5mmol/L, the model assumes that the absolute reduction with evolocumab would be 0.97mmol/L rather than 1.5mmol/L. This is likely to be conservative for evolocumab (as this therapy is associated with the largest reduction in LDL-C).

For the scenario evaluating evolocumab plus statins versus ezetimibe plus statins (referred to as Scenario 1 in the CS,¹³ page 181 - base case analyses A, C and G), the reduction in CV events compared with background therapy is determined by: (a) the baseline LDL-C at entry of the trial; (b) the relative difference in LDL-C between evolocumab/ezetimibe and background statins (treatment difference) at the mean of week 10/12, and; (c) the relationship between absolute reductions in LDL-C and reductions in first CV events.

This is different in the scenario evaluating evolocumab monotherapy versus ezetimibe monotherapy in patients for whom statins are contraindicated or not tolerated (referred as Scenario 2 in the CS,¹³ page 181 - base case analyses B, D and H) whereby the reduction in CV events is determined by: (a) the baseline LDL-C at entry of the trial (rather than LDL-C at 12 weeks); (b) the relative difference in LDL-C between evolocumab (or ezetimibe) and baseline LDL-C at entry of the trial (difference from baseline) rather the treatment difference at the mean of week 10/12, and; (c) the relationship between absolute reductions in LDL-C and reductions in CV events.

For Scenarios 3 and 4 (see CS¹³ page 181 - scenario analyses E,F, I and J) whereby evolocumab is used in combination with ezetimibe, the company's model assumes that the treatment effect of evolocumab is sequential to the treatment effect of ezetimibe, i.e. the treatment effect for evolocumab is applied after adjusting for the effect of ezetimibe (representing the new baseline LDL-C level). As an illustrative example, assuming that the population has a baseline LDL-C of 2.5mmol/L and ezetimibe reduces LDL-C to 2.0mmol/L, the treatment effect of evolocumab is applied to the post-ezetimibe LDL-C (2.0mmol/L) rather than the pre-ezetimibe LDL-C (2.5mmol/L).

(iii) Estimation of transition probabilities in people receiving evolocumab, ezetimibe or evolocumab plus ezetimibe

The transition probabilities for patients receiving statins (for patients who are able to take statins) or no treatment (for patients for whom statins are contraindicated or not tolerated) estimated in Step (i) are adjusted using the relative reduction in CVD events estimated in Step (ii) using the following formula:

$$\text{Probability after treatment} = 1 - \exp((\text{CTTC rate ratio}^{\text{absolute LDL-C reduction}}) \times \log(1 - \text{probability baseline})) \text{ [iii]}$$

The transition probabilities estimated in Step (i) that are adjusted by the treatment effects estimated in Step (ii) are summarised in Figure 7.

It should be noted that the CS states that “patients in HF health states (either single or combined) experience no further treatment effect due to LDL-C lowering for risk of recurrent HF since findings suggest lack of benefit for lipid-lowering therapies once patients experience HF on events such as CHD death” (CS,¹³ page 197). This appears to be inconsistent with what is done in the company's model whereby a reduction in LDL-C in people with HF (either acute, post-health state or combined health state) is associated with a reduction in CHD death.

Figure 7: Health state transitions and applied treatment effects (reproduced from CS,¹³ Figure 5-6, page 200)

FROM	TO	NoCVD	ECVD	ACS	IS	HF	PostACS	PostIS	PostHF	CHDdeath	ISdeath	NonCVDdeath	IS +PostACS	PostIS +ACS	PostIS +PostACS	HF +PostACS	PostHF +ACS	PostHF +PostACS	HF +PostIS	PostHF +IS	PostHF +PostIS	HF +PostIS +PostACS	PostHF +PostIS +ACS	PostHF +PostIS +PostACS	PostHF +PostIS +PostACS
NoCVD		#	TE	TE	TE	TE				TE	T	T													
ECVD			#	TE	TE	TE				TE	T	T													
ACS				TE			#			TE	T	T	TE			TE									
IS					TE			#		TE	T	T		TE					TE						
HF						T			#	TE	T	T					TE			TE					
PostACS				TE			#			TE	T	T	TE			TE									
PostIS					TE			#		TE	T	T		TE					TE						
PostHF						T			#	TE	T	T					TE			TE					
IS+PostACS										TE	T	T	TE	TE	#							TE			
PostIS+ACS										TE	T	T	TE	TE	#							TE			
PostIS+PostACS										TE	T	T	TE	TE	#							TE			
HF+PostACS										TE	T	T				T	TE	#						TE	
PostHF+ACS										TE	T	T				T	TE	#						TE	
PostHF+PostACS										TE	T	T				T	TE	#						TE	
HF+PostIS										TE	T	T							T	TE	#			TE	
PostHF+IS										TE	T	T							T	TE	#			TE	
PostHF+PostIS										TE	T	T							T	TE	#			TE	
HF+PostIS+PostACS										TE	T	T										T	TE	TE	#
PostHF+PostIS+ACS										TE	T	T										T	TE	TE	#
PostHF+PostACS+IS										TE	T	T										T	TE	TE	#
PostHF+PostIS+PostACS										TE	T	T										T	TE	TE	#

Complementary	#
Transition	T
Transition with treatment effect	TE

ACS - acute coronary syndrome; CHD - coronary heart disease; CVD - cardiovascular disease; ECVD - established CVD; HF - heart failure; IS - ischaemic stroke.
Complementary defined as one minus all other transition probabilities in the row

(iv) Calculation of QALYs, costs and cost-effectiveness

Transition probabilities for each treatment group are generated according to Steps (i) to (iii) described above. For the composite health states, the highest transition probability is selected. For example, for an individual in the post-HF+stroke state, the probability of experiencing CHD death during the next cycle is calculated as the maximum of the probability of transiting from the post-HF state to the CHD death state and the probability of transiting from the stroke state to the CHD death state.

From the point at which transition probabilities are calculated, the model structure is straightforward. Simple matrix multiplication is used to calculate health state occupancy for each Markov cycle. The Markov trace is then half-cycle corrected.

Separate utilities are assigned to each of the model's health states. For composite health states, the lowest utility multiplier for individual states is selected. For example, the utilities for the individual post-HF and ischaemic stroke states are 0.683 and 0.628, respectively; thus for people in the post-HF+stroke state, a utility of 0.628 is applied. The impact of AEs on HRQoL is not included in the company's model.

Cost components within the model include the cost of lipid-lowering therapy, administration training costs (evolocumab only), monitoring costs, costs of revascularisation procedures, health state costs and the costs of CV-related death. Costs associated with managing AEs are not included in the company's model. In a similar manner to the approach used to apply health utilities, health state costs for composite health states are based on the highest cost of individual states. For example, the annual health state costs for the individual post-HF and ischaemic stroke states are £1,078.26 and £4,063.60, respectively; for patients in the post-HF+stroke state, a health state cost of £4,063.60 is applied.

The application of different treatment effects on LDL-C (and subsequently CV events) leads to different trajectories through the model's health states for each option. Total lifetime QALYs are calculated by simply applying the state-specific utilities to the probabilities of residing in each state over the model time horizon. Total costs are calculated by multiplying the state-specific costs by the probabilities of residing in each health state and combining these with the costs of drug acquisition, training and monitoring, incident revascularisation procedures and CV death. Incremental cost-effectiveness is calculated in a piecewise fashion as the difference in costs divided by the difference in QALYs for competing options.

5.2.4 Evidence used to inform the company's model parameters

5.2.4.1 Summary of evidence sources used to inform the company's model parameters

Table 28 summarises the sources used to inform the model's parameter values. These are described in further detail in the subsequent sections.

Table 28: Summary of evidence sources used to inform the company's model parameters

Parameter/group	Evidence source
Baseline characteristics	
Initial health state distribution (non-familial primary and secondary prevention populations)	LAPLACE-2 ²³ (subgroup with LDL-C>2.5mmol/L)
Initial health state distribution (HeFH population)	RUTHERFORD-2 ²¹ modified ITT population
Baseline characteristics (non-familial primary and secondary prevention populations)	LAPLACE-2 ²³ (subgroup with LDL-C>2.5mmol/L)
Baseline characteristics (HeFH population)	RUTHERFORD-2 ²¹ modified ITT population
CV event risks	
Risk of first CVD event (people without history of CVD)	D'Agostino <i>et al</i> ⁵³ (Framingham Heart Study)
Risk of next CVD event (people with existing CVD)	Wilson <i>et al</i> ⁵⁴ (REACH Registry)
Risk of fatal CVD event (people with existing CVD)	Wilson <i>et al</i> ⁵⁴ (REACH Registry)
Calibration of risk predictions	
Calibration factors (non-familial primary and secondary prevention populations)	Company's CPRD/HES analysis ¹³
Calibration factor (HeFH population)	Benn <i>et al</i> ⁵⁵
Risk of specific CV events	
Probability of specific CV events	Company's multinomial model derived from CPRD/HES analysis ¹³
Treatment effects (LDL-C reduction and relationship to CV event risks)	
Relative reduction in LDL-C – evolocumab or ezetimibe plus statins versus statins at the mean of week 10/12	LAPLACE-2 ²³
Relative reduction in LDL-C – evolocumab or ezetimibe versus baseline	GAUSS-2 ²⁴
Relationship between LDL-C reduction and CV event reduction	Baigent <i>et al</i> ²⁸
Health-related quality of life	
State-specific health utilities	NICE CG181 ¹⁵ (original sources – Dolan <i>et al</i> ⁵⁶ Tsevat <i>et al</i> ⁵⁷ Goodacre <i>et al</i> ⁵⁸ Tengs <i>et al</i> ⁵⁹ and Lacey <i>et al</i> ⁶⁰
Resource costs	
Drug acquisition costs	BNF ⁶¹ and CS ¹³
s.c. injection training costs	NHS Reference Costs 2013/14 ⁶²
Monitoring costs	PSSRU ⁶³ and NHS Reference Costs 2013/14 ⁶²
Health state costs	Company's CPRD/HES longitudinal study ¹³
Costs of revascularisation	
Costs of CVD death	

5.2.4.2 Baseline characteristics

The company's model uses baseline individual characteristics in two ways: firstly to estimate the risk of CVD events and secondly to estimate the absolute reduction in LDL-C; these are in turn used to estimate the relative reduction in CVD events.

For the analyses of evolocumab in the non-familial primary prevention and secondary prevention populations, the company's model uses the subgroup of people enrolled within the LAPLACE-2 trial²³ who had a baseline LDL-C > 2.5 mmol/L. Baseline characteristics are based directly on the IPD for all variables (sex, age, SBP, HDL-C, diabetes, smoking, hypertension, total-cholesterol, LDL-C, triglycerides, BMI, previous events etc.), with the exception of the vascular beds and AF variables which were instead assumed to reflect the average values within the REACH Registry study⁵⁴ (see CS¹³ Table 5-5 footnotes, page 183). This has an impact on the predicted risk of CV events in people with a history of CVD only insofar as they are covariates in the REACH Registry risk equation but not the Framingham risk equation. The ERG notes that by using the baseline characteristics for most variables from the same source, the company's model maintains the correlation between variables.

For the analyses of evolocumab in the HeFH primary/secondary prevention population, the company's model uses baseline characteristics from the modified ITT population of the RUTHERFORD-2 trial.²¹ Similar to the analyses of the non-familial populations described above, baseline characteristics are based directly on the IPD for all variables (sex, age, SBP, HDL cholesterol, diabetes, smoking etc.), with the exception of the vascular beds and AF variables which were also instead assumed to reflect the average values within the REACH Registry study.⁵⁴ Again, this impact upon the predicted risk of CV events in the subset of patients with a history of CVD as they are included as covariates in the REACH Registry risk equations.

For the company's subgroup analyses in patients with existing CVD and additional risk factors (presence of diabetes, AF, number of vascular beds etc.), these variables are manually changed to reflect the characteristics of the subgroup whilst other characteristics are held at their observed values (rather than selecting out the subgroups of people within the trial who actually had these characteristics). This approach impacts upon the predicted risk of CVD events.

Whilst the analyses were removed by the company following the ERG's identification of the serious programming error (see Section 5.2.2), the company's analyses of the cost-effectiveness of evolocumab according to baseline LDL-C (3.5 mmol/L and 6.0 mmol/L) do not involve manipulating the IPD directly; instead, the average baseline LDL-C value is amended.

Within the analyses in the non-familial primary prevention population, all patients are assumed to enter the model in the “no CVD events” health state. The initial health state distribution within the non-familial secondary prevention population was based on the subset of patients enrolled within the LAPLACE-2 trial²³ who had a baseline LDL-C>2.5mmol/L. The initial health state distribution within the HeFH primary/secondary prevention population was based on the initial distribution of patients within the modified ITT analysis of the RUTHERFORD-2 trial.²¹

5.2.4.3 Prediction of CV event risk

Aggregate 10-year risk of CVD for people without a history of CVD

Irrespective of the analyses (non-familial primary hypercholesterolaemia/HeFH, statin tolerant/intolerant), the company’s model uses results from published sex-specific multivariable-adjusted Cox proportional-hazards regression models derived from the US Framingham Heart Study⁵³ to predict the aggregate 10-year risk of CVD events (fatal and non-fatal coronary, cerebrovascular, and peripheral arterial disease and heart failure) in patients without a history of CVD. This study was undertaken in the US in a cohort of 8,491 individuals. The CS¹³ states that this risk equation was selected based on a targeted literature review and that it was preferred to the QRISK2 risk equation (which is recommended in the UK) specifically because: (a) it includes a broader definition of CVD events and death (coronary death, MI, coronary insufficiency, and angina, cerebrovascular events including IS, haemorrhagic stroke, and TIA, peripheral arterial disease and HF); (b) it includes fewer variables to estimate baseline CVD risk (QRISK2 includes 14 variables whilst Framingham includes seven variables).

The general formula for the Framingham risk equation is presented below:

$$\hat{p} = 1 - S_0(t)^{\exp(\sum_{i=1}^p \beta_i X_i - \sum_{i=1}^p \beta_i \bar{X}_i)}, \quad [iv]$$

The coefficients of the risk equations for males and females are summarised in Table 29. The ERG notes that whilst not used in the economic model, the D’Agostino⁵³ paper reports a series of calibration factors that can be used to estimate the risk associated with individual CVD events (CHD, stroke, CHF and intermittent claudication [IC]).

As mentioned in Section 5.2.2, the Framingham risk predictions are adjusted subsequently to: (a) reflect the performance of the risk equation in the UK, and; (b) reflect the increased risk in HeFH compared with people without HeFH.

Table 29: Framingham risk equations used in company's model (patients without a history of CVD)

Variable	Coefficients by sex	
	Male	Female
$\beta \cdot \text{mean}(x)$	23.9802	26.1931
Constant	0.88936	0.95012
Log of age	3.06117	2.32888
Log of SBP if not treated	1.93303	2.76157
Log of SBP if treated	1.99881	2.82263
Log of total cholesterol	1.1237	1.20904
Log of HDL cholesterol	-0.93263	-0.70833
Diabetes	0.57367	0.69154
Smoking	0.65451	0.52873

HDL-C - high-density lipoprotein cholesterol; SBP - systolic blood pressure

Positive coefficients denote increased risk

It is important to note that baseline characteristics used in the company's model are assumed to be independent of whether an individual can or cannot take statins; in other words, the predicted aggregate 10-year risk of experiencing a CVD event is assumed to be the same irrespective of whether an individual is receiving statin therapy.

The ERG also notes that for the HeFH primary/secondary prevention population, which is comprised of a mix of patients who have a history of CVD and patients who have no history of CVD, the Framingham equation is used irrespective of whether patients in the trial (used in the economic model) have a history of CVD or not.

Aggregate 20-month risk of CVD events in people who have a history of CVD

For patients who have a history of CVD, the REACH Registry risk equations⁵⁴ are used to estimate the risk of subsequent CVD events. The REACH equations are international risk models estimated in 33,419 randomly selected individuals included in the REACH registry and validated in 16,270 individuals of the same registry. The models can be used to predict: (a) the 20-month risk of any secondary cardiovascular events (referred as “next cardiovascular event” by the authors), and; (b) the 20-month risk of cardiovascular death in outpatients with established atherothrombotic disease.

The 20-month risk for cardiovascular death is calculated as:

$$r = 1 - 0.97749 \exp(\sum \beta X - 4.03317) \quad [v]$$

The risk for next cardiovascular event is given as:

$$r = 1 - 0.93681 \exp(\sum \beta X - 2.68845) \quad [vi]$$

where β is the regression coefficient and X is the level for each risk factor.

The coefficients of the REACH Registry risk equations are summarised in Table 30.

Table 30: REACH Registry risk equations used in company's model (patients with a history of CVD)

Variable	Coefficients by type of CV event	
	Cardiovascular death	Next cardiovascular event
$\beta \cdot \text{mean}(x)$	4.03317	2.68845
Baseline risk	0.97749	0.93681
Male	0.24519	0.10246
Age	0.04966	0.03089
Diabetes mellitus	0.46141	0.37824
Event in previous year	0.26681	0.38168
Heart failure in previous year	0.89976	0.51873
Atrial fibrillation	0.42705	0.26652
Vascular beds	0.24928	0.30277
BMI < 20 kg/m ²	0.55132	0.31428
Smoking	0.30925	0.24121
Statins	-0.22296	-0.28332
Acetylsalicylic acid	-0.17968	-0.10151
Eastern Europe or Middle East	0.25934	0.27574
Japan or Australia	-0.65524	-0.31604

BMI - body mass index; CVD - cardiovascular disease; HDL-C - high-density lipoprotein cholesterol; REACH - REduction of Atherothrombosis for Continued Health. Positive coefficients denote increased risk

As discussed in Section 5.2.2, the company's model incorrectly assumes that the two risk equations (next cardiovascular event and cardiovascular death) are independent of each other. The risk equation for "next cardiovascular event" is assumed to represent the risk of the next non-fatal event and the risk equation for "cardiovascular death" is assumed to represent the risk of a fatal event. As with the Framingham equation, the CS¹³ states that the REACH equations were identified through a targeted literature review. The REACH Registry equations were selected for use in the company's model as they predict aggregated CVD risk of recurrent non-fatal and fatal CV events rather than individual events.

The REACH Registry risk equations are used for both the analyses undertaken in the non-familial populations and the HeFH primary/secondary prevention population. The REACH equations are also used in the company's subgroup analyses in people with existing CVD, raised LDL-C and additional risk factors (such as presence of diabetes, AF or 2/3 vascular beds).

5.2.4.4 Calibration of risk predictions

Adjustment/calibration factors to reflect the performance of the risk equations to the UK (non-familial primary hypercholesterolaemia populations)

Whilst the company's model uses the risks predicted using the Framingham and REACH Registry risk equations to predict the probabilities of CVD events, the CS argues that these are not appropriate for the UK context and therefore require adjustment using a process referred to as "calibration." Appendix 10 of the CS¹³ presents details of a critical appraisal of sources used in NICE CG181 and considers these to be inappropriate for two key reasons: (i) because the sources are dated and (ii) because the sources do not relate to people considered to be at high-risk. The ERG notes however that it is unclear whether the company's definition of "high-risk" relates to a higher risk of CVD or whether this is defined solely according to raised LDL-C or presence of risk factors.

The company undertook a separate study linking data from the Clinical Practice Research Datalink (CPRD - primary care), Hospital Episode Statistics (HES - secondary care) and the Office for National Statistics (ONS – cause of death) to estimate "calibration factors" to be used in the health economic model to adjust the risks predicted using the Framingham and REACH equations to match CV event rates observed in the UK. CVD events were chosen to reflect the health states in the company's health economic model. In brief, this involved four steps:

- (i) Linking the data from the CPRD, HES and ONS. The discussion section of CS Appendix 11 mentions that only about half of the CPRD cohort could be linked to the HES and ONS data, thereby reducing the sample size.
- (ii) Estimating the "observed" crude CV event rates in the CPRD and HES datasets in 5 populations: (a) people with diabetes free of CVD at baseline; (b) people with existing ECVD; (c) people with existing ACS; (d) people with existing IS, and; (e) people with existing HF. Crude CV event rates were calculated by dividing event counts by person-years of follow-up. CV event rates are stratified by the time period of follow-up (acute - one year; versus long-term - after year 1).
- (iii) Estimating the predicted risk of CVD events using the Framingham and REACH equations in the CPRD and HES datasets.
- (iv) Comparing the "observed" and predicted risks and calculating calibration factors to adjust the risk of CVD events calculated using the Framingham and REACH equations in the health economic model. As the Framingham and REACH Registry equations predict the 10-year and 20-month probabilities respectively, the company states that two adjustments were made: (a) adjusting the probability into yearly rates, and; (b) removing the effect of age. However, the CS contains very limited details regarding this process.

The calibration factors used in the company’s model (referred to as mean rate ratios in the CS¹³) are presented in Table 31. It should be noted that in order to reflect the model structure and logic, these calibration factors were estimated separately for acute and chronic events and are separated in terms of fatal and non-fatal events in patients with a history of prior CVD events. Further details on the company’s calibration approach are reported in CS Appendix 11.¹³

The CS¹³ (page 191) acknowledges some of the limitations of the approach used, notably the potential mismatch between CVD events included in the risk equations and those included in the CPRD/HES dataset.

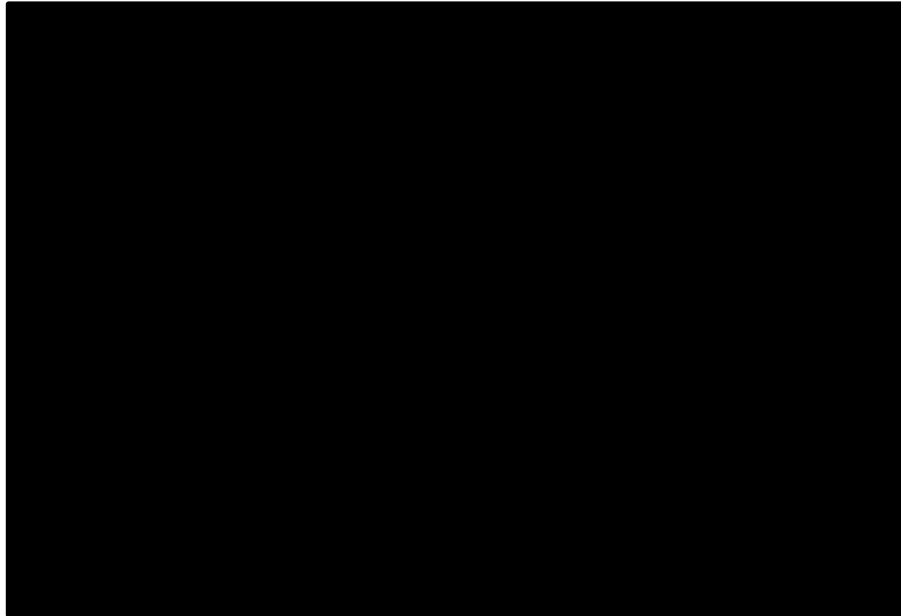
odds ratios (ORs) for coronary artery disease (CAD) as a function of the Dutch Lipid Clinic Network (DLCN) criteria for a diagnosis of FH in individuals on and off lipid-lowering medication from the general population, based on an unselected community-based population of 69,016 participants in Copenhagen. Within this study, amongst individuals who were not treated with cholesterol-lowering therapies, the adjusted OR for coronary artery disease was 13.2 (95%: 10.0 – 17.4) for those with definite/probable FH and 4.8 (4.3-5.3) for those with possible FH, compared with individuals with unlikely FH not treated with cholesterol-lowering therapies. Amongst individuals receiving cholesterol-lowering therapies, the authors report ORs of 10.3 (7.8 –13.8) and 14.8 (12.9 –17.1) respectively, compared with unlikely FH not treated with cholesterol-lowering therapies.

By pooling these data, the company adjusted the baseline CV risk predicted using the Framingham and REACH equations by a relative risk of 7.1 (95% CI 5.7, 8.7) to reflect the increased risk in the HeFH population. In the original CS, the company stated that this relative risk was calculated by pooling the statin and no statin groups and states that this was done *“to represent real-world treatment practice, accounting for the mix of primary and secondary prevention patients as well as different treatment paradigms”* (see CS¹³ page 191). Following clarification, the company provided details on these calculations and showed that a simple pooling of data was conducted. The CS further states that *“the rate ratio was validated through estimation of a 10-year risk of CV events for the RUTHERFORD-2 patient population.”* It is however unclear how the rate was validated.

5.2.4.5 Risk of specific CV events

Given that the Framingham and REACH Registry risk equations predict the aggregate risk of CVD events, the company’s model uses data from the CPRD/HES dataset to apportion the aggregate CVD risks to specific CVD events by age. Multinomial logistic regression models were calculated from the CPRD/HES datasets to estimate the proportion of events that were non-fatal ACS, HF, IS and CV death (IS death and CHD death) in the secondary prevention cohorts, and the proportion of events that were ECVD, non-fatal ACS, HF, IS and CV death in the diabetes primary prevention cohort. The regression models and details are available in CS Appendix 11.¹³ An example of the event distribution by age for patients with prior ACS is shown in Figure 8.





It should be noted that the multinomial models include both fatal and non-fatal events. As the company's model separates fatal and non-fatal secondary CVD events, a normalisation adjustment is made within the economic model to estimate the split of fatal and non-fatal CVD events separately as these are assumed to be independent.

5.2.4.6 Treatment effects – relative reduction in LDL-C for evolocumab and/or ezetimibe

The treatment effect estimates used in the economic model are presented in Table 32.

Table 32: Mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe when used in combination with statins or as monotherapy (adapted from CS,¹³ Table 5-10, page 193)

Outcome	Evolocumab 140mg Q2W	Evolocumab 420mg QM	Ezetimibe 10mg od ^b
Combination with a statin (based on LAPLACE-2)			
Mean percent change from baseline ^a (95% CI) [SE]	-71.77 (-74.69, -68.85) [1.49]	-69.12 (-73.49, -64.76) [2.23]	-26.56 (-30.70, -22.42) [2.11]
Monotherapy (based on GAUSS-2)			
Mean percent change from baseline ^a (95% CI) [SE]	-57.10 (-60.84, -53.36) [1.90]	-55.82 (-58.88, -52.76) [1.55]	-17.83 (-21.01, -14.65) [1.62]

CI - confidence interval; LDL-C - low-density lipoprotein cholesterol; od - once daily; Q2W - every 2 weeks; QM - monthly; SE - standard error

^aLeast squares mean from the repeated measures model which includes treatment group, stratification factors (from IVRS), scheduled visit, dose frequency and the interaction of treatment with scheduled visit as covariates.

^bBased on post hoc pooled analysis of all ezetimibe arms and all placebo arms in LAPLACE-2 and GAUSS-2, respectively.

For people who are able to take statins, the company uses the treatment effect from the LAPLACE-2 trial,²³ calculated as the percent change from the LDL-C at the mean of week 10/12 in patients on

evolocumab and ezetimibe (in addition to a statin) compared with the LDL-C at the mean of week 10/12 in patients receiving statin therapy only (note that CS Table 5-10 incorrectly states that this reflects the change from baseline). The CS¹³ (page 193) further states that the treatment effect from the LAPLACE-2 trial was assumed to be generalisable to the HeFH population given the absence of a head-to-head trial of evolocumab versus ezetimibe (with or without a statin) in patients with HeFH and due to the consistency in the treatment effect of evolocumab regardless of individual population and individual characteristics, dosing regimen and presence and type of background lipid-lowering therapy. The CS also mentions that *“this approach is supported by the economic evaluation of ezetimibe that was utilised in NICE TA132, in which an assumption was made that the treatment effect of ezetimibe in non-HeFH patients was generalisable to patients with HeFH, in the absence of HeFH-specific effectiveness data”* (see CS¹³ page 193).

For patients for whom statins are contraindicated or not tolerated, the company’s model uses the treatment effect from the GAUSS-2 trial,²⁴ calculated as the percentage change in LDL-C at the mean of weeks 10/12 for evolocumab and ezetimibe compared with the LDL-C at baseline (entry into the trial). The treatment effect from GAUSS-2 was also assumed to be generalisable to the HeFH population.

The CS¹³ (page 193) states that the treatment effects were taken from the calculated percent change at the mean of 10/12 weeks as this provides a time-averaged efficacy estimate over week 10 and week 12 and because the calculated approach to LDL-C assessment (rather than the reflexive approach) reflects best clinical practice and is in line with the marketing authorisation for evolocumab.²⁶ The treatment effect is assumed to apply indefinitely whilst on treatment. The company states (see CS¹³ page 193) that this assumption is supported by findings from the ongoing OSLER 1/2 long-term extension studies which show that LDL-C reductions are maintained for more than two years.

5.2.4.7 Relationship between the absolute LDL-C reduction and CVD event reduction

The link between absolute reduction in LDL-C and reduction in CVD events was based on a published meta-analysis of 26 trials conducted by the CTT collaboration.²⁸ This meta-analysis reported a proportional reduction in specific CV events per mmol/L reduction in LDL-C. The meta-analysis used by the company reports the rate reduction in CV events calculated across 26 statin trials whereby statins were compared with other lipid-lowering agents or placebo, including five trials (referred to as “more vs less”) in which more intensive regimens were compared with less intensive regimens.

The model uses results from the subgroup analysis of the five “more vs less” trials where possible, with the exception of death events. The CS¹³ (page 197) justifies this choice as the populations and interventions in the studies within this meta-analysis were deemed to be more representative of the

high-risk CV individuals eligible for treatment with evolocumab. It should be noted that the relationship estimated from these five trials corresponds to the reduction in first CVD event only in patients with a history of CVD. The rate ratios used in the company's health economic model are summarised in Table 33.

Table 33: Proportion of change in CVD event risk per mmol/L LDL-C change (reproduced from CS¹³ Table 5-12 page 197)

CV event	Rate ratio (95% CI)	Source	Reference
ACS	0.71 (0.58, 0.87)	Figure 2. More vs. less statins (non-fatal MI)	Baigent <i>et al</i> 2010 ²⁸
Revascularisation	0.66 (0.60, 0.73)	Figure 2. More vs. less statins (any coronary revascularisation)	
IS	0.69 (0.50, 0.95)	Figure 2. More vs. less statins	
HF	0.71 (0.58, 0.87)	Assumption: equal to ACS in the model	N/A
CHD death	0.80 (0.74, 0.87)	Figure 5. (CHD)	Baigent <i>et al</i> 2010 ²⁸
Stroke death ^a	1.04 (0.77, 1.44)	Figure 5. (IS)	

a Rate ratio assumed to be 1.00.

ACS - acute coronary syndrome; CHD - coronary heart disease; CI - confidence interval; CV - cardiovascular; CVD - cardiovascular disease; HF - heart failure; IS - ischaemic stroke; LDL-C - low-density lipoprotein cholesterol; MI - myocardial infarction; N/A - not applicable

The company's model makes the following assumptions regarding the relationship between reductions in LDL-C and reductions in CV events:

- The benefits manifest immediately (year 1 onwards).
- The relationship between reductions in LDL-C and CVD events (which relate to the effect on the first CVD event) observed in the CTTC meta-analysis is also representative of the effect that would be observed for the reductions in subsequent CV events.
- The relative reduction in CVD event rate per mmol/L reduction in LDL-C is independent of baseline levels, familial or non-familial hypercholesterolaemia, prognostic factors such as age, gender, co-morbidities (e.g. diabetes), and CV history or burden.
- LDL-C cannot reduce to a level below 40mg/L (equivalent to 1.03mmol/L)
- The CS further states that “*the rate ratio for new onset HF is equal to that for MI. Patients in the HF health states (either individual states or composite states) experience no further treatment effect due to LDL-C lowering for risk of recurrent HF since findings suggest lack of benefit for lipid-lowering therapies once patients experience HF on events such as CHD death.*”
- The treatment effect for ACS is applied for patients transitioning from the “No CVD” state to the “ECVD” state.
- A treatment effect for revascularisation procedures has been applied to the ‘post-ACS’ health state alone. This impacts only on costs since revascularisation procedures are not included as separate health states.

- The rate ratio for stroke death is equal to one. This has been assumed because a non-significant effect was observed for LDL-C reduction for this CV event (RR = 1.041; 95% CI 0.77-1.41).

It should be noted that the company assesses the validity of their approach by providing a comparison with data from a pre-specified exploratory analysis of adjudicated CV events in OSLER and OSLER-2 which showed statistically significant reductions in CV events of over 50% after approximately 1 year of treatment with evolocumab plus standard of care versus standard of care alone, together with data from the IMPROVE-IT trial which demonstrated that ezetimibe added to simvastatin further lowered LDL-C and significantly reduced the occurrence of a composite endpoint of CV death, MI, unstable angina requiring hospitalisation, coronary revascularisation, or stroke compared with statin alone ($p=0.016$). However, on page 144 of the CS,¹³ the company recognises that the OSLER extension studies were not powered for CVD outcomes, that the numbers are very small, that the populations are mixed, and that the results are therefore highly uncertain.

5.2.4.8 Health related quality of life

The CS includes details of a systematic review of studies estimates of HRQoL of various CV states (see CS,¹³ Section 5.4). This was an update of a previous review (conducted in 2012) which was re-run in January 2015. Searches for HRQoL studies were conducted in MEDLINE and EMBASE by applying a quality of life filter to a list of CV events of interest. According to the text of the CS¹³ (page 206), a total of 171 studies were included in the review (although the ERG notes that the PRISMA diagram presented on page 207 indicates that 173 studies were included). The CS also provides details of a *de novo* time trade-off (TTO) study undertaken by the company.

Neither the company's systematic review nor the Amgen TTO study is used to inform the utilities used in the company's base case analyses. Instead, utility values were based on those used in the model developed to inform NICE CG181.¹⁵ The company justifies this choice on the basis that these utility values were deemed "*to be robust and suitable for a UK assessment of lipid-lowering therapy*" (see CS¹³ page 219). The TTO study is used in the company's scenario analyses (see Section 5.2.6). The company states that HRQoL estimates based on NICE CG181 were mostly patient-reported using the EQ-5D questionnaire, and collected in the UK.

The precise sources used to inform the health utilities in the company's model are not clear from the CS; Table 5-17 of the CS simply lists the source of these values as NICE CG181.¹⁵ The original sources of the utility values used in the company's model are summarised in Table 34, together with brief details of the study type, population, instrument used and approach used to derive each estimate.

The model assumes that utility is dependent on age, based on an analysis of the UK EQ-5D valuation study⁵⁶ reported by Ward *et al.*⁶⁴ Ward *et al* modelled a linear relationship between age and utility whereby utility decreases with increasing age with intercept=1.060 and gradient=-0.004.

The utility multiplier for the “No CVD” state is assumed to be 1.00, hence the utility score applied in the model is simply the age-adjusted utility for the general population.

The utility score for the ECVD state was based on a study of TTO valuations for 67 individuals who had recently experienced an MI; a utility multiplier of 0.88, based on the average TTO value for all 67 respondents, is used in the company’s model.

For the acute ACS state, a utility multiplier of 0.77 is applied based on an RCT of an observational chest unit versus routine care for people with acute undifferentiated chest pain.⁵⁸ Within the trial reported by Goodacre *et al.*,⁵⁸ health utility was assessed using the EQ-5D questionnaire at two days, one month and six months following the initial visit. The values used in the model appear to represent the average of the 6-month EQ-5D scores across both trial arms. The utility for the post-ACS state was assumed to be the same as that for the ECVD state, based on Tsevat *et al.*⁵⁷

For the IS state, utilities were based on a meta-analysis of HRQoL estimates for stroke.⁵⁹ Based on a hierarchical linear model (HLM) meta-regression of studies reporting elicited TTO estimates from community members, Tengs *et al.*⁵⁹ report TTO utilities of 0.52 for major stroke, 0.68 for moderate stroke, and 0.87 for minor stroke. An overall utility for stroke was calculated by weighting utilities of stroke according to severity by their respective frequencies as reported in a cost of illness model reported by Youman *et al.*⁶⁵ The same utility multiplier (relative to age-adjusted background utility) is used for both the acute stroke and post-stroke states.

The utility multiplier for the acute HF state was taken from a longitudinal study relating to a consecutive sample of 229 people discharged from hospital after acute MI⁶⁰ (rather than people with HF). This study reports EQ-5D utilities at 6-weeks and at 1-year. The utility score at 6-weeks (utility = 0.683) was used in the company’s model. The same utility multiplier (relative to age-adjusted background utility) is used for both the acute HF state and post-HF states.

Table 34: Health utilities used in the company's model

Health state	Utility value (95% CI)	Original source	Study type	Population	Instrument	Derivation
Background utility						
No CVD	Age-adjusted	Dolan <i>et al</i> , ⁵⁶ Ward <i>et al</i> ⁶⁴	Health valuation study	General population	EQ-5D	Linear association between age and utility
Utility multiplier (relative to age-adjusted background utility)						
No CVD	1.00	Assumption	n/a	n/a	n/a	n/a
ECVD	0.88 (0.84, 0.92)	Tsevat <i>et al</i> ⁵⁷	Health valuation study	People who had recently had an MI	TTO	Mean of all valuations equal to 0.88
ACS	0.77 (0.73, 0.81)	Goodacre <i>et al</i> ⁵⁸	RCT	People with acute, undifferentiated chest pain	EQ-5D	Mean EQ-5D in both groups at 6 months
IS	0.63 (0.55, 0.71)	Tengs <i>et al</i> ⁵⁹	Meta-analysis (meta-regression)	Studies reporting on severity of stroke	TTO	Utility by severity weighted by frequencies reported by Youman <i>et al</i> ⁶⁵
HF	0.68 (0.64, 0.72)	Lacey <i>et al</i> ⁶⁰	Longitudinal study	People recovering from an acute MI	EQ-5D	Post-MI 6-week mean
Post-ACS	0.88 (0.84, 0.92)	Tsevat <i>et al</i> ⁵⁷	Health valuation study	People who had recently had an MI	TTO	Mean of all valuations equal to 0.88
Post-IS	0.63 (0.55, 0.71)	Tengs <i>et al</i> ⁵⁹	Meta-analysis (meta-regression)	Studies reporting on severity of stroke	TTO	Utility by severity weighted by frequencies reported by Youman <i>et al</i> ⁶⁵
Post-HF	0.68 (0.64, 0.72)	Lacey <i>et al</i> ⁶⁰	Longitudinal study	People recovering from an acute MI	EQ-5D	Post-MI 6-week mean

CVD – cardiovascular disease; ECVD – established cardiovascular disease; IS – ischaemic stroke; HF – heart failure; MI – myocardial infarction; EQ-5D – Euroqol 5-Dimensions; TTO – time trade off

The company's model assumes that neither ezetimibe nor evolocumab is associated with a decrement in HRQoL. This is justified by the company as ezetimibe is an oral agent which is administered daily whilst evolocumab is a subcutaneously injectable drug (individuals use a prefilled pen that auto-injects the drug when pressed).

5.2.4.9 Resource costs

The CS¹³ presents the methods and results of a systematic review of studies reporting direct cost estimates for the treatment of specific CV events. Searches were undertaken in MEDLINE, EMBASE, EconLit and NHS EED for studies indexed during the period 1 January 2000 to 31 March 2015. In addition, conference abstracts from the ISPOR, AHA, ACC, ESC, and EAS conferences during the period 2013 to 2014 were also searched. The review included 48 studies. A summary of those studies which used a Markov approach and which adopted a lifetime time horizon are summarised in Table 5-20 of the CS (see CS,¹³ page 227). However, the findings of this review are not directly used to inform the company's *de novo* health economic analysis.

Drug acquisition costs

Table 35 summarises the drug acquisition costs for evolocumab, ezetimibe and statins included in the company's model. The costs of atorvastatin 20mg, atorvastatin 80mg and ezetimibe 10mg were based on the list prices sourced from the NHS Drug Tariff.⁶¹ The annual per patient costs of 20mg atorvastatin and 80mg atorvastatin were estimated to be £18.38 and £35.33, respectively. The annual per patient cost of 10mg ezetimibe was estimated to be £342.97. At the time of writing, the cost of evolocumab had not been listed on the BNF;⁶¹ this cost was instead sourced from the company.¹³ The annual per patient cost for 140mg evolocumab Q2W was assumed to be [REDACTED] whilst the annual per patient cost for 420mg evolocumab QM was assumed to be [REDACTED]

Table 35: Description of interventions/comparators assessed in the company's model (adapted from CS,¹³ Table 5-21, page 229)

Drug	Formulation	Dosing description	Cost per pack	Units per pack	Doses per year	Annual cost	Source
Evolocumab	140mg PFP	140mg q2w	[REDACTED]	2	26	[REDACTED]	CS ¹³
	140mg PFP	420mg qm	[REDACTED]	2	36	[REDACTED]	NHS Drugs Tariff ⁶¹
Ezetimibe	10mg tablet	10mg od	£26.31	28	365	£342.97	
Atorvastatin	20mg tablet	20mg od	£1.41	28	365	£18.38	
	80mg tablet	80mg od	£2.71	28	365	£35.33	

PFP - prefilled pen; q2w - every 2 weeks; qm - monthly; SC - subcutaneous

Other costs used in the company's model

Table 36 summarises the other cost components used in the company's model.

Table 36: Other costs included in the company's model

Cost parameter	Cost	Source
Training and monitoring costs		
Cost s.c. injection training	£84.00*	Curtis 2014 ⁶³
Cost monitoring year 1	£238.72	Based on NHS Reference Costs 2013/14 ⁶² and Curtis 2014 ⁶³
Cost monitoring subsequent years	£101.08	
Health state costs		
No CVD (annual)	£0.00	Company's CPRD/HES longitudinal study ¹³
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	
Other		
CHD death (once only cost)	£717.96	
Stroke death (once only cost)	£1,847.92	
Revascularisation	£5,648.60	

s.c. – subcutaneous; CVD – cardiovascular disease; ECVD – established cardiovascular disease; ACS – acute coronary syndromes; HF – heart failure; CHD – coronary heart disease; CPRD - Clinical Practice Research Datalink; HES – Hospital Episode Statistics

* Applied only to the evolocumab group

Training

Patients receiving evolocumab are assumed to receive training for self-administration by a nurse upon initiation of treatment. A one-off cost is assumed at entry into the model. The company assumes that patients receive 1 hour of nurse training at a cost of £84.00 based on the cost per hour for a nurse (day ward, including staff nurse) derived from the PSSRU.⁶³

Monitoring

The company's model assumes that no additional monitoring is required for people receiving evolocumab over and above those which are part of routine clinical practice and assumed the annual monitoring costs to be £238.72 for the first year and £101.08 for subsequent years. Patients are assumed to require an initial appointment at initiation and a subsequent follow-up in the lipid clinic to assess treatment efficacy and tolerability (two appointments in first year). Subsequently, patients are assumed to be treated in primary care and incur one appointment every year. The company states that monitoring costs associated with tests and appointments following discharge are based on assumptions made by the Guideline Development Group for CG181¹⁵ and cost are taken from the UK tariff.^{62,63}

Health state costs

Health state costs were based on a retrospective longitudinal observational cohort study undertaken using data from the CPRD and HES.^{13,66} These data were used to estimate acute and long-term health

care resource use and costs associated with first and subsequent CV events. The analysis used data for individuals from between January 2006 and March 2012 to construct a cohort of 24,093 individuals who were aged ≥ 18 years, who were hospitalised for their first CV event, had received at least two prescriptions for lipid-lowering therapy (statins, ezetimibe, fibrates, nicotinic acid, or bile acid sequestrants) in the 180 days prior to the event and for whom at least 12 months of data prior to the index date and 30 days afterwards were available from both the CPRD and HES. Individuals were classed as “low-risk” or “high-risk” on the basis of prior conditions. The “high-risk” individuals (n=17,685) had a prior diagnosis of diabetes, peripheral arterial disease, ischaemic heart disease [excluding MI or unstable angina], or angina pectoris, whilst the “low-risk” individuals (n=6,408) did not have any of these conditions. A third group was formed from both the high-risk and low-risk groups, comprising of those individuals who experienced a second CV event (n=5,274).

Individuals were followed from the date of the first CV event to either the next CV event or until the final follow-up date (March 2012). The costs associated with specific CV events were estimated based on resource use for each individual during the three intervals: (i) the baseline period (12-months prior to an event); (ii) the acute period (6-months after an event), and; the long-term period (the subsequent 30 months). Resource use in the study included healthcare visits to general practitioners, referrals to specialists (as reported in CPRD), CV and non-CV hospitalisations (intensive care unit, cardiovascular ward/clinic, general ward, surgical procedures, and emergency room visits, all as reported by HES), and prescriptions for medications (including lipid-lowering therapy, antihypertensive therapy, antithrombotic therapy, and anti-diabetic therapy). Unit costs were based on the PSSRU,⁶³ NHS Reference Costs 2013/14⁶² and the NHS Drugs Tariff.⁶¹ In order to produce annual acute costs for use in the model, the acute and long-term costs were combined (assuming that the total annual event cost is comprised of 6 months in the acute state and 6-months in the annual state).

Revascularisation costs

The company assumed a revascularisation cost of £5,648.60 based on the CPRD/HES study.¹³ The company assumed that all people in the ACS health state undergo a revascularisation procedure and 10% of people in the post-ACS health state undergo a revascularisation procedure annually. The CS¹³ (page 223) states that these assumptions are in line with NICE CG181¹⁵ and that no revascularisation cost was included for stable angina in the company’s model, hence this is likely to be conservative.

Costs of CV-related death

The costs associated with death due to fatal ischaemic stroke and death due to CHD were estimated from the CPRD study.¹³ These were assumed to be £717.96 and £1,847.92, respectively. These costs are applied in the model only to patients transiting to these states.

5.2.5 Summary of analyses presented within the CS

The range of the economic analyses presented in the CS are summarised in Table 37.

- (i) **Base case analyses** (see CS,¹³ Sections 5.7 to 5.10, analyses A, D G and H). For the non-familial primary prevention population, the company's base case analyses are presented as threshold analyses of 10-year CVD risk. Analyses are presented for comparisons of evolocumab plus statins versus ezetimibe plus statins in patients who are able to tolerate statins (ST population) and evolocumab versus ezetimibe in patients for whom statins are contraindicated or not tolerated (SI population). For the non-familial secondary prevention population and the HeFH primary/secondary population, cohort-based cost-effectiveness analyses are presented for comparisons of evolocumab plus statins versus ezetimibe plus statins for the ST population and evolocumab versus ezetimibe for the SI population. Results are presented as ICERs based on point estimates of parameters.
- (ii) **Scenario analyses for evolocumab plus ezetimibe combination therapy** (see CS,¹³ Section 5.12, Analyses E, F, I and J). Scenario analyses are presented for comparisons of evolocumab plus ezetimibe plus statins versus ezetimibe plus statins for the ST population and evolocumab plus ezetimibe versus ezetimibe for the SI population. Results for these scenarios are presented as ICERs based on point estimates of parameters.
- (iii) **Probabilistic sensitivity analyses** (see CS,¹³ Section 5.11). Probabilistic sensitivity analysis (PSA) results are presented for all comparisons presented in the base case analysis (analyses A, D, G and H). For the non-familial primary prevention population, PSA results are presented in terms of the probability that evolocumab (with statins or as monotherapy) produces the greatest net benefit at willingness-to-pay (WTP) thresholds of £20,000 per QALY gained and £30,000 per QALY gained at the 10-year CVD risk levels required to achieve those thresholds within the deterministic analysis. Probabilistic ICERs are not reported for these threshold analyses. For the non-familial secondary prevention population and the HeFH primary/secondary prevention population, results are presented in terms of probabilistic ICERs, cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).
- (iv) **Deterministic sensitivity analyses** (see CS,¹³ Section 5.11). Deterministic sensitivity analyses were conducted only for those base case comparisons of evolocumab plus statins versus statins in the non-familial primary prevention ST population (based on a cohort analysis rather than according to LDL-C threshold), the non-familial secondary prevention ST population (analysis C) and the HeFH primary/secondary prevention ST population (analysis G). DSA results are presented as tornado diagrams.
- (v) **Additional scenario analyses** (see CS,¹³ Section 5.12). Additional scenario analyses are presented to assess the cost-effectiveness of evolocumab plus statins versus ezetimibe plus statins according to the severity of hypercholesterolaemia based on LDL-C at baseline; these

analyses are presented only for the non-familial secondary prevention ST population (analysis C) and the HeFH primary/secondary prevention ST population (analysis G). Further scenario analyses were also conducted to assess the impact of monthly evolocumab dosing, treatment durations of 5-, 10- and 20-years, alternative discount rates, risk capping at age 75, the use of costs derived from NICE CG181,¹⁵ the use of TTO utility estimates derived from the Amgen-sponsored utility study and the use of alternative assumptions regarding nurse training. These additional analyses are presented only for the base case comparisons of evolocumab plus statins versus statins in the non-familial primary prevention ST population (based on the cohort rather than LDL-C threshold), the non-familial secondary prevention ST population (analysis C) and the HeFH primary/secondary prevention ST population (analysis G).

- (vi) **Subgroup analyses** (see CS,¹³ Section 5.13). The CS presents three sets of subgroup analyses; these are reported only for the comparison of evolocumab plus statins versus ezetimibe plus statins in the non-familial secondary prevention ST population (analysis C).
- a. *Individual risk factors*. The following risk factors were explored: LDL-C 3.0mmol/L to 6.0mmol/L in increments of 0.5mmol/L, gender, presence of diabetes, number of vascular beds (2 or 3), presence of atrial fibrillation, CV events in the previous year (characterised as the starting state for the model).
 - b. *Combinations of individual risk factors with baseline LDL-C, age and sex*. Analyses were presented for people with individual risk factors (diabetes, AF, 2/3 vascular beds and history of CVD events) combined with baseline LDL-C 3.5-4.5mmol/L, sex and age.
 - c. *Combinations of two risk factors with baseline LDL-C, age and sex*. Analyses were presented for people with two risk factors (including diabetes, AF, 2/3 vascular beds and history of ACS) combined with baseline LDL-C 3.0-4.0mmol/L, sex and age.

Table 37: Summary of results presented within the CS¹³

Analysis	Population	Analysis type	Base case /scenario analysis	Intervention	Comparator	Types of analyses undertaken for comparison			
						Deterministic/probabilistic	DSA	Scenario analyses	Subgroup analyses
A	Non-familial PP, ST	Threshold	Base case	Evolocumab+statins	Ezetimibe+statins	Both	No*	No*	No
B	Non-familial PP, SI	Threshold	Base case	Evolocumab	Ezetimibe	Both	No*	No*	No
C	Non-familial SP, ST	Cohort	Base case	Evolocumab+statins	Ezetimibe+statins	Both	Yes	Yes	Yes
D	Non-familial SP, SI	Cohort	Base case	Evolocumab	Ezetimibe	Both	No	No	No
E	Non-familial SP, SI	Cohort	Scenario	Evolocumab+ezetimibe	Ezetimibe	Deterministic	No	No	No
F	Non-familial SP, ST	Cohort	Scenario	Evolocumab+ezetimibe+statins	Ezetimibe+statins	Deterministic	No	No	No
G	HeFH PP/SP, ST	Cohort	Base case	Evolocumab+statins	Ezetimibe+statins	Both	Yes	Yes	No
H	HeFH, PP/SP, SI	Cohort	Base case	Evolocumab	Ezetimibe	Both	No	No	No
I	HeFH PP/SP, SI	Cohort	Scenario	Evolocumab+ezetimibe	Ezetimibe	Deterministic	No	No	No
J	HeFH PP/SP, ST	Cohort	Scenario	Evolocumab+ezetimibe+statins	Ezetimibe+statins	Deterministic	No	No	No

PP – primary prevention; SP – secondary prevention; ST – statin tolerant; SI – statin intolerant; HeFH - Heterozygous familial hypercholesterolemia; DSA – deterministic sensitivity analysis

* Deterministic sensitivity analyses and scenario analyses undertaken for overall primary prevention cohort rather than for those with 10-year CV risk threshold (see CS¹³ Figure 5-20 and Table 5-64)

5.2.6 Cost-effectiveness results presented within the CS

5.2.6.1 Base case cost-effectiveness results (deterministic)

Table 38 summarises the deterministic cost-effectiveness results presented within the CS.¹³ For the sake of brevity, and in line with the final NICE scope,⁴ results are presented only for the comparison of evolocumab (with or without statins) versus ezetimibe (with or without statins).

Non-familial primary prevention population (analyses A and B)

Within the non-familial primary prevention ST population (analysis A), the company's threshold analyses indicate that in people with a baseline LDL-C of 3.5mmol/L, the ICER for evolocumab plus statins versus ezetimibe plus statins would be below £30,000 per QALY gained in people with a 10-year CVD risk of 79% (or higher). The corresponding 10-year risk thresholds for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 73% and 70%, respectively. Within the non-familial primary prevention SI population (analysis B) with a baseline LDL-C of 3.5mmol/L, the ICER for evolocumab versus ezetimibe would be below £30,000 per QALY gained in people with a 10-year CVD risk of 81% (or higher). The corresponding 10-year risk thresholds for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 75% and 71%, respectively.

The company's analyses suggest that it is not possible under any combination of baseline LDL-C and 10-year CVD risk for evolocumab to achieve an ICER below £20,000 per QALY gained.

Non-familial secondary prevention population (analyses C and D)

Within the non-familial secondary prevention ST population (analysis C), the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.44 QALYs at an additional cost of £51,407 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £116,713 per QALY gained. Within the non-familial secondary prevention SI population (analysis D), the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.42 QALYs at an additional cost of £50,542 as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £119,971 per QALY gained.

HeFH primary/secondary prevention population (analyses G and H)

Within the HeFH primary/secondary prevention ST population (analysis G), the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.20 QALYs at an additional cost of £53,565 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £44,741 per QALY gained. Within the HeFH primary/secondary prevention SI population (analysis H), evolocumab monotherapy is expected to produce an additional 1.10 QALYs at an additional cost of £51,749 as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £47,193 per QALY gained.

Table 38: Summary of company's cost-effectiveness results (deterministic)

Analysis	Population characteristics and comparison	Evolocumab		Ezetimibe		Incremental		
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER
Non-familial primary prevention population - threshold analysis (λ=£30,000/QALY)								
Analysis Ai	LDL-C=2.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Aii	LDL-C=3.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Aiii	LDL-C=3.5, ST (evo+statins vs eze+statins), 10yr risk=79%	8.15	£56,110	6.74	£13,952	1.41	£42,158	£29,896
Analysis Aiv	LDL-C=4.0, ST (evo+statins vs eze+statins), 10yr risk=73%	8.95	£59,792	7.40	£13,577	1.55	£46,215	£29,864
Analysis Av	LDL-C=4.5, ST (evo+statins vs eze+statins), 10yr risk=70%	9.46	£62,016	7.83	£13,232	1.63	£48,784	£29,962
Analysis Bi	LDL-C=2.5, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bii	LDL-C=3.0, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Biii	LDL-C=3.5, SI (evo vs eze), 10-year risk=81%	7.58	£53,626	6.27	£14,344	1.31	£39,282	£29,980
Analysis Biv	LDL-C=4.0, SI (evo vs eze), 10-year risk=75%	8.34	£57,135	6.90	£14,075	1.44	£43,059	£29,954
Analysis Bv	LDL-C=4.5, SI (evo vs eze), 10-year risk=71%	8.92	£59,743	7.38	£13,775	1.54	£45,968	£29,939
Non-familial primary prevention population - threshold analysis (λ=£20,000/QALY)								
Analysis Avi	LDL-C=2.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Avii	LDL-C=3.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Aviii	LDL-C=3.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Aix	LDL-C=4.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Ax	LDL-C=4.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bvi	LDL-C=2.5, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bvii	LDL-C=3.0, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bviii	LDL-C=3.5, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bix	LDL-C=4.0, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bx	LDL-C=4.5, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Non-familial secondary prevention population - cohort analysis								
Analysis C	ST (evo+statins vs eze+statins)	8.06	£71,709	7.62	£20,302	0.44	£51,407	£116,713
Analysis D	SI (evo vs eze)	7.94	£70,912	7.52	£20,371	0.42	£50,542	£119,971
HeFH primary/secondary prevention population - cohort analysis								
Analysis G	ST (evo+statins vs eze+statins)	10.05	£72,262	8.86	£18,697	1.20	£53,565	£44,741
Analysis H	SI (evo vs eze)	9.69	£70,754	8.6	£19,005	1.10	£51,749	£47,193

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe; LDL-C – low-density lipoprotein cholesterol

5.2.6.2 Probabilistic sensitivity analysis results

Table 39 summarises the probabilities that evolocumab (with or without statins) produces more net benefit than ezetimibe (with or without statins) at WTP thresholds of £20,000 per QALY gained and £30,000 per QALY gained, respectively.

Non-familial primary prevention population (analyses A and B)

Within the non-familial primary prevention ST population who have a baseline LDL-C of 3.5mmol/L and a 10-year CVD risk of 79%, the probability that evolocumab plus statins produces more net benefit than ezetimibe plus statins at a WTP threshold of £30,000 per QALY gained is estimated to be 0.38. The corresponding probabilities for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 0.41 and 0.37, respectively. Within the non-familial primary prevention SI population who have a baseline LDL-C of 3.5mmol/L, the probability that evolocumab produces more net benefit than ezetimibe at a WTP threshold of £30,000 per QALY gained is estimated to be 0.42. The corresponding probabilities for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 0.43 and 0.42, respectively.

Non-familial secondary prevention population (analyses C and D)

Within the non-familial secondary prevention ST population, the probabilistic ICER for evolocumab plus statins versus ezetimibe plus statins is reported to be £119,012 per QALY gained. This is slightly higher than the deterministic estimate of £116,713 per QALY gained. The probability that evolocumab plus statins produces more net benefit than ezetimibe plus statins in this population is expected to be approximately zero. Within the SI population, the probabilistic ICER for evolocumab versus ezetimibe is reported to be £123,780 per QALY gained. This is again slightly higher than the deterministic estimate of £119,971 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe in this population is expected to be approximately zero.

HeFH primary/secondary prevention population (analyses G and H)

Within the HeFH primary/secondary prevention ST population, the probabilistic ICER for evolocumab plus statins versus ezetimibe plus statins is reported to be £46,412 per QALY gained. This is slightly higher than the deterministic estimate of £44,741 per QALY gained. The probability that evolocumab plus statins produces more net benefit than ezetimibe plus statins in this population is expected to be approximately zero. Within the HeFH primary/secondary prevention SI population, the probabilistic ICER for evolocumab versus ezetimibe is reported to be £48,362 per QALY gained. This is also slightly higher than the deterministic estimate of £47,193 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe in this population is expected to be approximately zero.

Table 39: Summary of probabilistic sensitivity analysis results

Analysis	Population characteristics and comparison	Probabilistic ICER	Probability evolocumab optimal at WTP threshold	
			λ=£20,000/QALY gained	λ=£30,000/QALY gained
Non-familial primary prevention population - threshold analysis (λ=£30,000/QALY)				
Analysis Ai	LDL-C=2.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Ai	LDL-C=3.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Aiii	LDL-C=3.5, ST (evo+statins vs eze+statins), 10yr risk=79%	NR	n/a	0.38
Analysis Aiv	LDL-C=4.0, ST (evo+statins vs eze+statins), 10yr risk=73%	NR	n/a	0.41
Analysis Av	LDL-C=4.5, ST (evo+statins vs eze+statins), 10yr risk=70%	NR	n/a	0.37
Analysis Bi	LDL-C=2.5, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Bi	LDL-C=3.0, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Biii	LDL-C=3.5, SI (evo vs eze), 10-year risk=81%	NR	n/a	0.42†
Analysis Biv	LDL-C=4.0, SI (evo vs eze), 10-year risk=75%	NR	n/a	0.43†
Analysis Bv	LDL-C=4.5, SI (evo vs eze), 10-year risk=71%	NR	n/a	0.42†
Non-familial primary prevention population - threshold analysis (λ=£20,000/QALY)				
Analysis Avi	LDL-C=2.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Avii	LDL-C=3.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Aviii	LDL-C=3.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Aix	LDL-C=4.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Ax	LDL-C=4.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Bvi	LDL-C=2.5, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Bvii	LDL-C=3.0, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Bviii	LDL-C=3.5, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Bix	LDL-C=4.0, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Bx	LDL-C=4.5, SI (evo vs eze), not achievable	n/a	n/a	n/a
Non-familial secondary prevention population - cohort analysis				
Analysis C	ST (evo+statins vs eze+statins)	£119,012	0.00	0.00
Analysis D	SI (evo vs eze)	£123,780	0.00	0.00
HeFH primary/secondary prevention population - cohort analysis				
Analysis G	ST (evo+statins vs eze+statins)	£46,412	0.00	0.00
Analysis H	SI (evo vs eze)	£48,362	0.00	0.00

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe; LDL-C – low-density lipoprotein cholesterol; WTP – willingness-to-pay

† The £20,000/QALY threshold referred to in Table 5-54 is mislabelled and should refer to the probability of being optimal at £30,000 per QALY gained

5.2.6.3 Scenario analysis results – evolocumab in combination with ezetimibe

Table 40 summarises the results of the company's scenario analyses in which evolocumab is given in combination with ezetimibe (with/without concomitant statins).

Non-familial secondary prevention population (analyses E and F)

Within the non-familial secondary prevention SI population (analysis E), the company's scenario analysis suggests that evolocumab plus ezetimibe is expected to produce an additional 0.49 QALYs at an additional cost of £55,158 compared with ezetimibe; the resulting ICER is estimated to be £112,561 per QALY gained. Within the ST population (analysis F), evolocumab plus ezetimibe plus statins is expected to produce an additional 0.44 QALYs at an additional cost of £55,872 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £126,849 per QALY gained.

HeFH primary/secondary prevention population (analyses I and J)

For the HeFH primary/secondary prevention SI population (analysis I), the company's scenario analysis suggests that evolocumab plus ezetimibe is expected to produce an additional 1.29 QALYs at an additional cost of £56,950 as compared against ezetimibe monotherapy; the resulting ICER is expected to be £44,224 per QALY gained. Within the ST population (analysis J), evolocumab plus ezetimibe plus statins is expected to produce an additional 1.26 QALYs at an additional cost of £58,503 as compared against ezetimibe plus statins; the resulting ICER is expected to be £46,592 per QALY gained.

Table 40: Summary of company's scenario analysis results (evolocumab plus ezetimibe - deterministic)

Analysis	Population characteristics and comparison	Evolocumab plus ezetimibe		Ezetimibe		Incremental		
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER
Non-familial secondary prevention population – cohort analysis								
Analysis E	SI (evo+eze vs eze)	8.01	£75,528	7.52	£20,371	0.49	£55,158	£112,561
Analysis F	ST (evo+eze+statins vs eze+statins)	8.06	£76,174	7.62	£20,302	0.44	£55,872	£126,849
HeFH primary/secondary prevention - cohort analysis								
Analysis I	SI (evo+eze vs eze)	9.88	£75,955	8.6	£19,005	1.29	£56,950	£44,224
Analysis J	ST (evo+eze+statins vs eze+statins)	10.11	£77,200	8.86	£18,697	1.26	£58,503	£46,592

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe; LDL-C - low-density lipoprotein cholesterol

5.2.6.4 Deterministic sensitivity analysis results (evolocumab plus statins versus ezetimibe plus statins)

The company's DSA results are summarised in Figures 9 to 11. Within the non-familial primary and secondary prevention populations, the five most influential parameters were the treatment duration, the relationship between LDL-C reduction and CHD death, the impact of ezetimibe on LDL-C, the CPRD calibration rate ratios and the relationship between LDL-C reduction and ischaemic stroke death. Within the HeFH primary/secondary prevention population, the five most influential parameters were the treatment duration, the relationship between LDL-C reduction and CHD death, the impact of ezetimibe on LDL-C, the HeFH calibration rate ratio and the relationship between LDL-C reduction and ischaemic stroke. It is noteworthy that the ICERs for evolocumab in all three populations remain consistently greater than £30,000 per QALY gained for all sensitivity analyses.

Figure 9: Tornado diagram for evolocumab plus statins versus ezetimibe plus statins in the primary hypercholesterolaemia LDL-C>2.5mmol/L primary prevention population (reproduced from CS,¹³ Figure 5-20, page 267)

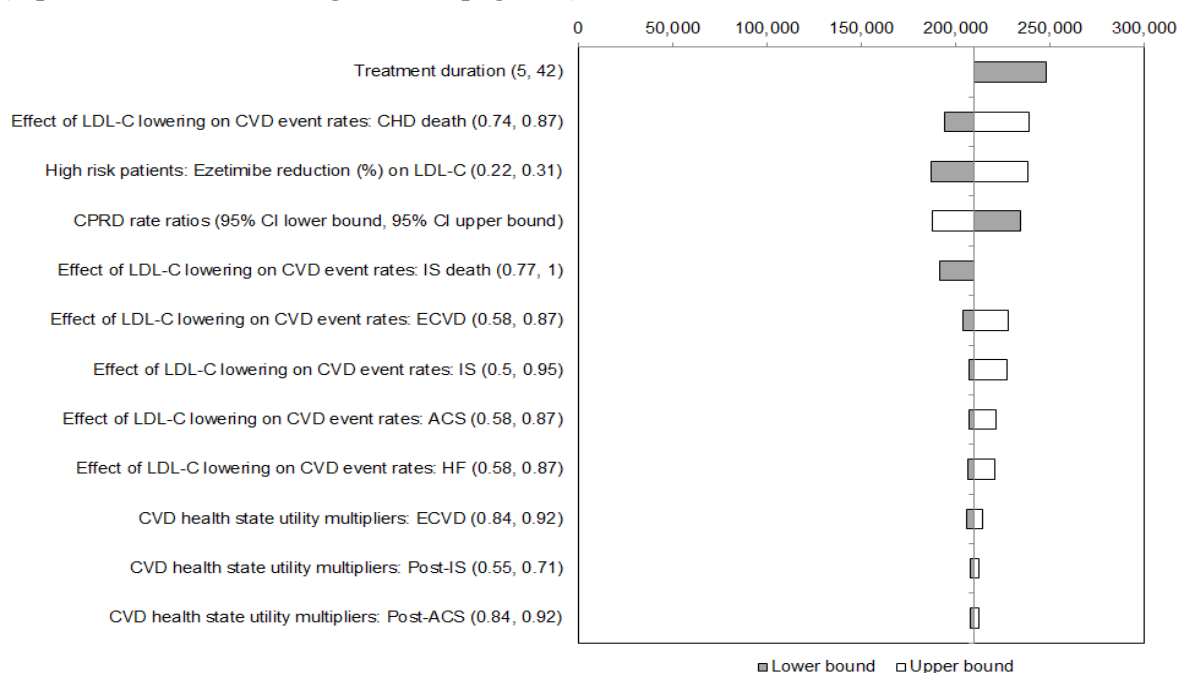


Figure 10: Tornado diagram for evolocumab plus statins versus ezetimibe plus statins in primary hypercholesterolaemia LDL-C>2.5mmol/L secondary prevention population (reproduced from CS,¹³ Figure 5-21, page 267)

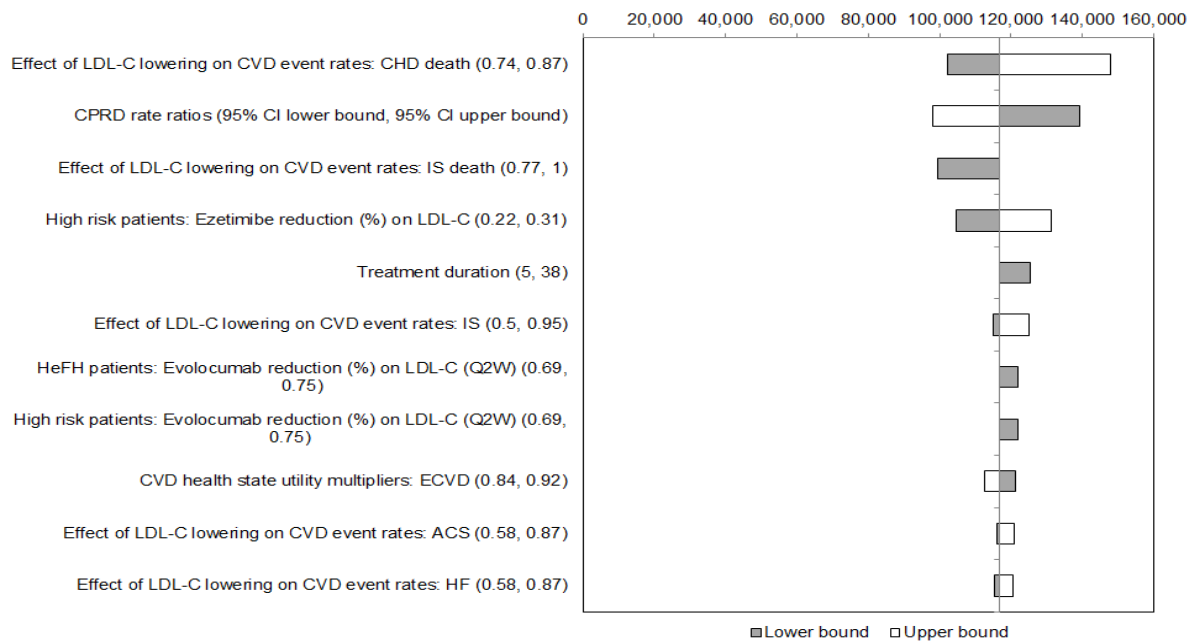
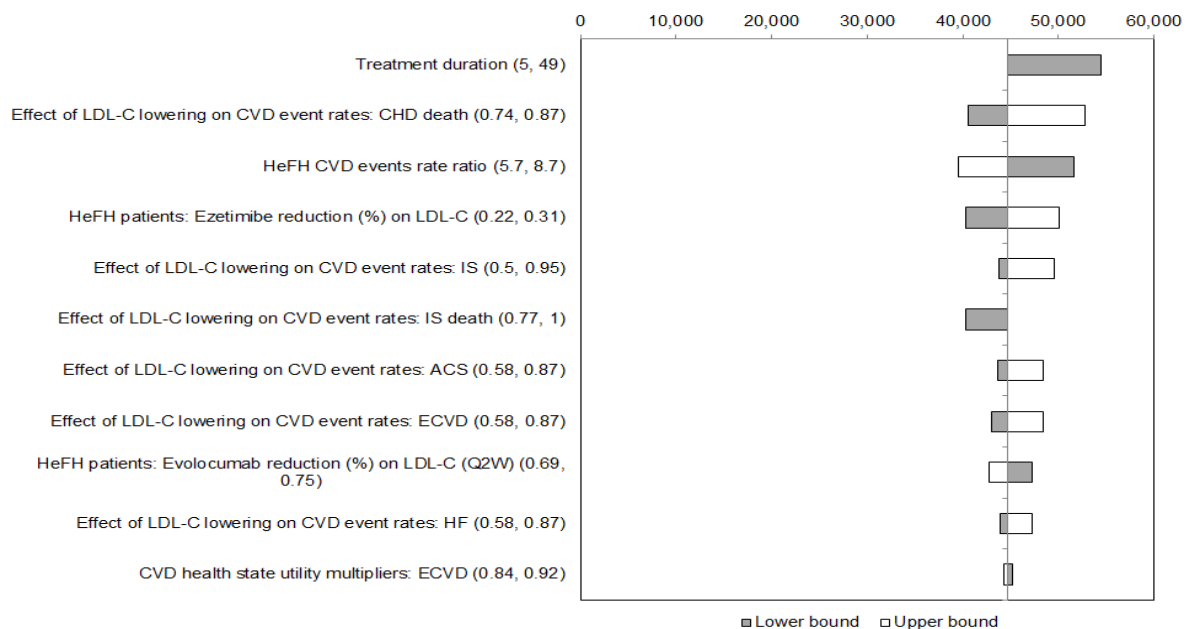


Figure 11: Tornado diagram for evolocumab plus statins versus ezetimibe plus statins in HeFH primary and secondary prevention population (reproduced from CS,¹³ Figure 5-22, page 268)



5.2.6.6 Additional scenario analyses

Severity of hypercholesterolaemia according to baseline LDL-C (analyses C and G only)

Within the non-familial secondary prevention ST population (analysis C), the ICERs for evolocumab plus statins versus ezetimibe plus statins in patients with LDL-C values of 3.0mmol/L and 6.0mmol/L, the ICERs are estimated to be £146,532 per QALY gained and £91,341 per QALY gained, respectively.

Within the HeFH primary/secondary prevention ST population (analysis G), the ICER for evolocumab plus statins versus ezetimibe plus statins in people with LDL-C values of 3.0mmol/L and 6.0mmol/L are £62,432 per QALY gained and £36,212 per QALY gained, respectively.

Other scenario analyses (analyses A, C and G only)

Within the non-familial primary prevention ST population, the base case ICER for evolocumab plus statins versus ezetimibe plus statins for the overall cohort is reported to be £210,093 per QALY gained. It should be noted that this ICER does not appear anywhere else in the CS.¹³ Within this population (see CS¹³ Table 5-64), the lowest reported ICER for evolocumab plus statins versus statins relates to the scenario in which the evolocumab QM dose is used; the ICER is reported to be £76,325 per QALY gained. However, the ERG notes that this is an error since the scenario assumes that the monthly evolocumab dose is both less effective and more expensive than the Q2W dose used in the company's base case analysis. A re-run of this analysis undertaken by the ERG indicates that the ICER for evolocumab plus statins versus ezetimibe plus statins within this scenario is considerably higher at £299,916 per QALY gained. Within the non-familial primary prevention population scenario analyses, the highest ICER was reported for the scenario in which costs were undiscounted and health outcomes were discounted at a rate of 6% per annum; in this scenario, the ICER for evolocumab plus statins versus ezetimibe plus statins was £559,793 per QALY gained.

Within the non-familial secondary prevention ST population, the lowest ICER reported relates to the scenario in which health utilities were taken from the Amgen TTO utility study; in this scenario the ICER for evolocumab plus statins versus ezetimibe plus statins was reported to be £88,572 per QALY gained. The highest ICER was reported for the scenario in which costs were undiscounted and health outcomes were discounted at a rate of 6% per annum; in this scenario, the ICER for evolocumab plus statins versus ezetimibe plus statins was £258,684 per QALY gained.

In the HeFH primary/secondary prevention ST population, the lowest ICER was reported for the scenario in which costs and health outcomes were undiscounted; in this scenario, the ICER evolocumab plus statins versus ezetimibe plus statins was £34,407 per QALY gained. The highest ICER was reported for the scenario in which costs were undiscounted and health outcomes were

discounted at a rate of 6% per annum; in this scenario, the ICER evolocumab plus statins versus ezetimibe plus statins was £105,987 per QALY gained.

5.2.6.7 Subgroup analyses

Individual risk factors (analysis C only)

In the company's analysis of individual risk factors in the non-familial secondary prevention ST population, the reported ICERs for evolocumab plus statins versus ezetimibe plus statins range from £76,451 per QALY gained (people with 3 vascular beds) to £224,001 per QALY gained (all patients assumed to enter the model in the acute IS health state).

Combination of one additional risk factor and baseline LDL-C, age and sex (analysis C only)

In the company's analysis of individual risk factors combined with baseline LDL-C, age and sex in the non-familial secondary prevention ST population, the reported ICERs for evolocumab plus statins versus ezetimibe plus statins range from £61,380 per QALY gained (LDL-C=4.5mmol/l, male, age+10years, 3 vascular beds) to £250,530 per QALY gained (LDL-C=3.5mmol/L, female, cohort age, history of acute IS).

Combination of two additional risk factors and baseline LDL-C, age and sex (analysis C only)

In the company's analysis of two additional risk factors combined with baseline LDL-C, age and sex undertaken in the non-familial secondary prevention ST population, the reported ICERs for evolocumab plus statins versus ezetimibe plus statins range from £49,528 per QALY gained (LDL-C=4.0mmol/L, male, age+10years, diabetes and ACS) to £98,100 per QALY gained (LDL-C=3mmol/L, female, age=cohort, AF and 2 vascular beds).

5.2.6.8 Amended model results

As discussed in Section 5.2.2, during the clarification stage of the appraisal, the ERG identified a serious programming error within the company's model whereby it was possible for many of the transition probabilities, and hence the health state populations in the Markov trace, to be negative. This is clearly mathematically inconsistent. Consequently, NICE submitted a request to the company to rectify the error. In response, the company submitted an amended model and an addendum detailing revised results produced using this amended model. The addendum⁵² stated:

“As noted by the ERG, non-fatal and fatal CV events are estimated independently. As such, in certain extreme scenarios of CV risk, negative transition probabilities may occur. This issue has precipitated in the manufacturer submission (NHS list price) in the threshold analyses for patients ‘without existing CVD’, whereby such extreme scenarios have been modelled on the basis of CVD risk to demonstrate cost-effectiveness according to willingness-to-pay thresholds. Therefore, we

acknowledge that the analyses for this population (at NHS list price) are invalid due to this finding and have been revised.

Additionally, it has been identified that for the heterozygous familial hypercholesterolaemia (HeFH) population with previous history of heart failure, some transition probabilities are negative for patients above 90 years of age. On examination of the Benn, et al (2010) publication that has been used as the basis for the HeFH CV event rate calibration, we note that the prevalence of heart failure is not reported. In the absence of this information and additional data, we have removed the heart failure history risk adjustment for HeFH patients. This prevents the occurrence of negative transitions in patients above 90 years of age; and may result in conservative estimates for other younger populations.

Therefore, the cost effectiveness analyses have been updated for these populations:

Patients without existing CVD

- *Threshold analysis according to CVD risk and willingness-to-pay thresholds*
- *Probabilistic sensitivity analyses*

Patients with HeFH

- *Base case results*
- *Sensitivity analyses (deterministic and probabilistic)*
- *Scenario analyses”*

On the basis of the addendum document text, reproduced above, the company’s analyses within the non-familial primary prevention population are considered to be “invalid” and therefore the ERG would advise that these are disregarded. With respect to the non-familial secondary prevention population, the company’s amendment does not affect this population hence the analyses remain unchanged and the company’s preferred estimates of the cost-effectiveness of evolocumab in this population are as reported above. With respect to the HeFH primary/secondary prevention population, the model has been amended; the impact of this amendment on the base case and scenario analyses is summarised in Tables 41 and 42. The ERG’s concerns regarding the original submitted model and the amended model are discussed in detail in Section 5.3.

(i) Base case cost-effectiveness results (amended model)

The base case and scenario analysis ICERs for evolocumab in the HeFH primary/secondary prevention population presented in the company’s addendum⁵² are higher than those reported in the

original CS.¹³ For the HeFH primary/secondary prevention ST population (analysis G), the company's amended base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.15 QALYs at an additional cost of £73,620 as compared with ezetimibe plus statins; the resulting ICER is estimated to be £47,195 per QALY gained. The probabilistic ICER is slightly higher at £48,664 per QALY gained. The probability that evolocumab plus statins produces more net benefit than ezetimibe plus statins is approximately zero at a WTP threshold of £30,000 per QALY gained. In the HeFH primary/secondary prevention SI population (analysis H), evolocumab monotherapy is expected to produce an additional 1.05 QALYs at an additional cost of £52,486 as compared against ezetimibe monotherapy; the resulting ICER is expected to be £49,900 per QALY gained. The probabilistic ICER is higher at £51,061 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe is approximately zero at a WTP threshold of £30,000 per QALY gained.

The company's scenario analysis in the HeFH primary/secondary SI prevention population (analysis I) suggests that, evolocumab plus ezetimibe is expected to produce an additional 1.24 QALYs at an additional cost of £57,664 as compared against ezetimibe monotherapy; the resulting ICER is expected to be £46,685 per QALY gained. In the ST population (analysis J), evolocumab plus ezetimibe plus statins is expected to produce an additional 1.20 QALYs at an additional cost of £59,174 as compared against ezetimibe plus statins; the resulting ICER is expected to be £49,138 per QALY gained.

Other results presented in the company's addendum

Deterministic sensitivity analyses (analysis G only)

The company's amended DSA results are similar to those presented within the CS.¹³ Within the amended analysis, the five most influential variables remain the same as those within the CS (treatment duration, relationship between LDL-C reduction and CHD death, the impact of ezetimibe on LDL-C, the HeFH calibration rate ratio and the relationship between LDL-C reduction and ischaemic stroke).

Severity of hypercholesterolaemia according to baseline LDL-C (analysis G only)

For the HeFH primary prevention/secondary prevention ST population (analysis G), the ICERs for evolocumab plus statins versus ezetimibe plus statins in patients with LDL-C values of 3.0mmol/L and 6mmol/L, the ICERs are £66,196 per QALY gained and £37,995 per QALY gained, respectively. These values are slightly higher than those presented within the CS.¹³

Other scenario analyses (analysis G only)

In the HeFH primary/secondary prevention ST population, the lowest ICER was reported for the scenario in which costs and health outcomes were undiscounted; for this scenario, the ICER evolocumab plus statins versus ezetimibe plus statins was £36,339 per QALY gained. The highest ICER was reported for the scenario in which costs were undiscounted and health outcomes were discounted at a rate of 6% per annum. For this scenario, the ICER evolocumab plus statins versus ezetimibe plus statins was £112,741 per QALY gained. These values are also higher than those presented in the CS.¹³

Table 41: Amended base case and scenario analysis results for HeFH primary and secondary prevention analyses

Analysis	Population characteristics and comparison	Evolocumab		Ezetimibe		Incremental		
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER
HeFH primary and secondary prevention - cohort analysis - base case analyses								
Analysis G	ST (evo+statins vs eze+statins)	10.17	£73,620	9.02	£19,431	1.15	£54,189	£47,195
Analysis H	SI (evo vs eze)	9.82	£72,303	8.77	£19,817	1.05	£52,486	£49,900
HeFH primary and secondary prevention - cohort analysis - scenario analyses								
Analysis I	SI (evo+eze vs eze)	10.01	£77,481	8.77	£19,817	1.24	£57,664	£46,685
Analysis J	ST (evo+eze+statins vs eze+statins)	10.23	£78,604	9.02	£19,431	1.20	£59,172	£49,138

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe

Table 42: Amended summary of probabilistic sensitivity analysis results

Analysis	Population characteristics and comparison	Probabilistic ICER evolocumab+/-statins vs. ezetimibe+/-statins	Probability evolocumab+/-statins optimal at willingness-to-pay threshold	
			λ=£20,000/QALY gained	λ=£30,000/QALY gained
HeFH primary and secondary prevention - cohort analysis				
Analysis G	ST (evo+statins vs eze+statins)	£48,664	0.00	0.00
Analysis H	SI (evo vs eze)	£51,061	0.00	0.00

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe

5.3 Critical appraisal of the company's health economic analysis

5.3.1 Methods for reviewing the company's economic evaluation and model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which the analysis is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists^{48,67} to critically appraise the company's model and analysis.
- Scrutiny of the company's model by health economic modellers and discussion of identified issues amongst all members of the ERG.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and assumptions underlying the company's model.
- A partial re-build of the deterministic version of the company's model to assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any errors in the implementation of the model. It should be noted that this double-programming exercise was undertaken using the transition probabilities calculated within the company's model and did not include the replication of these by the ERG.
- Examination of concordance between the description of the model reported within the CS¹³ and the company's executable model.
- Replication of the base case results, PSA, 1-way sensitivity analysis and scenario analysis presented within the CS.¹³
- Checking of parameter values used in the company's model against the original data sources.

The ERG notes that the methods and results of the economic analysis presented in the CS are reported over more than 110 pages, and are accompanied by several detailed appendices covering specific elements of the model, including the methods for estimating calibration factors and reviews of "real-world" studies, resource valuation studies and risk equations. Consequently, the critical appraisal presented in this section refers to the most important issues identified by the ERG. It is possible that given the wealth of information submitted by the company, the ERG critique may not be exhaustive and some less substantial sources of bias may not have been identified.

5.3.2 Summary of main issues identified within the critical appraisal

Box 2 summarises the main issues identified within the ERG's critical appraisal of the company's submitted health economic analysis. These issues are discussed in further detail in the subsequent sections.

Box 2: Summary of main issues identified within the critical appraisal of the company's model

1. Deviations from the NICE Reference Case⁶⁸
2. Concerns regarding the conceptualisation and implementation of the company's model structure and logic
3. Concerns regarding the populations and baseline characteristics included in the company's analyses
4. Issues regarding the use of CVD risk equations and the need for subsequent calibration
5. Concerns regarding the derivation of calibration factors to adjust the baseline risk of CVD for the raised LDL-C analysis
6. Issues surrounding the derivation of the calibration factor to adjust the baseline risk of CVD for people with HeFH
7. Concerns regarding the appropriateness of treatment effects
8. Comments regarding the relationship between LDL-C reduction and CVD events
9. Limited relevance of health utility estimates
10. Discrepancies in the cost parameters used in the company's model
11. Errors in the interpretation/reporting of health economic results

(1) Deviations from the NICE Reference Case

Table 43 summarises the extent to which the company's submitted health economic analysis adheres to the NICE Reference Case.⁶⁸

Table 43: Adherence of the company's economic analysis to the NICE Reference Case

Attribute	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The scope of the company's health economic analysis is partly in line with the NICE scope. Within the non-familial primary hypercholesterolaemia population, the company focuses on a subgroup (those with LDL-C > 2.5 mmol/L for non-familial) of patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies, would be considered. It is unclear whether this modelled population fully reflects the population of people unable to reach LDL-C goals with the maximum tolerated dose of a statin. The ERG also notes that the analysis of the HeFH population is presented for a combined population of those patients who have a history of CVD and those who do not have a history of CVD. The ERG would suggest that for clinical and economic reasons, these populations should be considered separately.
Comparator(s)	As listed in the scope developed by NICE	The comparators used are in line with the final NICE scope. ⁴ Ezetimibe (alone or in combination with statins) is considered in all analyses. Comparisons against statins alone are also presented within the CS, ¹³ although the ERG notes that these are not included within the final NICE scope. ⁴
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health benefits relate to those enjoyed by NHS patients.
Perspective on costs	NHS and PSS	An NHS perspective is considered. Costs borne by PSS are excluded from the company's economic analysis.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The model estimates the incremental cost per QALY gained for evolocumab (with/without ezetimibe and or/statin therapy) versus ezetimibe (with/without statin therapy).
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A lifetime horizon is used in the company's base case analysis. Shorter time horizons are considered within the company's scenario analyses.
Synthesis of evidence on health effects	Based on systematic review	The risk of CVD events is derived from two published algorithms: the Framingham equations⁵³ for first CVD events, and the REACH Registry equations⁵⁴ for subsequent CVD events. These risks are then adjusted using a process of calibration. The main efficacy parameters (relative reductions in LDL-C) are taken from the LAPLACE-2 trial for patients who are able to take statins and from GAUSS-2 for patients for whom statin therapies are contraindicated or not tolerated. These are individual studies included within the company's systematic review. The relationship between a reduction in LDL-C and CVD events is taken from a meta-analysis published by the CTTC.

Attribute	Reference case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health outcomes are valued using QALYs. Utility values are taken from a range of sources; these are however dated and are not all are measured using the EQ-5D questionnaire but are instead based on TTO valuations. Some utility values used do not correspond to the health state intended to be reflected in the company's model.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
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	The company's model uses cost estimates taken from the NHS Drugs Tariff, ⁶¹ NHS Reference Costs, ⁶² the PSSRU ⁶³ and an analysis of CPRD/HES data. ¹³ The cost of evolocumab was sourced from the company. ¹³
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits are discounted at 3.5%

The company's health economic model partly meets the requirements of the NICE Reference Case.⁶⁸ Within the analyses of the non-familial populations, the company's model includes only patients with a baseline LDL-C > 2.5mmol/L. Clinical advice received by the ERG suggests that the inclusion of a population only with an LDL-C > 2.5mmol/L is likely to exclude most UK individuals. Clinical experts suggested that most UK individuals with CVD currently attain a target of LDL-C of 2mmol/L on statins. Hence, clinical experts felt that the population included in the economic model is likely to be a small residual population of people in the UK. It is also unclear whether this specifically reflects the population of people unable to reach LDL-C goals with the maximum tolerated dose of a statin, as indicated within the wording of the marketing authorisation for evolocumab.²⁶ It is further noteworthy that within the HeFH population, the model evaluates a mixed population of patients who have a history of CVD events and people who have no history of CVD. Clinical advice received by the ERG suggests that it may be more appropriate to evaluate these two populations separately. The ERG notes that the ICERs for both separate populations are however similar, based on the submitted company's model. The interventions and comparators included in the company's model are appropriate and reflect the marketing authorisation for evolocumab. The time horizon, perspective and discount rate

are appropriate. No additional equity weighting is applied to estimated QALY gained. Issues surrounding the prediction of baseline risk, relative treatment effects, the measurement and valuation of HRQoL and costs are detailed in the subsequent sections.

(2) Concerns regarding the conceptualisation and implementation of the company's model structure and logic

The ERG has a number of concerns regarding the company's implemented model: some of these represent major mathematical errors whilst others indicate the improper use of the available evidence. Consequently, the ERG has serious doubts regarding the validity of the results presented within the CS and would advise considerable caution in their interpretation and use in informing decision-making. The main concerns identified by the ERG can be separated into four sets of issues: (a) the company's general modelling approach; (b) the conceptual representation of the condition; (c) the model process and logic; and; (d) model implementation and misspecification of evidence inputs. These conceptual and structural problems are complex and intertwined, and the resolution of individual issues in isolation would not result in an appropriate or credible model. Rather, the ERG considers that the joint resolution of these problems would require a 'full' rethinking of the model's logic. As such, their impact on the expected cost-effectiveness of evolocumab is not clear. It should also be noted that based on the company's existing model structure and the information provided within the CS,¹³ the ERG is unable to amend the company's model to produce an analysis which aligns a logically consistent model structure with conceptually appropriate model inputs.

(a) General modelling approach

The company's model adopts a cohort Markov approach. Whilst previous economic evaluations of cholesterol lowering therapies have also followed this general methodology, this imposes significant constraints and a number of assumptions are required in order to relax the "memoryless" property of the Markov approach. This is particularly relevant in instances whereby the model is required to account for patients' histories of multiple CVD events and whereby the risk of such events is ongoing over time. Whilst the derivation of the Markov trace and subsequent costs and health effects in the company's model is straightforward (see Section 5.2.2), the preceding derivation of calibrated baseline event risks is convoluted and difficult to follow, both in terms of logic and implementation using mathematical formulae. Although this issue is minor compared with the other structural issues described below, implementing the model as a patient-level simulation may have increased the transparency and flexibility of the model, required fewer assumptions to account for previous CV events and may have obviated problems relating to the handling of competing risks of first and subsequent fatal and non-fatal CVD events.

(b) Conceptual representation of the condition

Health states within the company's model are defined by CVD events; this is appropriate for modelling cholesterol lowering therapies. However, the choice of which health states (CVD events) should be included in the model is a matter of debate. The company conducted an impressive review of 108 previous economic models; one of these included studies related to the model developed to inform NICE CG181.¹⁵ However, as noted in Section 5.1, the CS provides only a very brief summary of the included studies and the extent to which this review has been used to inform the company's model structure is unclear. In particular, the ERG notes that the health states used in the company's model are different to those used in the NICE CG181 model.¹⁵ The CS does not include a description of how the health states were selected nor does it explain why these should be considered more relevant than those states included in the NICE CG181 model (or indeed within any of the other 107 published economic evaluations identified within the company's review).

In particular, the company's model has the following features: (a) the inclusion of HF as a health state; (b) the inclusion of only IS as opposed to any stroke (e.g. haemorrhagic), and; (c) the use of composite health states which include a combination of up to three individual health states (e.g. ACS plus post-IS plus post-HF). The ERG has concerns regarding the inclusion of the HF state given the paucity of data on the impact of cholesterol lowering therapies on this type of event or the impact of CHD death following HF. This issue is recognised within the CS¹³ (page 197), hence its inclusion in the model is unclear. Notably, the CS states that *"patients in HF health states (either single or combined) experience no further treatment effect due to LDL-C lowering for risk of recurrent HF since findings suggest lack of benefit for lipid-lowering therapies once patients experience HF on events such as CHD death"* (CS¹³ page 197). This appears to be inconsistent with what is done in the company's model whereby a reduction in LDL-C in patients with HF (in either an acute, post-event state or combined health state) is associated with a reduction in CHD death. Furthermore, the company does not provide any justification regarding the inclusion of only IS. However, the ERG notes that based on the CTTC meta-analysis,²⁸ the effect of LDL-C reduction, which is used as a surrogate for CVD event reduction, is greater for IS compared with any stroke (RR = 0.69 for IS versus 0.74 for any stroke). Further, whilst it is plausible that people may experience multiple different types of CV events over their lifetime, there are no data available to inform these transitions and therefore the company's model makes a number of arbitrary assumptions regarding maximum event risk to in order populate these cells in the transition matrix. This may be considered to increase uncertainty rather than accuracy in the model's results.

As described in Section 5.2, the company's model uses absolute LDL-C reduction as a surrogate for relative reduction in CVD events. The ERG notes that LDL-C reduction has been accepted as a surrogate in previous appraisals.¹⁴ Little justification is provided regarding why other potential

surrogates such as HDL-C or total cholesterol were not considered. Clarification was requested from the company regarding the use of this surrogate in the economic model (see clarification response,³⁵ question B10). In their response, the company stated:

“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. This evidence comes from a range of studies including epidemiological studies, genetic variants (both gain-of-function and loss-of-function), and interventional studies with LDL-C-lowering therapies. In contrast, 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. Therefore, other markers were not considered. Although evolocumab also has a significant positive effect on other lipid markers (e.g. non-HDL-C and Lp[a]), the primary effects of evolocumab are on LDL-C. We anticipate that improvements in these other markers may contribute to reduction in CV risk, but in the absence of data supporting the impact of altering these markers on CV risk, they were not used in the model as a surrogate.” (Clarification response,³⁵ question B10).

Whilst the ERG acknowledges the lack of data on the impact of evolocumab on CVD events, it is important to reiterate that the reliance on the use of a surrogate endpoint contributes to the overall uncertainty in the model. Given the current clinical evidence base, it remains unclear whether evolocumab is associated with a benefit in terms of reduced CVD events and specifically whether the effect of evolocumab would be commensurate with benefits observed for other lipid-lowering therapies (e.g. statins and ezetimibe).

(c) Model process and logic

For the analysis of patients with non-familial primary hypercholesterolaemia (based on a subset of the LAPLACE-2 trial²³), the company’s model uses a three-step approach to estimate the risk of CVD events. This involves: (i) using of the Framingham⁵³ and REACH Registry⁵⁴ equations to predict the baseline risk of CVD events depending on individual characteristics in a subset of the LAPLACE-2 trial; (ii) estimating calibration factors to adjust predictions from the Framingham and REACH equation to “real world data” (estimated from the company’s analysis of CPRD/HES data), and; (iii) adjusting the baseline risks estimated using the Framingham and REACH Registry equations by these estimated calibration factors.

The ERG has concerns regarding this overall modelling approach. Specifically, the ERG believes the approach used by the company to be circular, overly-complicated and counter-intuitive, as it requires a number of assumptions and adjustments when estimating and applying the calibration factors (see

Section 5.2.2). The ERG notes that based on information provided within the CS¹³ and during the clarification process,³⁵ the baseline risk of experiencing CV events could have been estimated directly from the company's CPRD and HES analysis, and that the use of the Framingham and REACH equations is not necessary as it does not appear to provide additional information compared with using the CPRD and HES data. In effect, the company's approach involves estimating CV risk using equations then adjusting these to reflect real-world CPRD/HES data rather than using the CPRD/HES data directly. The ERG sought clarification from the company regarding this matter (see clarification response,³⁵ question B33). The company's response stated that:

“...the economic model could indeed have directly used the CPRD study event rates to model an overall high-risk population as per the study cohort definitions. However, this approach would not have permitted us to assess specific high-risk populations such as those with existing CVD with 1 or 2 additional risk factors who remain at the highest residual risk.”

The ERG considers the company's response to be unsatisfactory because: (a) the analyses in individuals with additional risk factors (AF and 2/3 vascular beds) are presented only within the company's subgroup analyses and do not reflect the main population specified in the NICE scope,⁴ and; (b) the company's analysis in patients with existing CVD with one or two additional risk factors employs arbitrary manipulations of the IPD which will ultimately produce biased risk estimates. The ERG considers that it would have been more appropriate to estimate baseline CVD risk from the CPRD/HES data and to subsequently adjust these using relative risks from the published literature to reflect these additional risk factors. It is also noteworthy that the company's process for estimating CVD risk in all populations requires several other assumptions (e.g. removing the effect of age and sex), the validity of which are unclear.

(d) Model implementation and misspecification of evidence inputs

Upon scrutinising the company's model, the ERG identified a number of inconsistencies and errors in the model's implementation and logic, which appear to be due to a misinterpretation or misuse of evidence. These are described in below.

Firstly, the company's model treats the predictions from the Framingham⁵³ and REACH Registry⁵⁴ risk equations as event rates (see CS,¹³ Figure 5-4, page 182). However, in response to a request for clarification from the ERG, the company recognised that the risk predicted by these equations are actually probabilities which are bounded between 0 to 1 (see clarification response,³⁵ question B17).

In addition, the company's model misinterprets what the REACH Registry risk equations⁵⁴ are predicting. As detailed in Section 5.2, the REACH Registry risk equations predict: (i) the risk of any

“next cardiovascular event”, which includes any fatal and non-fatal CVD events, and; (ii) the risk of “cardiovascular death” which includes only fatal events. However, the company treats predictions from the REACH Registry risk equations for “next cardiovascular event” and “cardiovascular death” as being independent of one another and assumes that the risk for “next cardiovascular event” predicted by the REACH Registry equation includes only non-fatal events. This is incorrect and was confirmed through correspondence between the ERG and the author of the REACH Registry paper.⁵⁴ This has important implications in that it invalidates the calibration factors estimated using the CPRD/HES dataset and also inflates the number of non-fatal CVD events predicted by the model. Since the model artificially inflates total CVD risk, the ICERs for evolocumab are likely to be underestimated.

Further, since the model estimates the risk of fatal and non-fatal CVD events separately and without constraint, this leads to mathematical inconsistencies when the risk of fatal and non-fatal CVD events is high. Consequently, when the sum of predicted probabilities for fatal and non-fatal CVD events exceeds 1, this leads to a situation whereby some of the transition probabilities and health state populations become negative. This error is accentuated by the use of calibration factors which have been estimated independently for fatal and non-fatal events. As discussed in Section 5.2, this unequivocal error was raised by the ERG at the clarification stage in order to provide the company with an opportunity to re-submit an amended version of the model which was mathematically sound. In response, the company recognised that results for the non-familial population were “invalid” due to the presence of negative probabilities, yet the amended model did not include a correction of the underlying mathematical inconsistency. Instead, the company introduced arbitrary adjustments to some transition probabilities to prevent the model from generating negative probabilities for the HeFH population; this amendment results in slightly lower CV risks for the HeFH population. The ERG notes that whilst this is a structural problem, the company’s amendment treats this as a parametric issue. The ERG highlights that it should not be possible under any combination of model parameter inputs for transition probabilities or health state populations to be negative, even at the highest levels of predicted CV risk. Despite the company’s amendment to the model, negative probabilities are still possible when different input parameters are used, for example, when the cap for age is increased from 85 to 90 years, or when the adjustment factors for the HeFH population are increased to the upper CI reported within the CS.¹³ As such, the company’s amended model does not resolve the problem, it simply makes it less visible.

There also appears to be some confusion and inconsistency in terms of the general logic of the company’s model. The company estimates the risk of CVD using baseline characteristics at entry into the LAPLACE-2/RUTHERFORD-2 trials and uses the LDL-C at baseline to represent the risk of CVD for people treated with statins. However, the model then applies the treatment effect (a relative

reduction in LDL-C) for ezetimibe and evolocumab calculated from the treatment difference (statins versus ezetimibe or evolocumab) at the mean of weeks 10/12, rather than based on the change from baseline. The ERG believes there is a mismatch as the treatment effect used in the model does not match the baseline LDL-C level from which it is estimated. This leads to a larger treatment effect being used in the model (treatment difference of -71.8% at week 10/12 against statins vs. -64.33% from baseline in the LAPLACE-2 trial). The impact on the ICER is unclear as this over-estimates the absolute reduction in LDL-C and hence also the relative reduction in CVD events. However, the ERG notes that this inconsistency affects both the ezetimibe and evolocumab groups and is somewhat mitigated by the constraint included in the company's model whereby LDL-C after treatment cannot decrease below 40mg/L (equivalent to 1.03mmol/L).

With respect to the HeFH population, the CS¹³ (page 191) acknowledges the lack of a specific CV risk equation for these patients. Hence, the company's model estimates the risk of CVD events using the Framingham⁵³ and REACH Registry⁵⁴ risk equations in the RUTHERFORD-2 trial and then adjusts this using a relative risk for the HeFH population based on Benn *et al.*⁵⁵ The ERG considers this to be inappropriate since the baseline risk in the non-HeFH population used in the company's model already reflects people who are at a higher risk due to higher baseline cholesterol. A more appropriate approach would have involved applying the HeFH adjustment factor to the baseline risk of CVD for the general population; this would have been consistent with the nature of the relative risk estimated within the Benn study.

As a consequence of these problems, the ERG urges caution in the interpretation and use of all of the results presented in the CS¹³ and the subsequent addendum.⁵²

(3) Concerns regarding the populations and baseline characteristics included in the company's analyses

Baseline characteristics for the non-familial primary hypercholesterolaemia population are taken from a subset of the LAPLACE-2 trial; for the HeFH population, these are based on the modified ITT population of the RUTHERFORD-2 trial. These are used to estimate baseline CVD risk then to calculate the absolute LDL-C reduction for evolocumab and ezetimibe. The ERG notes that there is uncertainty with respect to whether the populations included in the LAPLACE-2 and RUTHERFORD-2 trials are representative of primary hypercholesterolaemia people in England (see Chapter 4). Whilst the company's analysis of the non-familial population includes only those patients in LAPLACE-2 who had a baseline LDL-C > 2.5mmol/L, it is unclear whether this truly reflects a high-risk population who may benefit from treatment using evolocumab. The ERG also notes that the model assumes the same baseline characteristics in terms of age, gender, LDL-C and other covariates (and hence the same baseline risk of CVD events) for patients who are able to take statins and those

for whom statins are contraindicated or not tolerated. It is likely that CVD risk is related to whether a patient's LDL-C can be controlled using statins; as such the use of baseline characteristics from the GAUSS-2 trial may be more appropriate for the evaluation of patients who are unable to take statins. The CS¹³ (page 174) makes the following statement regarding why data from the LAPLACE-2 and RUTHERFORD-2 trials were assumed for both statin tolerant and intolerant populations:

“LAPLACE-2 and RUTHERFORD-2 were used instead of GAUSS-2, since patients that are intolerant or contraindicated to statins are anticipated to have a greater severity of hypercholesterolaemia as they cannot achieve adequate LDL-C control with lipid-lowering therapies (e.g. low dose statin or alternative lipid-lowering therapy). Baseline LDL-C levels were 2.7 mmol/L to 2.9 mmol/L, 3.9 mmol/L to 4.2 mmol/L, and 5.0 mmol/L to 5.1 mmol/L in LAPLACE-2, RUTHERFORD-2 and GAUSS-2, respectively. Therefore, the LAPLACE-2 and RUTHERFORD-2 patient populations were used with additional cost-effectiveness analyses based on severity of hypercholesterolaemia (baseline LDL-C) to represent populations that are intolerant or contraindicated to statins.” (CS,¹³ page 174)

This argument appears somewhat contradictory in that the CS argues that the average LDL-C level is higher in statin intolerant patients, yet the company's model uses the LDL-C from LAPLACE-2 (which includes primarily statin tolerant patients) and is lower than what was observed in the GAUSS-2 trial. The ERG believes that the GAUSS-2 population would be more representative of patients for whom statin therapy is contraindicated or not tolerated. The ERG acknowledges that assumptions would be required for the evaluation of the HeFH population.

The CS¹³ (page 174) further states that: *“the patient populations from LAPLACE-2 and RUTHERFORD-2 were used since statin intolerance or contraindication is considered a subgroup of the primary hypercholesterolaemia and mixed dyslipidaemia, and HeFH populations.”* Whilst the ERG believes the statement from the company to be correct, it should be noted that as the LAPLACE-2 and RUTHERFORD-2 trials include a mix of people who are able to take statins and who are contraindicated or intolerant to statin therapies, the analyses presented by the company for patients who are able to take statins (which are based on the treatment effect calculated across of the overall LAPLACE-2 and RUTHERFORD trials) actually reflect the results for the overall population which includes a mixture of statin tolerant and intolerant populations.

The ERG also questions the baseline characteristics used within the company's subgroup analyses. The company conducted a number of analyses in people with diabetes, AF or 2/3 vascular beds. In these analyses, the company's model assumes that all patients have the specific subgroup characteristic, whilst all other baseline characteristics are held at their observed baseline values.

However, people with diabetes, for instance, are likely to have different characteristics to those patients included in the LAPLACE-2 trial, specifically in terms of cholesterol level, history of CVD and other risk factors.⁴⁵ The ERG sought clarification on why the company adopted this approach, rather than selecting out the smaller subset of patients who actually had these particular characteristics (see clarification response,³⁵ question B15). In response, the company did not provide a rationale but instead provided a comparison of predicted CVD risk for patients with diabetes in the LAPLACE-2 trial (n=61) versus the company's subgroup approach. Whilst the predicted risks using the alternative approaches were broadly in agreement, the ERG believes that the approach used by the company is arbitrary and notes that people with type 1, newly diagnosed or poorly diagnosed type 2 diabetes were excluded from the trial, thereby limiting the relevance of the comparison provided in the company's response.

(4) Issues regarding the use of CVD risk equations and the need for subsequent calibration

As discussed above, the ERG has concerns regarding the need to use risk equations in the model (with subsequent calibration) rather than using direct data on observed CVD event rates, and the misinterpretation and use of the REACH Registry⁵⁴ risk equations. In addition, the ERG has concerns regarding the choice of risk equations and how these are used in the company's model. Whilst alternative risk equations are available (e.g. the QRISK2,²² upon which the model developed to inform NICE CG181¹⁵ was based), the company's model uses the US Framingham risk equation⁵³ to estimate the 10-year risk of CVD in people without a history of CVD. The CS¹³ justifies this choice based on three points:

- (i) The US Framingham risk equations⁵³ include a broader definition of events compared with the UK QRISK2 equations.²² Whilst this is true, the ERG considers this argument to be mitigated by the fact that the company then calibrates the Framingham risk estimates using data from CPRD/HES.
- (ii) Fewer variables are required to estimate the 10-year risk of CVD using the Framingham equations compared with the QRISK2 equations.²² The ERG sought clarification regarding which additional variables would be required and whether these would be available in the evolocumab trials (see clarification response,³⁵ question B12). In response, the company provided a table summarising the variables in QRISK2 that fully align, partially align or do not align with data collected within the evolocumab trials. The ERG agrees that using QRISK2 would have been more difficult and would have required further assumptions, compared with the US Framingham risk equation.
- (iii) The CS¹³ asserts that CVD event rates would need to be calibrated irrespective of the choice of risk equation. The ERG requested clarification from the company regarding the basis of this assertion (see clarification response,³⁵ question B14). The company responded that calibration is necessary for two reasons: (a) the narrower definition of CVD events based on

the QRISK2 equations, and; (b) the representation of a higher risk population within the company's economic model. Whilst the arguments suggested by the company are reasonable, the ERG notes that whilst not stated explicitly, the US Framingham equation suffers from the same biases as the QRISK2 equations as this was not developed in a high-risk population.

Overall, whilst the ERG considers that the QRISK2 equation would require additional assumptions compared with the Framingham risk equations and that other risk equations are available, the arguments provided by the company appear insufficient in that they suggest that neither Framingham nor QRISK2 are appropriate and that the use of either would require calibration and/or adjustment.

In the secondary prevention setting, the REACH equations include a variable for whether the individual is receiving statin treatment or not. This variable is set to "yes" both in the analyses for patients who are able to take statins and for patients who are unable to take statins. The ERG believes that the variables should be set to "no" for the analyses relating to patients for whom statin therapy is contraindicated or not tolerated. This is likely to increase the risk of CVD in statin intolerant populations and likely to result in an improvement in the ICER for evolocumab.

Within the non-familial secondary prevention subgroup analyses which include diabetes as an additional risk factor, the company's model estimates CV risk using the REACH equations together with arbitrary assumptions regarding the presence/absence of particular baseline characteristics. The ERG considers that whilst the REACH Registry equations include a variable for diabetes, the UK Prospective Diabetes Study (UKPDS) could have been used. The ERG sought clarification from the company regarding why the UKPDS risk engine was not used to assess CV risk in the diabetic population and to discuss the limitations of using the Framingham equations in the diabetic population in the CPRD dataset (see clarification response,³⁵ question B13). In response, the company stated that *"The UK Prospective Diabetes Study (UKPDS) risk equation is indeed relevant for estimating risk of a first CV event in a diabetic population without existing CVD. As a diabetic population was not specifically modelled, we did not feel it was necessary to use this risk equation to estimate baseline CV risk"* (Clarification response,³⁵ question B13). Whilst no analysis is presented for primary prevention in people with diabetes, the ERG disagrees with the response provided by the company as the UKPDS risk equations can also be used to estimate the risk of subsequent CV events and therefore could have been used for the secondary prevention analyses in patients with diabetes. It should be noted that for primary prevention, the QRISK2 risk assessment tool is recommended to assess CVD risk in people with type 2 diabetes.

As noted above, the analyses undertaken in the HeFH population reflects a mixture of those people who have a history of CVD and those who do not. Advice received by the ERG suggests that from a

clinical perspective, it would make more sense to consider the two populations separately. Further, from an economic standpoint, the same is true as combining the two separate populations groups may lead to erroneous recommendations on the use of health technologies which are efficient in one population but not in another. Within the HeFH primary/secondary prevention analysis, the Framingham and REACH equations are applied to the entire cohort of people recruited into the trial, irrespective of their history of CVD. This is not appropriate, as the Framingham equations are appropriate only in people without a history of CVD and the REACH equations are appropriate only in people with a history of CVD. The ERG sought clarification from the company regarding why the 10-year risk was calculated for the overall population in the RUTHERFORD-2 trial in the HeFH population (see clarification response,³⁵ question B31). In response, the company stated that: *“the Framingham equation was only applied for transitions for HeFH patients without existing CVD (i.e. primary prevention). The primary and secondary prevention populations in HeFH were not evaluated separately to reflect the decision problem. The economic model cannot assess primary and secondary prevention cohorts simultaneously, therefore average cohort patient characteristics from the primary and secondary prevention population from RUTHERFORD-2 are used for the cost-effectiveness analysis.”*

The ERG considers the response from the company to be unsatisfactory and somewhat contradictory. For clarity, in the company’s implemented model, the 10-year risk of CVD estimated using the Framingham equation is estimated from the entire RUTHERFORD-2 trial population; this risk is only applied for the transition between the no CVD to CVD states. The company appears to suggest that the primary and secondary prevention analyses cannot be estimated simultaneously. The ERG disagrees with this statement as this is what is currently done in the model, i.e. a proportion of the cohort enters the model in the no CVD state and the remaining patients enter the model in the ECVD and post-event states. The model does however have the functionality to consider the primary prevention and secondary prevention HeFH populations separately. The ERG notes that the NICE scope does not specify whether the population should be evaluated separately or as a combined group.

(5) Derivation of calibration factors to adjust the baseline risk of CVD for the raised LDL-C analysis
The CS contains only limited information regarding the process of calibration of risk factors. However, the company also submitted an accompanying appendix which provides further details on the methodology adopted. Owing to time constraints, the ERG was unable to provide a full assessment of this but note several concerns regarding the derivation and validation of the company’s calibration factors:

- (a) Given the lack of reliability of the Framingham equations in people with diabetes, it is uncertain if the resulting calibration factors would be appropriate for the population included

in the economic model which does not reflect a diabetic population. The extent of this potential bias is uncertain.

- (b) The company appears to have made a complicated age adjustment in order to be able to compare the predictions from the risk equations with the event rates in the CPRD/HES data. The comparability of the two is unclear.
- (c) The calibration factors estimated for secondary prevention of non-fatal events are incorrect due to the misuse of the REACH equations, as described above.
- (d) A number of assumptions are also made when the baseline characteristics are not available in the CPRD/HES data (e.g. presence of AF and number of vascular beds). These variables are used to predict the risk of secondary events, and therefore may bias the REACH predictions and associated calibration factors.
- (e) Linking data from the CPRD, HES and ONS meant that only half of the people could be linked and included in the analysis. This reduces the sample size and is likely to introduce selection biases. The extent of this bias is uncertain.

In brief, the ERG has concerns regarding the calibration factors and re-iterate that estimating the event rate from the CPRD/HES data may have produced less bias than predicting CV risk using risk equations which were considered by the company *a priori* to produce inaccurate predictions of CV event risk.

(6) Issues surrounding the derivation of the calibration factor to adjust the baseline risk of CVD for people with HeFH

The company assumes a relative risk of 7.1 for CVD events for People with HeFH (relative to people without HeFH), based on study reported by Benn *et al.*⁵⁵ The ERG sought clarification from the company regarding the derivation of their estimated relative risk. Following clarification, the ERG is satisfied with the mathematical approach used by the company to calculate this parameter value. However, the ERG questions the value used for the following reason. The Benn *et al.*⁵⁵ study provided a comparison of the risk of CVD events between the general population and patients with HeFH. However, in the company's model, this relative risk is applied to an already high-risk population (people with an LDL-C > 2.5 mmol/L). As such, this is likely to over-estimate the risk of CVD events in the company's analyses within the HeFH population. The magnitude of this bias is uncertain. Furthermore, a UK study by Neil *et al.*⁶⁹ reported a lower standardised mortality ratio (SMR) for CHD in people treated with statins; the SMR was 1.03 for primary prevention and 3.88 for secondary prevention in people aged between 20 to 79 years old. A broadly similar SMR was reported in a recent Norwegian study based on registry data from 4,688 male and female individuals from the Unit for Cardiac and Cardiovascular Genetics (UCCG) Registry with verified molecular genetic diagnosis of familial hypercholesterolemia linked to the Norwegian Cause of Death Registry. The study

reported that compared with the Norwegian population, CVD mortality was significantly higher in the UCCG Registry in all age groups younger than 70 years (SMR 2.29, 95% CI 1.65 to 3.19 in men and women combined; SMR 2.00, 95% CI 1.32 to 3.04 in men; SMR 3.03, 95% CI 1.76 to 5.21 in women). The SMR across all ages (including people over the age of 70 years old) was 1.56 (1.41 in males and 1.75 in females).

The ERG recognises that there are methodological and country differences between the studies that may explain estimated differences in risk. The ERG believes that data from the Neil *et al*⁶⁹ study may be more appropriate as this is a UK source. Furthermore, estimates from this study are in line with recent data reported in Norway. However, several assumptions would be required as this study only reported on differences in the risk of fatal events. It is also worth noting that a UK study showed that people with treated HeFH are not at increased risk of fatal stroke compared with general population.⁷⁰ The ERG notes that assuming a lower HeFH adjustment factor (which is more plausible) would lead to (potentially substantial) increases in the ICER for evolocumab in the HeFH population.

(7) Concerns regarding the appropriateness of treatment effects

For the analyses in people who are able to take statins, the company applied the treatment effect (reduction in LDL-C) calculated from the treatment difference at the mean of week 10/12 between evolocumab and ezetimibe compared with statins. As mentioned above, the ERG believes that the treatment effect calculated from change from baseline is more appropriate. The ERG is generally satisfied with the company's approach for using the mean of week 10/12. The company also uses the pooled treatment effect calculated from a random effects model. Given the absence of heterogeneity, the ERG considers this to be unnecessary.

For the non-familial population analyses in patients who are able to take statins, the company uses the treatment effect calculated from the overall LAPLACE-2 trial population despite including only a subset of this population in the health economic model. Clarifications were requested from the company to provide additional analyses of treatment effect for the subgroup of people included in the model (i.e. patients in the LAPLACE-2 trial with an LDL-C > 2.5 mmol/L) for primary prevention and secondary prevention separately (see clarification response, question B4). The treatment effects were provided by the company (available in the clarification response document); however, given the structural issues in the model, these were not considered further by the ERG.

For the HeFH analysis in patients who are able to take statins, the company uses the treatment effect from the LAPLACE-2 trial rather than the RUTHERFORD-2 trial, despite the latter specifically relating to the population under consideration. The company provides three reasons for this: (i) the absence of head-to-head data in HeFH for evolocumab plus statins versus ezetimibe plus statins; (ii)

the treatment effects from LAPLACE-2 and GAUSS-2 are deemed to be generalisable to the HeFH population since the treatment effect of evolocumab was consistent regardless of the population and individual characteristics, evolocumab dosing regimen (140 mg Q2W or 420 mg QM), and presence and type of background lipid-lowering therapy, and; (iii) this approach was used in NICE TA132 whereby the treatment effect of ezetimibe in people without HeFH was assumed to be generalisable to people with HeFH.

The ERG believes that the treatment effect for evolocumab from the RUTHERFORD-2 trial should be used for the HeFH population who are able to take statins. Whilst the ERG recognises the lack of effectiveness data for ezetimibe, the ERG notes that the treatment difference (calculated using the random effects model) between statin and evolocumab Q2W at the mean of week 10/12 appears to be statistically greater in the LAPLACE-2 trial (non-familial) compared with the RUTHERFORD-2 trial (HeFH population) with no overlap between the confidence intervals: LAPLACE-2 trial (-71%; -74.7% to -68.9%) vs. RUTHERFORD-2 trial (-61.3%; -67.2% to -55.4%). The ERG believes that a better approach would have been to use the treatment effect calculated from the RUTHERFORD-2 trial for evolocumab and possibly to make a conservative assumption for ezetimibe assuming the effect from the LAPLACE-2 trial or alternatively, to calculate the treatment effect between ezetimibe and evolocumab from the LAPLACE-2 trial and to apply this treatment effect to the evolocumab treatment effect from the RUTHERFORD-2 population.

In patients unable to take statins, the company uses the treatment effect from baseline from the GAUSS-2 trial for both the non-familial and HeFH populations. The ERG is generally satisfied with the approach used by the company in the absence of data for this population.

Within the model, the company assumes that the treatment effect is maintained indefinitely based on evidence from the OSLER studies which demonstrate a sustained reduction in LDL-C up to 2 years. It is however uncertain if the treatment effect would be maintained beyond this point.

The treatment effects from the LAPLACE-2 and RUTHERFORD-2 trials are used independent of baseline characteristics and presence of diabetes or risk factors. It is unclear whether the treatment effect would be the same between the overall population and people with diabetes or other risk factors.

Finally, for the analyses whereby evolocumab is used in combination with ezetimibe, the company assumed that the treatment effect of evolocumab would be sequential to the treatment effect following ezetimibe, i.e. that the treatment effect of evolocumab versus statins would apply to the LDL-C following ezetimibe. This is uncertain.

(8) Comments regarding the relationship between LDL-C reduction and CVD events

Findings from the CTTC meta-analysis are used to represent the relationship between LDL-C reduction and reduction in CVD events. Despite the source being appropriate, the ERG notes that it is unclear from the CS how this source was identified and whether a systematic review was conducted to identify if alternative sources would have been more appropriate.

Data from the five trials comparing “less versus more” intensive lipid lowering therapies were used, rather than the overall 26 trials included in the meta-analysis. The ERG was satisfied with the rationale provided by the company. The ERG notes that the five trials were conducted in secondary prevention (i.e. people with a history of CVD). It is unclear whether the relationship would be the same in the primary prevention setting. The company also acknowledges that the relationship was for the first (recurrent) CV event and that it is unclear whether the relationship would be maintained for subsequent events.

Assumptions are made by the company which may be considered to be matters of judgement. The company assumes that the relationship between LDL-C reduction and non-fatal MI would hold for HF (first event). The ERG questions this assumption as there is little evidence on the impact of LDL-C reduction on HF. The company further states in the CS (page 194) that *“the rate ratio for new onset HF is equal to MI. Patients in HF health states (either single or combined) experience no further treatment effect due to LDL-C lowering for risk of recurrent HF since findings suggest lack of benefit for lipid-lowering therapies once patients experience HF on events such as CHD death.”* This appears to be inconsistent with what is done in the company’s model where a reduction in LDL-C in people with HF (either acute, post-health state or combined health state) is associated with a reduction in CHD death.

Similarly, the company also uses the relationship observed for non-fatal MI (secondary prevention) for patients transitioning from “No CVD” to “ECVD.” Whilst the ERG recognises the lack of data; this assumption is essentially arbitrary.

The company further assumes that the relative reduction in CV event rate per mmol/L reduction in LDL-C is independent of baseline levels, familial or non-familial hypercholesterolaemia, prognostic factors such as age, gender, co-morbidities (e.g. diabetes), and CV history or burden. The ERG is satisfied with this assumption as this is supported by subgroup analysis in the CTTC meta-analysis.

The company uses a relative risk of 1 (no effect associated with LDL-C reduction) for death due to stroke, rather than the value of 1.04 reported in the CTTC meta-analysis; this is due to the lack of

statistical significance in this outcome. The ERG considers that the reported relative risk of 1.04 should have been used, allowing for the impact of uncertainty in this parameter to be handled within the PSA. Similarly, the company use a relative risk of 0.80 (0.74, 0.87) for CHD death based on the broader set of 26 trials, rather than the five “more versus less” subgroup. The ERG believes that the value of 0.85 from the five “more vs less” trials should have been used for consistency.

The ERG notes also that the relative reduction in fatal CV event rate per mmol/L reduction in LDL-C from the CTTC meta-analysis is applied independently of previous events. This is unlikely to be correct as the reduction in fatal CV events is correlated with the reduction in non-fatal events. However, the ERG recognises the difficulties in including correlation within the model.

(9) Limited relevance of health utility estimates

The company’s estimates of HRQoL were based on estimates used within the model developed to inform NICE CG181.¹⁵ Whilst the company undertook a large systematic review of studies reporting on health utilities associated with individual or multiple CV events (see CS,¹³ Section 5.4), this is not used in any way to inform the company’s *de novo* model. Further, as mentioned in Section 5.2.4.8, the sources of these studies and the instruments used to generate health utilities are not clearly presented within the CS. Of the seven acute and post-event state utilities used in the model, only three of these (ACS, HF and post-HF) are based on EQ-5D valuations; all other health utilities have been taken from studies using the TTO method. This does not satisfy the requirements of the NICE Reference Case.⁶⁸ It is also worth noting that for the HF and post-HF EQ-5D valuations, the health state being valued in the study actually relates to people who have experienced an MI.⁶⁰ Similarly, the health utility for the ECVD state is taken from a study in which people had recently experienced an MI.⁵⁷ Had the company chosen utility studies from their literature review, it is unclear whether such interpolation between valuations for different events would have been necessary. Overall, the ERG considers that the selected health utilities in some instances deviate from the NICE Reference Case and the relevance of some of the valuations to the modelled health states is unclear.

It should also be noted that the linear relationship assumed between age and health utility based on the Dolan EQ-5D valuation study⁵⁶ is crude. A more recent equation based on data from the Health Survey for England (HSE) has been published.⁷¹ The ERG considers that this would have provided a better indication of the relationship between age and background HRQoL.

(10) Discrepancies in the cost parameters used in the company’s model

Overall, the ERG does not have major concerns regarding the costs used in the company’s model, but note that there are some discrepancies.

Advice received from expert advisors to the ERG suggests that the patent for ezetimibe is due to expire in 2018. Whilst the company's model uses current NHS Drug Tariff prices for ezetimibe, it may have been prudent to explore the impact of lower acquisition costs for ezetimibe on the cost-effectiveness of evolocumab.

The ERG also notes that the current prices reported by the Commercial Medicines Unit (CMU)⁷² for atorvastatin are slightly lower than those used in the company's model (atorvastatin 20mg [28 tabs] – eMit price=£1.02 vs NHS Drugs Tariff =£1.41; atorvastatin 80mg [28 tabs] – eMit price £1.90 vs NHS Drugs Tariff=£2.71). This discrepancy has only a very minor impact upon the cost-effectiveness of evolocumab in the statin tolerant population.

The ERG notes also that there are discrepancies in the assumptions regarding monitoring between the CS¹³ and the company's model, and that neither reflects the assumptions used in the model developed to inform NICE CG181.¹⁵ Resource use associated with monitoring assumed in NICE CG181,¹⁵ the CS¹³ and the company's model are summarised in Table 44.

As shown in Table 44, the discrepancy between the CS and the model is minor and is a result of different assumptions regarding LFTs tests and HbA1c test costs. The assumptions employed by the Guideline Development Group (GDG) lead to a lower monitoring cost for subsequent years as they include fewer GP visits. Since the costs of monitoring are low and are common to each treatment group, they do not have a material impact upon the ICER for evolocumab versus ezetimibe, irrespective of the assumptions used.

Health state costs

The ERG is generally satisfied with the health state costs used as these are broadly similar to those estimated within NICE CG181.¹⁵ However, the ERG notes that there may be some double counting due to the separate inclusion of revascularisation costs which may already be accounted for in other health state costs.

Table 44: Resource use associated with monitoring reported in the CS,¹³ NICE CG181¹⁵ and company's model

Resource component	Year 1			Subsequent years			Unit cost reported in CS ¹³	Source
	CS ¹³	Company's model	NICE CG181 ¹⁵	CS ¹³	Company's model	NICE CG181 ¹⁵		
Appointments								
Lipid clinic	2	2	n/a	0	0	n/a	£87.77	NHS Reference Costs 2013/14 ⁶² Curtis <i>et al</i> ⁶³
GP appointment	1	1	1.2	2	2	1	£45.00	
HCA appointment	1	1	2	1	1	1	£6.46	
Blood tests								
Total cholesterol	3	3	2	2	1	1	£1.18	NHS Reference Costs 2013/14 ⁶²
HDL cholesterol	3	3	2	1	1	1	£1.18	
LFT	2	2	2	1	0	1	£1.18	
HbA1 _c	1	1	0	1	1	0	£1.18*	
Totals (assuming GDG assumptions for all items except lipid clinic appointments and based on CS-reported unit costs)								
Total monitoring cost	£238.72	£238.72	£249.56	£102.38	£101.08	£56.19		

*Unit cost of £2.25 applied in company's model

(11) Errors in the interpretation/reporting of health economic results

There are several problems regarding the interpretation of the results presented within the CS. These concern: (a) errors in the interpretation of the results presented in the tables within the CS; (b) reporting of redundant ICERs in the CS, and; (c) misinterpretation of the primary prevention LDL-C threshold analyses.

(i) Errors in the interpretation of the results presented in the tables within the CS

With reference to the company's subgroup analyses of individual risk factors combined with baseline LDL-C, age, and gender (see CS¹³ Table 5-69, and accompanying text on page 279), the CS states:

“Secondly, the impact of combining one of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 5 69). The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000. These results indicate that evolocumab can be considered a cost-effective treatment option in patients with a baseline LDL-C of 3.5 mmol/L and one the following risk factors, when age and gender are taken into consideration:

- *diabetes mellitus*
- *CV risk factors deemed at equivalent risk to diabetes mellitus:*
 - *moderate to severe CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²)*
 - *two or more documented acute ischaemic CV events or revascularisation procedures*
 - *Elevated plasma Lp(a) ≥ 77 mg/dL (≥ 90% centile)*
- *three vascular beds*
- *acute coronary syndrome (ACS) in the past 12 months*
- *other CV conditions that significantly elevate risk of further CV events: atrial fibrillation”*

With reference to the company's subgroup analyses of two risk factors combined with baseline LDL-C, age, and gender (see CS¹³ Table 5-70, and accompanying text on page 281), the CS states:

“Thirdly, the impact of combining two of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 5 70). The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000. These results indicate that evolocumab can be considered a cost-effective treatment option in patients with a baseline LDL-C of 3.0 mmol/L and two of the following risk factors, when age and gender are taken into consideration:

- *diabetes mellitus*
- *CV risk factors deemed at equivalent risk to diabetes mellitus:*
 - *moderate to severe CKD (eGFR < 60 mL/min/1.73 m²)*

- *two or more documented acute ischaemic CV events or revascularisation procedures*
- *Elevated plasma Lp(a) ≥ 77 mg/dL ($\geq 90\%$ centile)*
- *two or more vascular beds*
- *ACS in the past 12 months*
- *other CV conditions that significantly elevate risk of further CV events: heart failure (HF) and atrial fibrillation”*

The ERG notes however that none of the ICERs presented in Table 5-69 or Table 5-70 are below £30,000 per QALY gained. In response to a request for clarification from the ERG, the company stated:

“We can confirm that this text is not applicable to the cost-effectiveness results presented for patients with existing CVD and one or two additional risk factors since all the values in the tables are above £30,000 per QALY gained.” (clarification response,³⁵ question B6).

The ERG suggests that these statements within the CS should be disregarded.

(ii) Reporting of redundant ICERs in the CS¹³

Page 160 of the CS¹³ states that *“The incremental cost per QALY gained is approximately £15,119 to £18,200 for evolocumab versus ezetimibe in patients with HeFH when assessed across the four treatment scenarios.”* As shown in Table 38, the deterministic ICERs for evolocumab versus ezetimibe based on the company’s original model (pre-amendment) are in the range £44,741 to £47,193 per QALY gained. The ICERs reported on page 160 of the CS do not appear anywhere else within the submission. In response to a request for clarification on this matter, the company confirmed that the text quoted above was made in error, and stated:

“The cost-effectiveness results summarised in Section 5, page 160 of the evidence submission, should indeed reflect the incremental cost-effectiveness ratios (ICERs) presented in Tables 5-27, 5-42, 5-47, 5-62 and 5-63 of the evidence submission” (clarification response,³⁵ question B7).

The ERG again suggests that this statement within the CS is disregarded.

(iii) Misinterpretation of the primary prevention LDL-C threshold analyses.

Within the non-familial primary prevention population, the CS presents threshold analyses to identify the minimum 10-year risk required in order for evolocumab (with or without statins) to be considered cost-effective at thresholds of £20,000 per QALY gained or £30,000 per QALY gained when

compared against ezetimibe (with or without statins, see Table 38). Following the identification of the error resulting in negative transition probabilities, the company declared these analyses to be “invalid.” In spite of this, the ERG also has concerns regarding what these threshold analyses were actually suggesting. According to the CS¹³ (pages 23, 173 and 241), the threshold analyses were conducted “*to establish the minimum 10-year CVD risk (measured using a risk assessment tool such as QRISK2) at which treatment with evolocumab in accordance with its MA would be deemed a cost-effective use of NHS resources according to willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained.*” There are two problems associated with the company’s interpretation. First, the company’s model uses Framingham to predict 10-year CV risk in people with no history of CVD. Whilst the Framingham risk equations are effectively bypassed within their threshold analyses by directly inputting the 10-year CV risk level (rather than using the risk equation to generate this), the casemix of people with a risk of x at 10-years calculated using Framingham would be different from that for people with a risk of x at 10-years as calculated using the QRISK2 equation. Secondly, the company’s threshold analyses estimate the optimum threshold based on the risk of experiencing one or more events at 10-years; this is based on the proportion of people who have transited to one of the acute or post-event health states at 10-year in the model (i.e. the sum of the acute and post-event health state populations in the Markov trace at 10-years). Both the QRISK2 and the Framingham equations estimate the 10-year risk of experiencing a first CV event, rather than multiple CV events. Consequently, by considering both the first event and any subsequent events at 10-years the company’s model over-predicts the risk threshold.

Model errors and other issues surrounding model implementation

The ERG partially rebuilt the company’s model in order to assess the logic of the company’s model structure, to draw out any unwritten assumptions and to identify any errors in the implementation of the model. Due to the complexity of the methods by which the company’s model estimates transition probabilities using CVD event risks, age- and sex-adjustments, calibration and the distributions of fatal/non-fatal events, the ERG’s double-programming exercise started from the point at which the baseline transition probabilities had been estimated (i.e. these baseline probabilities were taken directly from the company’s model). The model rebuild was undertaken to estimate costs and health outcomes for evolocumab plus statins, ezetimibe plus statins and statins alone for three scenarios: (i) the LAPLACE-2 high-risk primary prevention cohort-based cost-effectiveness analysis (as presented in CS¹³ Table 5-64); (ii) the LAPLACE-2 high-risk secondary prevention cohort-based cost-effectiveness (as presented in CS¹³ analysis C); and (iii) the HeFH primary and secondary prevention cohort-based cost-effectiveness (as presented in CS¹³ analysis G). Table 45 presents a comparison of total QALYs and costs for each option across each of these three analyses, as estimated by the company’s model and the ERG’s rebuilt model. As shown in Table 45, the results of the ERG’s double-programming exercise are almost exactly the same results as the company’s model, with only

a very slight discrepancy in estimates of total costs. As such, the ERG is satisfied that the Markov component of the company's model has been implemented correctly and without significant error. Ultimately, the more substantive issues relate to the conceptualisation and implementation of the model, specifically in terms of deriving the baseline risks and treatment effects, as described above.

Table 45: Comparison of company's model and ERG's rebuilt model

	Company's model		ERG rebuilt model		Difference	
Primary prevention (based on LAPLACE-2 LDL-C>2.5mmol/L)						
Option	QALYs	Costs	QALYs	Costs	QALYs	Costs
Statins	11.56	£5,412.39	11.563	5412.390	0.00	£0.00
Ezetimibe+statins	11.84	£9,867.56	11.84	£9,867.56	0.00	£0.00
Evolocumab+statins	12.15	£75,020.08	12.15	£75,020.31	0.00	-£0.23
Secondary prevention (based on LAPLACE-2 LDL-C>2.5mmol/L)						
Option	QALYs	Costs	QALYs	Costs	QALYs	Costs
Statins	7.28	£17,959.38	7.28	£17,959.38	0.00	£0.00
Ezetimibe+statins	7.62	£20,302.09	7.62	£20,302.09	0.00	£0.00
Evolocumab+statins	8.06	£71,709.45	8.06	£71,710.11	0.00	-£0.65
HeFH (based on RUTHERFORD-2)						
Option	QALYs	Costs	QALYs	Costs	QALYs	Costs
Statins	8.04	£17,244.06	8.04	£17,244.06	0.00	£0.00
Ezetimibe+statins	8.86	£18,696.88	8.86	£18,696.88	0.00	£0.00
Evolocumab+statins	10.05	£72,262.24	10.05	£72,262.77	0.00	-£0.53

5.4 Conclusions of the cost effectiveness section

The CS includes a systematic review of economic evaluations of lipid-lowering therapies together with a *de novo* model-based economic evaluation to assess the incremental cost-effectiveness of evolocumab versus ezetimibe (both with or without statins) for the treatment of patients with LDL hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia.

The company's systematic review included 108 previously published economic evaluations. One of the included studies is the model developed to inform NICE CG181.¹⁵ None of these assessed the cost-effectiveness of evolocumab.

The company developed a *de novo* health economic model to assess evolocumab versus ezetimibe (both with and without statins) in three populations:

- (i) People with non-familial primary hypercholesterolaemia who have no history of CVD (primary prevention);
- (ii) People with non-familial primary hypercholesterolaemia who have existing CVD (secondary prevention), and;
- (iii) People with HeFH, comprising a mix of people who have no history of CVD and people who have existing CVD (primary and secondary prevention).

For all three populations, separate analyses are presented for people who are able to take statins (denoted ST) and for people for whom statins are contraindicated or not tolerated (denoted SI). The company's base case assesses evolocumab with/without statins; additional scenario analyses are presented in which evolocumab is used in combination with ezetimibe.

The company's base case model adopts a Markov approach and evaluates costs and health outcomes from the perspective of the NHS over a lifetime horizon. The model includes 24 mutually exclusive health states which include three individual "acute" event states (where patients remain for a maximum duration of one year unless they experience the same event during the next cycle), five individual "chronic" event states (including three "post-event" health states - post-ACS, post-IS and post-HF, as well as no CVD and ECVD), and thirteen composite CVD health states (including "acute" and "post-event" health states, which contain either two or three individual health states), and three death states (CHD death, stroke death and death due to other causes). The model is evaluated using an annual cycle length and is half-cycle corrected. Baseline characteristics for the non-familial primary and secondary prevention populations were based on IPD for a subset of people from the LAPLACE-2 trial²³ (those with LDL-C > 2.5mmol/L), whilst baseline characteristics for the HeFH population were based on IPD from the modified ITT population of the RUTHERFORD-2 trial.²¹ The model uses risk equations from the Framingham Heart Study and REACH Registry to predict CV risk and then adjusts these using calibration factors derived from an analysis of the CPRD/HES¹³ or using literature.⁵⁵ For patients who are able to take statins, LDL-C treatment effects were based on the LAPLACE-2 trial.²³ For patients for whom statins are contraindicated or not tolerated, treatment effects were based on the GAUSS-2 trial.²⁴ The impact of lowering lipid levels was modelled based on an assumed relationship between LDL-C reduction and CV event reduction.²⁸ Health utilities were based on EQ-5D or TTO studies used in the NICE CG181 model.¹⁵ Costs were based on the NHS Drugs Tariff,⁶¹ NHS Reference Costs⁶² the PSSRU⁶³ and a CPRD/HES costing analysis.¹³

The company's original base case model indicates the following results. Within the non-familial primary prevention ST population, the company's threshold analyses indicate that in people with a baseline LDL-C of 3.5mmol/L, the ICER for evolocumab plus statins versus ezetimibe plus statins would be below £30,000 per QALY gained in people with a 10-year CVD risk of 79% (or higher). The corresponding 10-year risk thresholds for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 73% and 70%, respectively. Within the non-familial primary prevention SI population with a baseline LDL-C of 3.5mmol/L, the ICER for evolocumab versus ezetimibe would be below £30,000 per QALY gained in people with a 10-year CVD risk of 81% (or higher). The corresponding 10-year risk thresholds for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 75% and 71%, respectively. Within the non-familial secondary prevention ST population, the company's base case analysis suggests that evolocumab plus statins is

expected to produce an additional 0.44 QALYs at an additional cost of £51,407 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £116,713 per QALY gained (probabilistic ICER=£119,012 per QALY gained). Within the non-familial secondary prevention SI population, the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.42 QALYs at an additional cost of £50,542 as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £119,971 per QALY gained (probabilistic ICER=£123,780 per QALY gained). Within the HeFH primary/secondary prevention ST population, the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.20 QALYs at an additional cost of £53,565 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £44,741 per QALY gained (probabilistic ICER=£46,412 per QALY gained). Within the HeFH primary/secondary prevention SI population, evolocumab monotherapy is expected to produce an additional 1.10 QALYs at an additional cost of £51,749 as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £47,193 per QALY gained (probabilistic ICER=£48,362 per QALY gained).

The ERG critically appraised the company's economic analysis and partially double-programmed the company's health economic model using transition probabilities derived from the company's model. Whilst the ERG's rebuild of the Markov component of the model did not identify any major problems, serious programming/logic errors were identified in the transition probabilities used in the company's model whereby under certain combinations of parameter inputs, some of the model's transition probabilities and hence health state populations became negative. The ERG requested that the company submit an amended model which rectifies this problem. In response, the company acknowledged the problem and suggested that their results for the non-familial primary prevention population should be considered to be "invalid." The company also submitted an amended model and accompanying addendum⁵² which includes an additional assumption which affects the risk predictions in the HeFH primary/secondary prevention population. The results for the non-familial secondary prevention population were unaffected by the company's amendments to the model.

The amendment to the company's model indicates the following results. Within the HeFH primary/secondary prevention ST population, the company's amended base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.15 QALYs at an additional cost of £73,620 as compared with ezetimibe plus statins; the resulting ICER is estimated to be £47,195 per QALY gained (probabilistic ICER=£48,664 per QALY gained). Within the HeFH primary/secondary prevention SI population, evolocumab monotherapy is expected to produce an additional 1.05 QALYs at an additional cost of £52,486 as compared against ezetimibe monotherapy; the resulting ICER is expected to be £49,900 per QALY gained (probabilistic ICER=£51,061 per QALY gained).

The ERG has a number of concerns regarding the company's implemented model; some of these represent major mathematical errors whilst others indicate the improper use of the available evidence. Consequently, the ERG has serious doubts regarding the validity of the results presented within the CS and would advise considerable caution in their interpretation and use in informing decision-making. The key issues identified by the ERG are briefly summarised in Table 46. Owing to the problems discussed in Section 5.3, the ERG did not consider it appropriate or valuable to undertake additional exploratory analyses using either the original or amended versions of the company's model.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Table 46 summarises the main concerns expressed by the ERG following the critical appraisal of the CS and submitted company's model.

Table 46: Summary of key concerns identified by the ERG

Deviations from the NICE reference case • Only the subgroup of patients with LDL-C>2.5mmol/L is included in the non-familial analyses • Difficulties in interpreting results from the mixed (primary and secondary prevention) HeFH population
Concerns regarding the conceptualisation and implementation of the company's model structure and logic • Use of a Markov approach which lacks flexibility. • Conceptual representation of the condition (choice of health states, use of LDL-C reduction as a surrogate for CVD events). Lack of clarity on selection and appropriateness of health states included in the company's model. • Model process and logic (circular approach). Direct data on CVD events from CPRD/HES could have been used directly to estimate CVD event probabilities. • Model implementation and misspecification of evidence inputs (including misinterpretation of the REACH predictions, absence of constraints leading to negative probabilities, inconsistent approach to estimating treatment effects and the baseline LDL-C, over-estimation of event risk in the HeFH population).
Concerns regarding the baseline characteristics/populations included in the company's analyses • Uncertainty with respect to whether the populations included in the LAPLACE-2 and RUTHERFORD-2 trials are representative of patients with primary hypercholesterolaemia in England. • Inclusion of only those patients in LAPLACE-2 who had a baseline LDL-C>2.5mmol/L. It is unclear whether this truly reflects a high-risk population who may benefit from treatment using evolocumab. • Same baseline characteristics assumed for patients who are able to take statins and those for whom statins are contraindicated or not tolerated. • Arbitrary manipulation of trial data for the subgroup analyses in patients with diabetes and/or additional risk factors
Issues regarding the use of CVD risk equations and the need for subsequent calibration • Use of risk equations rather than direct data on event rates • Misuse of the REACH equations • Use of the Framingham and REACH equations for the HeFH population

Concerns regarding the derivation of calibration factors to adjust the baseline risk of CVD for the raised LDL-C analysis • Estimation of calibration factors for primary prevention in people with diabetes. It is uncertain if the resulting calibration factors would be appropriate for the population included in the economic model which does not have diabetes. • Complicated age adjustment used to compare the predictions from the risk equations with the event rates in the CPRD/HES data. • Calibration factors estimated for secondary prevention for non-fatal events incorrect due to the misuse of the REACH equations. • Assumptions used whereby baseline characteristic variables are not available in the CPRD/HES dataset (AF and number of vascular beds). • Potential selection biases. Linking data from the CPRD, HES and ONS meant that only half of the people could be linked and included in the analysis.
Issues surrounding the derivation of the calibration factor to adjust the baseline risk of CVD for people with HeFH • Benn <i>et al</i>⁵⁵ compares CVD event risk between the HeFH population and the general population. Application of this relative risk to an already high-risk population (LDL-C$\geq$2.5mmol/L is likely to over-estimate CVD event risk for patients with HeFH. • Other sources suggest a lower risk of CVD in the HeFH population.
Concerns regarding the appropriateness of treatment effects • Use of treatment difference at mean of week 10/12 between evolocumab and ezetimibe compared with statins rather than the difference from baseline • Use of treatment effect from LAPLACE-2 for the HeFH population (rather than RUTHERFORD-2) • Uncertainty regarding duration of LDL-C improvement.
Comments regarding the relationship between LDL-C reduction and CVD events • Assumed relationship for HF equal to relationship observed for non-fatal MI (this is a matter of debate as there is no evidence that LDL-C lowering is associated with a reduction in HF). • Use of a relative risk of 1.0 for IS death rather than 1.04 • Use of a relative risk of 0.8 for CHD death rather than 0.84 • Assumed relationship for ACS for people transitioning from 'No CVD' to 'ECVD'. • Unclear whether LDL-C reduction is associated with a reduction in CHD death following HF • Effect of LDL-C reduction is assumed to be independent between non-fatal and fatal CVD events
Limited relevance of health utility estimates • Systematic review of HRQoL studies does not appear to be used. • Of the seven acute and post-event state utilities used in the model, only three of these (ACS, HF and post-HF) are based on EQ-5D valuations.
Discrepancies in the cost parameters used in the company's model • Patent expiry of ezetimibe • Discrepancies in monitoring cost assumptions
Errors in the interpretation/reporting of health economic results • Errors in the interpretation of the results presented in the tables within the CS • Reporting of redundant ICERs in the CS • Misinterpretation of the primary prevention LDL-C threshold analyses.

As a consequence of the issues outlined in Table 46, the ERG has serious doubts regarding the validity of the cost-effectiveness results presented within the CS and would advise considerable caution in their interpretation and use in informing decision-making.

7 END OF LIFE

End of life criteria were not relevant to this submission.

8 OVERALL CONCLUSIONS

The principal efficacy review represents a good quality systematic review of four relevant, good quality RCTs. The trials were generally consistent with the NICE scope. The primary efficacy outcome was mean percentage change in LDL-C from baseline, and mean treatment difference across trial arms, at follow-ups of 12 weeks (LAPLACE-2, GAUSS-2, DESCARTES and RUTHERFORD-2) and 52 weeks (DESCARTES).

In the LAPLACE-2 trial, at 12 weeks, patients with primary hypercholesterolaemia on background atorvastatin therapy (intensive and non-intensive doses) had a treatment difference in mean percentage change in LDL-C from baseline of -46.9 (95% CI, -53.0 to -40.7, $p<0.001$) and -42.5 (95% CI, -47.9 to -37.0, $p<0.001$) for the Q2W and QM doses of evolocumab respectively, compared with ezetimibe (fixed effects model).

In the GAUSS-2 trial, at 12 weeks, patients with primary hypercholesterolaemia who were statin intolerant had a treatment difference in mean percentage change in LDL-C from baseline of -39.3 (95% CI, -45.0 to -33.5, $p<0.001$) and -38.1 (95% CI, -42.9 to -33.4, $p<0.001$) for the Q2W and QM doses of evolocumab compared with ezetimibe.

In the placebo-controlled RUTHERFORD-2 trial, at 12 weeks, patients with HeFH on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -62.7 (95% CI, -66.3 to -59.1) and -56.6 (95% CI, -60.9 to -52.3) for the Q2W and QM doses of evolocumab, respectively. The treatment difference in mean percentage change compared with placebo was -60.6 (95% CI, -66.7 to -54.5, $p<0.001$) and -60.3 (95% CI, -67.8, -52.9, $p<0.001$) for the Q2W and QM doses of evolocumab, respectively. The ERG received clinical advice that the HeFH population of the RUTHERFORD trial with a confirmed genetic mutation was higher than might be found in usual clinical practice in the UK, but the implications of this are unclear. The ERG also noted, following clinical advice, that the proportion of patients with CHD was higher in the intervention arms of the RUTHERFORD-2 trial (i.e. 30-36%) compared with what would be expected in clinical practice in a HeFH population, and was higher than the prevalence reported for the other three trials (e.g. LAPLACE-2 trial arm populations ranged from 17% to 24% with CHD characteristics).

In the placebo-controlled DESCARTES trial, patients with primary hypercholesterolaemia on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -50.6 (95% CI, -53.2 to -48.0) for the QM dose of evolocumab at 52 weeks. The

treatment difference in mean percentage change compared with placebo was -59.3 (95% CI, -63.8 to -54.9, $p<0.001$) at 52 weeks.

The results for other lipid parameters, such as non-HDL-cholesterol, HDL-cholesterol, triglycerides, apolipoprotein B and lipoprotein(a), were consistent with the results for LDL-C, and pre-specified subgroup analyses demonstrated that these results were not sensitive to the different doses of evolocumab, or other key variables, such as LDL-C baseline levels, severity of hypercholesterolaemia or CVD risk factors. The ERG noted that only 12-week evidence was available for the efficacy of the Q2W dose, while the QM dose had some data for 52 weeks. Additional clinical efficacy evidence was provided from a non-RCT study (TAUSSIG) and two open-label, extension trials (OSLER1 and 2). However, the extension studies included some trials with populations and/or comparators that were excluded from the principal review of four RCTs and it is unclear how these trials and the non-RCT study were identified for inclusion in the company's review. The inclusion of these studies was justified by the company on account of the longer-term evidence both from the extension studies and from TAUSSIG on the HeFH subgroup (36 weeks). An NMA was not performed, although this might have been possible using particular trial evidence from both the primary non-familial hypercholesterolaemia population and the HeFH subgroup.

The clinical effectiveness review found that evolocumab is efficacious at lowering LDL-C, but in itself this is not a clinically important outcome: its importance is derived from it being a surrogate for CVD. Although there is an established relationship between statin-generated LDL-C reduction and reduced CV events, the impact of evolocumab on CVD has not been demonstrated: there is little or no direct evidence on this relationship. The ongoing FOURIER trial (clinicaltrials.gov identifier NCT02207634) aims to evaluate the impact of evolocumab on CVD outcomes, but only in people who have already had a CV event. The ERG also noted that there was no evidence on the relative efficacy of evolocumab versus ezetimibe in the familial hypercholesterolaemia subgroup, or for evolocumab in combination with ezetimibe in any population, and there was little or no direct trial evidence for evolocumab in terms of health-related quality of life or apheresis.

The submission of safety evidence was a non-systematic review of good quality RCTs, providing evidence for up to two years. There were no obvious safety concerns, with most AEs being balanced across evolocumab and comparator trial arms, and very small numbers of SAEs. However, the ERG noted that relatively higher 12-week AE rates were reported in patients who had HeFH or who had primary non-familial hypercholesterolaemia and were statin-intolerant. Similarly, these rates were also relatively higher for trials with a longer follow-up duration. This suggests that some patient subgroups might experience more frequent events and that all patients are at risk of AEs over time, though the rates are generally similar to comparators. The ERG noted also that the longer-term

evidence presented was derived from some trials with populations who would not be eligible to receive evolocumab in clinical practice in the NHS (e.g. people who were not on maximum-tolerated doses of statins). More long-term data are therefore needed in relevant UK populations, although it is not clear whether ongoing trials will address this.

Based on the company model, the probabilistic ICERs for evolocumab against ezetimibe are above £119,000 per QALY gained within the non-familial population and are approximately £49,000 within the HeFH population. However, the ERG has a number of concerns regarding the company's implemented model; some of these represent major mathematical errors whilst others indicate the improper use of the available evidence. The key concerns identified by the ERG can be separated into four sets of issues: (a) the company's general modelling approach; (b) the conceptual representation of the condition; (c) the model process and logic; and; (d) model implementation and misspecification of evidence inputs. The ERG also expresses concerns regarding the conduct of the analysis for the HeFH population. These conceptual and structural problems are complex and intertwined, and the resolution of individual issues in isolation would not result in an appropriate or credible model. Rather, the ERG considers that the joint resolution of these problems would require a full "rethinking" of the model's logic. Consequently, the ERG has serious doubts regarding the validity of the results presented within the CS and would advise considerable caution in their interpretation and use in informing decision-making. As such, the expected cost-effectiveness of evolocumab in the non-familial and HeFH populations is unclear.

8.1 Implications for research

Future research should seek to address the following key areas of uncertainty:

- The efficacy of evolocumab in reducing the risk of CVD in all populations (adults with familial and non-familial primary hypercholesterolaemia), especially in comparison with ezetimibe.
- The efficacy of evolocumab in combination with ezetimibe compared with ezetimibe alone in all populations (adults with familial and non-familial primary hypercholesterolaemia).
- The impact of evolocumab on HRQoL and apheresis in the short- and long-term.

9. REFERENCES

1. Roth G, Finh S, Mikdad A, Aekplakorn W, Hasegawa T, Lim S. High total serum cholesterol, medication coverage and therapeutic control: an analysis of national health examination survey data from eight countries. *Bulletin of the World Health Organization* 2011;**89**:92-101.
2. Bhatnagar D, Soran H, Durrington P. Hypercholesterolaemia and its management. *British Medical Journal* 2008;**337**:a993.
3. Bhatnagar P, Wickramasinghe K, Williams J, Rayner M, Townsend N. The epidemiology of cardiovascular disease in the UK 2014. *Heart* 2015; 10.1136/heartjnl-2015-307516:1-8. <http://dx.doi.org/10.1136/heartjnl-2015-307516>
4. National Institute of Health and Care Excellence. *Single Technology Appraisal. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Final scope*; 2015.
5. Durrington P. Dyslipidaemia. *Lancet* 2003;**263**:717-31.
6. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, *et al.* Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *Journal of Clinical Lipidology* 2011;**5**:S1-8.
7. Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. *British Medical Journal* 1991;**303**:893-96.
8. Wierzbicki A, Humphries S, Minhas R. Guideline Development Group. Familial hypercholesterolaemia: summary of NICE guidance. *British Medical Journal* 2008;**337**:a1095.
9. Vandrovcova J, Thomas E, Atanur SA, Norsworthy PJ, Neuwirth C, Tan Y, *et al.* The use of next-generation sequencing in clinical diagnosis of familial hypercholesterolemia. *Genetics in Medicine* 2013;**15**:948-57.
10. Robinson JG. Management of familial hypercholesterolemia: a review of the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Manag Care Pharm* 2013;**19**.
11. Civeira F. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2004;**173**:55-68.
12. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, *et al.* Familial hypercholesterolaemia is underdiagnosed and undertreated in the general

- population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *European Heart Journal* 2013;**34**:3478–90a.
13. Amgen. *Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. Company evidence submission*; 2015.
 14. National Institute for Health and Care Excellence. *Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia*. NICE TA132. November 2007.
 15. National Institute for Health and Care Excellence. *Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease*. NICE CG181. July 2014.
 16. Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, *et al*. Efficacy and safety of alirocumab versus ezetimibe in statin-intolerant patients, with a statin-re-challenge arm: The ODYSSEY ALTERNATIVE randomized trial. *Journal of Clinical Lipidology* 2015;**epub ahead of print** doi: 10.1016/j.jacl.2015.08.006.
 17. Mancini GB, Baker S, Bergeron J, Fitchett D, Frohlich J, Genest J, *et al*. Diagnosis, prevention, and management of statin adverse effects and intolerance: proceedings of a Canadian Working Group Consensus Conference. *Canadian Journal of Cardiology* 2011;**27**:635-62.
 18. Cannon CP. IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). . *Presented at the American Heart Association Scientific Sessions, Chicago, November 15–18, 2014*.
 19. National Institute for Health and Care Excellence. Identification and management of familial hypercholesterolaemia. NICE CG71. August 2008.
 20. Weng S, Kai J, Neil H, Humphries S, Qureshi N. Improving identification of familial hypercholesterolaemia in primary care: Derivation and validation of the familial hypercholesterolaemia case ascertainment tool (FAMCAT). *Atherosclerosis* 2014;**238**:336-43.
 21. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, *et al*. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;**385**:331-40.
 22. Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. *British Medical Journal* 2010;**341**:c6624.

23. Robinson JG, Nedergaard BS, Rogers WJ, Flalkow J, Neutel JM, Ramstad D, *et al.* Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* 2014;**311**:1870-82.
24. Stros E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, *et al.* Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *Journal of American College of Cardiologists* 2014;**63**:2541-8.
25. Blom DJ, Hala T, Bolognese M, Lillstol MJ, Toth PD, Burgess L, *et al.* A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *New England Journal of Medicine* 2014;**370**:1809-19.
26. Committee for Medicinal Products for Human Use (CHMP). *Assessment report Repatha International non-proprietary name: evolocumab Procedure No. EMEA/H/C/003766/0000* 2015.
27. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, *et al.* ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *European Heart Journal* 2011;**32**:1769-818.
28. Baigent C, Blackwell L, Emberson J, Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670-81.
29. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**266**:1267-78
30. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *British Medical Journal* 2003;**326**:1423.
31. Anderson K, Odell P, Wilson P, Kannel W. Cardiovascular disease risk profiles. *American Heart Journal* 1991;**121**:293-8.
32. ClinicalTrials.gov. . *NCT01764633: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)* 2015. URL: <http://ClinicalTrials.gov/show/NCT01764633> (Accessed,10/9/15)

33. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, *et al.* Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *New England Journal of Medicine* 2015;**372**:1500-09.
34. Moher D LA, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine* 2009;**6**:e1000097.
35. Amgen. *Response to clarification questions. Single Technology Appraisal (STA). Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia*; 2015.
36. Cochrane Collaboration. *Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE*. 2008. URL: http://handbook.cochrane.org/chapter_6/box_6_4_c_cochrane_hsss_2008_sensmax_ovid.htm (Accessed 2 September 2015).
37. Hirayama A, Honarpour N, Yoshida M, Yamashita S, Huang F, Wasserman SM, *et al.* Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk—primary results from the phase 2 YUKAWA study. *Circulation Journal* 2014;**78**:1073-82.
38. Bruckert E, Blaha V, Stein E. Trial Assessing Long-Term Use of PCSK9 Inhibition in Patients with Genetic LDL Disorders (TAUSSIG): Efficacy and Safety in Patients with Familial Hypercholesterolemia Receiving Lipid Apheresis. *Poster presented at the AHA (American Heart Association) Scientific Sessions, 15–19 November 2014, Chicago, USA* 2014.
39. Abraha I, Cherubini A, Cozzolino F, De Florio R, Luchetta M, Rimland J, *et al.* Deviation from intention to treat analysis in randomised trials and treatment effect estimates: meta-epidemiological study. *British Medical Journal* 2015;**350**:h2445.
40. Talmud PJ, Shah S, Whittall R. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. *Lancet* 2013;**381**:1293–301.
41. Koren MJ, Scott R, Kim JB, Knusel B, Liu T, Lei L, *et al.* Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 2012;**380**:1995-2006.
42. Koren MJ, Lundqvist P, Bolognese M, Neutal JM, Monsalvo ML, Yang J, *et al.* Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III

- clinical trial of evolocumab. *Journal of the American College of Cardiologists* 2014;**63**:2531-40.
43. ClinicalTrials.gov. NCT01849497: a multi-center, randomized study in subjects with primary hypercholesterolemia or mixed dyslipidemia. 2015. URL: <http://ClinicalTrials.gov/show/NCT01849497> (Accessed,10/9/15)
 44. ClinicalTrials.gov. NCT01879319: a randomized, multi-center clinical study in subjects with hypercholesterolemia or mixed dyslipidemia 2015. URL: <http://ClinicalTrials.gov/show/NCT01879319> (Accessed,10/9/15)
 45. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;**371**:117–25.
 46. ClinicalTrials.gov. NCT02207634: Evaluating PCSK9 Binding antiBody Influence on Cognitive Health in High cardiovascular Risk Subjects (EBBINGHAUS) 2015. URL: (<https://clinicaltrials.gov/ct2/show/NCT02207634>). (Accessed,10/9/15).
 47. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AFH, *et al.* Simvastatin with or without ezetimibe in familial hypercholesterolemia. *New England Journal of Medicine* 2008;**358**:1431-43.
 48. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *British Medical Journal* 1996;**313**:275-83.
 49. Institute for Clinical and Economic Review. *PCSK9 inhibitors for treatment of high cholesterol: effectiveness, value, and value based price benchmarks*. Boston, US; 2015.
 50. Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L. Adolescent Overweight and Future Adult Coronary Heart Disease. *New England Journal of Medicine* 2007;**357**:2371-9.
 51. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. *American Journal of Public Health* 1987;**77**:1417-26.
 52. Amgen. Addendum. *Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia*. Company evidence submission; 2015.
 53. D'Agostino RBS, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, *et al.* General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;**117**:743-53.

54. Wilson P, D'Agostino RS, Bhatt D, Eagle K, Pencina M, Smith S, *et al.* An international model to predict recurrent cardiovascular disease. *American Journal of Medicine* 2012;**125**:695-703 e1.
55. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *Journal of Clin Epidemiology and Metabolism* 2012;**97**:3956-64.
56. Dolan P, Gudex C, Kind P, Williams A. The time trade-off method: results from a general population study. *Health Economics* 1996;**5**:141-54.
57. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. *American Heart Journal* 2001;**141**:727–34.
58. Goodacre S, Nicholl J, Dixon S, Cross E, Angelina K, Arnold J, *et al.* Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *British Medical Journal* 2004;**328**:254.
59. Tengs TO, Lin TH. A meta-analysis of quality of life estimates for stroke. *Pharmacoeconomics* 2003;**21**:191–200.
60. Lacey EA, Walters SJ. Continuing inequality: gender and social class influences on self perceived health after a heart attack. *Journal of Epidemiology and Community Health* 2003;**57**:622–7.
61. NHS. *NHS Electronic Drug Tariff*. 2015. URL: [http://www.drugtariff.nhsbsa.nhs.uk/#/00175224-FA/FA00175149/Part VIIIA products A](http://www.drugtariff.nhsbsa.nhs.uk/#/00175224-FA/FA00175149/Part%20VIII%20products%20A) (Accessed September 2015).
62. Department of Health. *NHS Reference Costs 2013 to 2014*. 2014. <https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014> (Accessed June 2015).
63. Curtis L. *Unit costs of health & social care 2013*. 2013 <http://www.pssru.ac.uk/project-pages/unit-costs/2013/> (Accessed August 2015).
64. Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al.* A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assessment* 2007;**11**.
65. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003;**21**:43–50.

66. Danese M, Gleeson M, Kutikova L. Data on file. Costs of cardiovascular (CV) events in the United Kingdom (UK) using real-world data. *Abstract submitted to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 18th Annual European Congress, 7–11 November 2015, Milan, Italy.* 2015.
67. Weinstein M, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, *et al.* Principles of good practice for decision analytic modeling in health care evaluation: Report of the ISPOR Task Force on good research practices--modeling studies. *Value in Health* 2003;**6**:9-17.
68. National Institute for Health & Care Excellence. Guide to the methods of technology appraisal. In: NICE Methods Guide. London: NICE; 2013.
69. Neil A, Cooper J, Betteridge J, Capps N, McDowell I, Durrington P, *et al.* Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *European Heart Journal* 2008;**21**:2625-33.
70. Huxley RR, Hawkins MH, Humphries SE, Karpe F, Neil HA. Risk of fatal stroke in patients with treated familial hypercholesterolemia: a prospective registry study. *Stroke; a journal of cerebral circulation* 2003;**34**:22-5.
71. Ara R, Brazier J. Populating an economic model with health state utility values: moving toward better practice. *Value in Health* 2010;**13**:509-18.
72. Commercial Medicines Unit. *Drugs and pharmaceutical electronic market information (eMit)*. 2015. URL: <https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit> (Accessed 15/08/2015)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia

Addendum #2

October 2015

File name	Version	Contains confidential information	Date
		Yes CIC: Redacted	November 2015

Overview:

This addendum provides details regarding amendments to the economic model associated with the Evidence Review Group (ERG) clarification request dated 11th August 2015 and subsequent ERG report received 25th September 2015.

Based on the amendments to the economic model, the cost effectiveness analyses have been updated for these populations (Appendix):

- Patients without existing CVD
- Patients with existing CVD
- Patients with HeFH

Notably, due to the challenges in interpretation of the threshold analyses for patients without existing CVD (ERG report page 131 to 132) and the very high levels of CVD risk previously estimated in order to demonstrate cost-effectiveness at willingness-to-pay thresholds of £20,000 and £30,000, these analyses have not been repeated.

1. Model implementation and misspecification of evidence inputs - REACH Registry Equation

The ERG report (page 117) states, *“the company...assumes that the risk for “next cardiovascular event” predicted by the REACH Registry equation includes only non-fatal events. This is incorrect and was confirmed through correspondence between the ERG and the author of the REACH Registry paper”*.

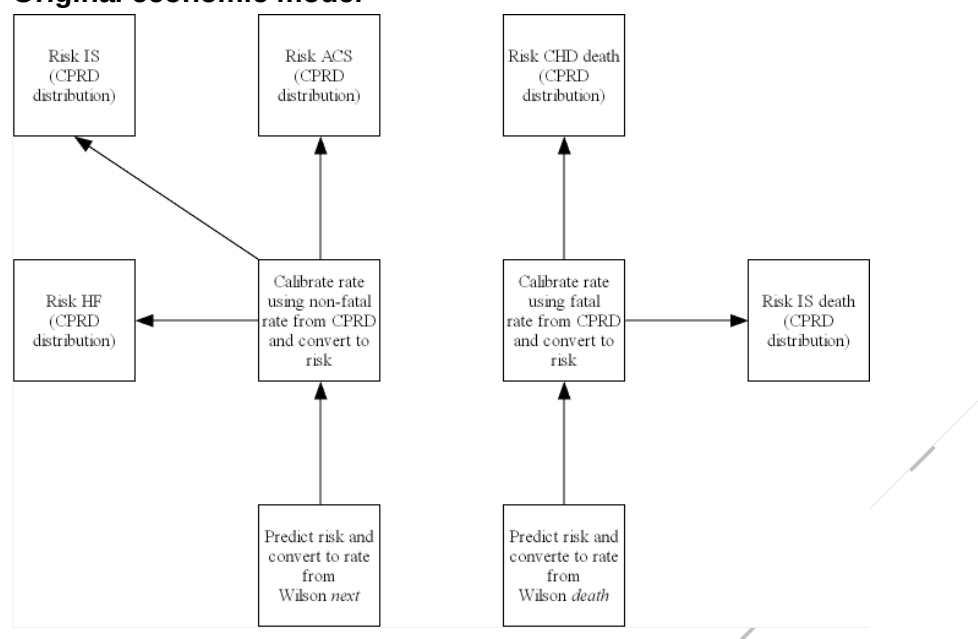
We thank the ERG for identifying this incorrect interpretation of the REACH Registry risk equation based on correspondence with the author.

We have undertaken the following steps to ensure the correct application of the REACH Registry equation for “next cardiovascular event” in the economic model:

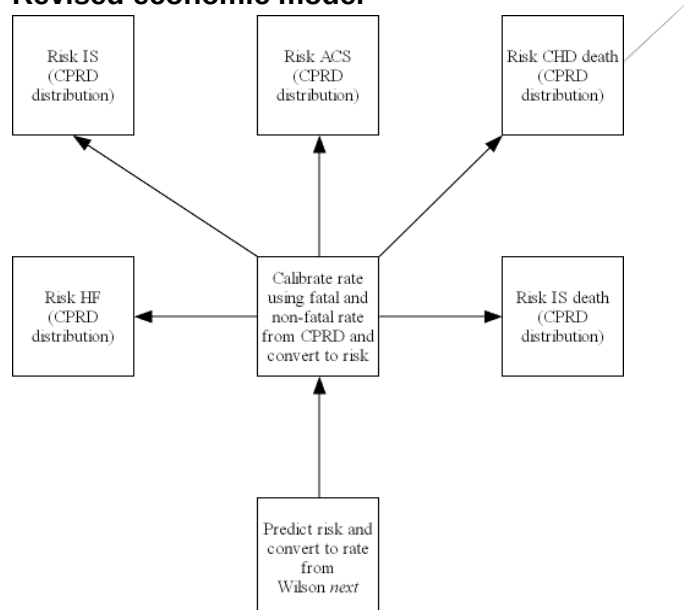
- Distribution of CV events recalculated based on the original multinomial models so the predicted risk from REACH Registry “next cardiovascular event” is now split among fatal and non-fatal CV events, mirroring the approach used for the Framingham equation.
- The new distribution of CV events is highlighted in yellow in worksheet ‘Events Distribution (model)’.
- Re-estimation of the calibration factors for non-familial populations (from CPRD) by comparing overall CV event rates (fatal and non-fatal) versus predictions from REACH Registry for “next cardiovascular event” (after conversion to rates), mirroring the approach for Framingham equation. The new calibration factors are highlighted in yellow in worksheet ‘Calibration’.
- Re-estimation of the calibration factors was undertaken since the REACH Registry “next cardiovascular event” was assumed to account for non-fatal events only and was therefore calibrated against CPRD non-fatal events (see updated Appendix 11 - Amgen Study Estimation and calibration of CV event rates). The predicted risk was split using only non-fatal event proportions (adding up to 1) from CPRD. REACH Registry “cardiovascular death” was calibrated against fatal events, and the risk predicted was split using fatal event proportions from CPRD (adding up to 1).
- The amendments are shown schematically in Figure 1.

Figure 1 Previous and current application of REACH Registry equation (Wilson, *et al.* 2012) in the economic model

Original economic model



Revised economic model



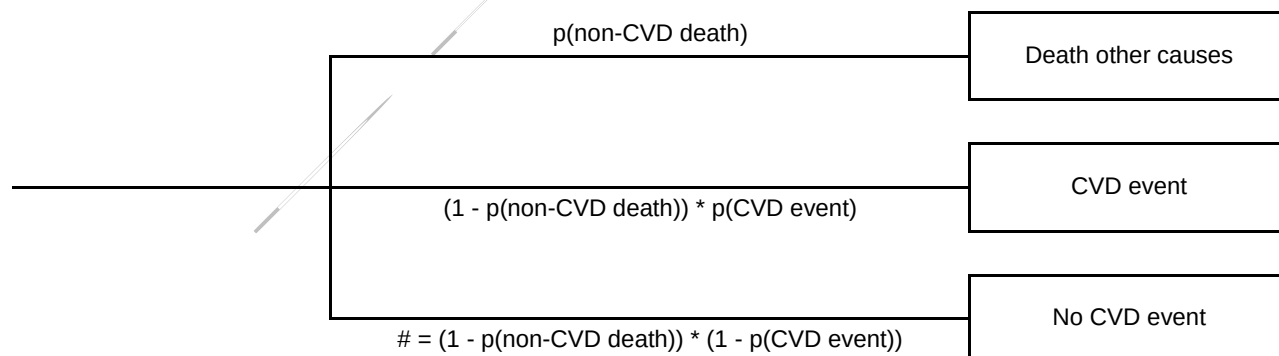
Amendments in the economic model are reflected in the following worksheets, 'Calibration', 'Events Distribution (model)', 'Baseline Risks (model)' and 'Calibrated Rates (model)'.

2. Model implementation and misspecification of evidence inputs – Negative transition probabilities

The ERG report (page 117) states, “Further, since the model estimates the risk of fatal and non-fatal CVD events separately and without constraint, this leads to mathematical inconsistencies when the risk of fatal and non-fatal CVD events is high. Consequently, when the sum of predicted probabilities for fatal and non-fatal CVD events exceeds 1, this leads to a situation whereby some of the transition probabilities and health state populations become negative”, and “The ERG notes that whilst this is a structural problem, the company’s amendment treats this as a parametric issue. The ERG highlights that it should not be possible under any combination of model parameter inputs for transition probabilities or health state populations to be negative, even at the highest levels of predicted CV risk. Despite the company’s amendment to the model, negative probabilities are still possible when different input parameters are used, for example, when the cap for age is increased from 85 to 90 years, or when the adjustment factors for the HeFH population are increased to the upper CI reported within the CS”.

We appreciate that the previous amendment was deemed methodologically insufficient by the ERG. Therefore we have undertaken the following alternative amendment to prevent the occurrence of negative transition probabilities in the economic model:

- A correction for competing risks (non-CVD mortality versus CV events) has been included in such a way that only patients alive from other causes are at risk of CV events (all transition probabilities have been corrected by a factor representing the probability of the complementary event of non-CVD mortality in each cycle). The correction is performed in worksheet ‘Baseline Risks (model)’.
- This is represented below:



Acute health states:

For example, 'No CVD' to 'ACS', worksheet 'Baseline Risks (model)', cell C145.

$= (1 - \text{EXP}(-\text{'Calibrated Rates (model)'}!C145)) * \text{'Events Distribution (model)'}!E145 * (1 - \text{'Rates \& non-CVD Utilities'}!AE145)$

Whereby:

- **Calibrated rate converted to a risk**
- **ACS proportion conditional on no previous event (CPRD)**
- **Adjustment for competing risks**

Combined health states:

Combined health states follow these rules in each cycle to ensure non-negative probabilities regardless the level of risk:

- If an acute CV event is included in the combined health state, the set of risks is that of the acute health state.
- In the case of combined health states of post-acute health states only, the set of risks of the post-acute health state with a higher calibrated rate is considered.

For example, 'post-ACS + post-IS' to 'ACS', worksheet 'Baseline Risks (model)', cell BA145.

=IF('Calibrated Rates (model)'!\$AV145>'Calibrated Rates (model)'!\$AW145,'Baseline Risks (model)'!AB145,'Baseline Risks (model)'!AG145)

Whereby:

- Compare the calibrated rates for patients with post-ACS and post-IS history
- If post-ACS calibrated rate is higher, take post-ACS to ACS risk
- If post-IS calibrated rates is higher, take post-IS to ACS risk

As calibrated rates are an aggregate (any CV event), the same decision rule would apply to all transitions to any CV event from 'post-ACS + post-stroke' combined health state.

The same logic applies to the maximum risks rule. For example, 'ACS' to 'ACS', worksheet 'Baseline Risks (model)', cell M145.

=IF('Calibrated Rates (model)'!\$AQ145>'Calibrated Rates (model)'!\$AS145,'Baseline Risks (model)'!C145,(1-EXP(-'Calibrated Rates (model)'!M145))*'Events Distribution (model)'!AC145*(1-'Rates & non-CVD Utilities'!AE145))

Whereby:

- Compare the calibrated rates for patients with no event and ACS history
- If no event calibrated rate is higher, take no event to ACS risk (this risk has been already applied the event distribution and adjustment of competing risk as per the example above)
- If ACS calibrated rate is higher, take ACS to ACS rate converted to a risk and apply ACS proportion conditional on previous ACS (CPRD) and the adjustment for competing risks

Previously, the maximum risk for the individual transitions was used in the economic model. Now, the full set of risks for the CV event with the highest calibrated rate is used instead. This amended approach ensures the sum of probabilities never exceeds 1. The economic model has also been tested for any negative probabilities at the very highest levels of risk. Trackers for negative probabilities have also been included in worksheets 'Prob_Backbone' to 'Prob_3LEvo', cell B222 for transparency.

3. Model implementation and misspecification of evidence inputs – LDL-C treatment effects

The ERG report (pages 117 to 188) states, “The company estimates the risk of CVD using baseline characteristics at entry into the LAPLACE-2/RUTHERFORD-2 trials and uses the LDL-C at baseline to represent the risk of CVD for people treated with statins. However, the model then applies the treatment effect (a relative reduction in LDL-C) for ezetimibe and evolocumab calculated from the treatment difference (statins versus ezetimibe or evolocumab) at the mean of weeks 10/12, rather than based on the change from baseline. The ERG believes there is a mismatch as the treatment effect used in the model does not match the baseline LDL-C level from which it is estimated. This leads to a larger treatment effect being used in the model (treatment difference of -71.8% at week 10/12 against statins vs. -64.33% from baseline in the LAPLACE-2 trial)”.

We acknowledge the ERG comments and have therefore amended the LDL-C treatment effects (Table 1):

- Mean percentage change from baseline (instead of versus placebo) used for non-familial population based on LAPLACE-2 for evolocumab and ezetimibe
- Mean percentage change from baseline used for HeFH based on RUTHERFORD-2 (instead of LAPLACE-2) for evolocumab
- Mean percentage change from baseline from LAPLACE-2 (instead of versus placebo) used for HeFH for ezetimibe in the absence of evidence.

Table 1 Mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe when used in combination with statins or as monotherapy

	Evolocumab 140 mg Q2W	Evolocumab 420 mg QM	Ezetimibe 10 mg OD^b
Non-familial: Combination with a statin (based on LAPLACE-2)			
Mean percent change from baseline ^a (95% CI) [SE]	-64.31 (-66.14, -62.49) [0.93]	-65.05 (-67.04, -63.05) [1.02]	-20.52 (-24.03, -17.00) [1.79]
Familial: Combination with a statin (based on RUTHERFORD-2)			
Mean percent change from baseline ^a (95% CI) [SE]	-62.66 (-66.18, -59.15) [1.78]	-64.74 (-68.06, -61.41) [1.68]	As per LAPLACE-2
Non-familial and familial: Monotherapy (based on GAUSS-2)			
Mean percent change from baseline ^a (95% CI) [SE]	-57.10 (-60.84, -53.36) [1.90]	-55.82 (-58.88, -52.76) [1.55]	-17.83 (-21.01, -14.65) [1.62]
References: LAPLACE-2 CSR Table 14-4.2.13 and LAPLACE-2 supplementary data table 14-4.6.2; RUTHERFORD-2 CSR Table 14-4.1.2 and GAUSS-2 CSR Tables 10-4 and 14-4.1.3 and GAUSS-2 supplementary data table 14-4.9.1			

	Evolocumab 140 mg Q2W	Evolocumab 420 mg QM	Ezetimibe 10 mg OD^b
^a Least squares mean from the repeated measures model which includes treatment group, stratification factors (from IVRS), scheduled visit, dose frequency and the interaction of treatment with scheduled visit as covariates. ^b Based on <i>post hoc</i> pooled analysis of all ezetimibe arms and all placebo arms in LAPLACE-2 and GAUSS-2, respectively. CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; OD, once daily; Q2W, every 2 weeks; QM, monthly; SE, standard error			

These amendments to the LDL-C lowering treatment effects have marginally lowered the ICER for evolocumab in patients with existing CVD and marginally increased the ICER for evolocumab in patients with HeFH when compared to the previous treatment effects used for these populations.

4. Additional amendments to the economic model

The following amendments have also been made to the economic model. Key changes have been marked in yellow to allow identification in the economic model.

Evolocumab price: Addition of selector in worksheet 'Main' to allow selection of the NHS list price or Patient Access Scheme price.

REACH Registry equation – statin variable: Addition of selector on worksheet 'Main' to allow selection (yes or no) for the statin indicator REACH Registry equation with regards the comments in the ERG report (page 130). This variable is still maintained as 'yes' for all the cost-effectiveness analyses presented in this document.

This is based on amendment to the equation, for example, worksheet 'LAPLACE-2 (SP)', cell AE7:

=IF(\$C7=0,-LN(1-(1-0.93681^EXP(0.10246*(1-\$C7)+0.03089*\$B7+0.24121*\$D7+0.37824*\$E7+0.31428*\$I7+0.30277*\$W7+0.38168*0+0.51873*0+0.26652*\$X7-0.28332*IF(AND(SI=1,StatinIndicatorWilson="No"),0,1)-0.10151*\$G7-2.68845))),""))

Appendix – Revised cost-effectiveness results

1.1 Base case results

The cost-effectiveness analysis has been conducted for the relevant populations within the decision problem according to the four treatment scenarios. Treatment scenarios for evolocumab and statin versus ezetimibe and statin (scenario 1), and evolocumab alone versus ezetimibe alone (scenario 2) are presented in full in this section. For brevity, the cost-effectiveness analyses for evolocumab and ezetimibe versus ezetimibe alone (scenario 3), and evolocumab, statin, and ezetimibe versus statin and ezetimibe (scenario 4) are presented as scenario analyses (Section 1.5). Summary details of these analyses are provided in Table 1.

Table 1 Modelled intervention and comparator for patients with and without existing CVD, and patients with HeFH

Pop.	Intervention	Comparator	Inc. costs	Inc. QALYs	ICER incremental (QALYs)	Analysis, Section, Tables
Without existing CVD	Evolocumab and statin	Ezetimibe and statin	██████	0.32	██████	Analysis A, Table 2 (previously threshold analyses)
	Evolocumab alone	Ezetimibe alone	██████	0.30	██████	Analysis B, Table 3 (previously threshold analyses)
	Evolocumab and ezetimibe	Ezetimibe alone	N/A	N/A	N/A	Not conducted
	Evolocumab, ezetimibe, and statin	Ezetimibe and statin	N/A	N/A	N/A	Not conducted
Existing CVD	Evolocumab and statin	Ezetimibe and statin	██████	0.39	██████	Analysis C, Table 4 to Table 8
	Evolocumab alone	Ezetimibe alone	██████	0.37	██████	Analysis D, Table 9 to Table 13
	Evolocumab and ezetimibe	Ezetimibe alone	██████	0.42	██████	Analysis E, Table 28
	Evolocumab, ezetimibe, and statin	Ezetimibe and statin	██████	0.44	██████	Analysis F, Table 29
HeFH	Evolocumab and statin	Ezetimibe and statin	██████	0.86	██████	Analysis G, Table 14 to Table 18
	Evolocumab alone	Ezetimibe alone	██████	0.82	██████	Analysis H, Table 19 to Table 23
	Evolocumab and ezetimibe	Ezetimibe alone	██████	0.96	██████	Analysis I, Table 30
	Evolocumab, ezetimibe, and statin	Ezetimibe and statin	██████	1.00	██████	Analysis J, Table 31
CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year;						

Additionally step-wise subgroup cost-effectiveness analyses for evolocumab and statin versus ezetimibe and statins are presented in Section 1.7 for patients with existing CVD at high residual risk due to additional risk factors.

1.2 Without existing CVD

Analysis A: Evolocumab and statin versus ezetimibe and statin

Base case incremental cost-effectiveness results

The incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin in patients with existing CVD is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 0.32 (Table 2).

Table 2 Analysis A: Base case incremental cost, incremental QALYs, and ICER for patients without existing CVD (evolocumab and statin versus ezetimibe and statin)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£5,313	11.62				
Ezetimibe and statin	£9,979	11.83	£4,667	0.20	£22,896	
Evolocumab and statin	[REDACTED]	12.14	[REDACTED]	0.52	[REDACTED]	[REDACTED]
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Analysis B: Evolocumab and statin versus ezetimibe and statin

Base case incremental cost-effectiveness results

The incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin in patients with existing CVD is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 0.30 (Table 3).

Table 3 Analysis B: Base case incremental cost, incremental QALYs, and ICER for patients without existing CVD (evolocumab alone versus ezetimibe alone)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
No lipid-lowering therapy	£5,025	11.62				
Ezetimibe alone	£9,767	11.80	£4,742	0.18	£26,434	
Evolocumab alone	[REDACTED]	12.10	[REDACTED]	0.48	[REDACTED]	[REDACTED]
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

1.3 Existing CVD

Analysis C: Evolocumab and statin versus ezetimibe and statin

Base case incremental cost-effectiveness results

The incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin in patients with existing CVD is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 0.39 (Table 4).

Table 4 Analysis C: Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab and statin versus ezetimibe and statin)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£18,745	7.61				
Ezetimibe and statin	£21,408	7.84	£2,663	0.23	£11,412	
Evolocumab and statin		8.23		0.63		

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Clinical outcomes – CV events

The base case undiscounted CV event rates for the secondary population for evolocumab in combination with statin versus ezetimibe in combination with statin are presented in Table 5. This indicates that evolocumab and statin is anticipated to prevent approximately 0.41 CV events compared with ezetimibe and statin.

Table 5 Analysis C: Base case undiscounted CV event rates

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.82	0.64	0.37	-0.26	0.26	62%
IS	0.12	0.09	0.05	-0.04	0.04	9%
HF	0.25	0.23	0.20	-0.03	0.03	6%
CHD death	0.41	0.36	0.27	-0.09	0.09	22%
IS death	0.09	0.09	0.10	0.01	0.01	2%
Total	1.68	1.41	1.00	-0.41	0.43	100%

ACS, acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; IS, ischaemic stroke

Disaggregated results – QALY gains by health state

Disaggregated QALYs for statin, ezetimibe and statin, and evolocumab and statin are presented in Table 6. This indicates a total QALY gain of 0.39 for evolocumab and statin compared with ezetimibe and statin.

Table 6 Analysis C: Base case summary of QALYs by health state

Health state	QALY: Statin	QALY: Ezetimibe and statin (comparator)	QALY: Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.30	0.23	0.14	-0.10	0.10	16%
IS	0.04	0.03	0.02	-0.01	0.01	2%
HF	0.08	0.07	0.07	-0.01	0.01	1%
ECVD	3.04	3.28	3.68	0.41	0.41	65%
Post-acute	4.15	4.23	4.33	0.10	0.10	16%
No CVD	0.00	0.00	0.00	0.00	0.00	0%
Total	7.61	7.84	8.23	0.39	0.63	100%
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – costs by health state

The base case disaggregated costs show that there is an anticipated saving of £ [REDACTED] associated with evolocumab and statin versus ezetimibe and statin when considering the health states. These savings are attributable to a reduction in ACS, IS, HF, CHD death, and revascularisation costs (Table 7).

Table 7 Analysis C: Base case summary of costs by health state

Health state	Cost: Statin	Cost: Ezetimibe and statin (comparator)	Cost: Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	£1,780	£1,380	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IS	£304	£234	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HF	£505	£468	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CHD death	£172	£150	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IS death	£91	£95	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ECVD	£2,378	£2,566	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Post-acute	£5,318	£5,318	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Revasc	£6,375	£4,863	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total	£16,923	£15,073	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke ;Revasc Revascularisation						

Summary of predicted resource use by category of cost

The resource use estimations show increased costs of £ [REDACTED] associated with evolocumab and statin compared with ezetimibe and statin over the time horizon (Table 8). The summary indicates that these are due to additional costs for medication, and monitoring and training for evolocumab.

Table 8 Analysis C: Base case summary of resource use by health state

Health state	Statin	Ezetimibe and statin	Evolocumab and statin	Increment	Absolute increase	Absolute increment

Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

		(comparator)				
Medication	£438	£4,819				
Monitoring and training	£1,385	£1,420				
Health states	£16,923	£15,169				
Total	£18,745	£21,408				

Analysis D: Evolocumab alone versus ezetimibe alone

Base case incremental cost-effectiveness results

The incremental cost per QALY gained for evolocumab alone versus ezetimibe alone in patients with existing CVD and whom are statin intolerant or contraindicated is £ [REDACTED] based on incremental costs of £ [REDACTED] and incremental QALYs of 0.37 (Table 9).

Table 9 Analysis D: Base case incremental cost, incremental QALYs and ICER for patients with existing CVD

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
No lipid-lowering therapy	£18,307	7.61				
Ezetimibe alone	£21,143	7.81	£2,835	0.20	£13,853	
Evolocumab alone	[REDACTED]	8.18	[REDACTED]	0.57	[REDACTED]	[REDACTED]
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Clinical outcomes – CV events

The base case undiscounted CV event rates for patients with existing CVD and whom are statin intolerant or contraindicated are presented in Table 10. This indicates that evolocumab alone is anticipated to prevent approximately 0.39 CV events compared with ezetimibe alone.

Table 10 Analysis D: Base case undiscounted CV event rates

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.82	0.66	0.41	-0.25	0.25	62%
IS	0.12	0.09	0.06	-0.04	0.04	9%
HF	0.25	0.23	0.21	-0.02	0.02	6%
CHD death	0.41	0.37	0.28	-0.08	0.08	21%
IS death	0.09	0.09	0.10	0.01	0.01	2%
Total	1.68	1.44	1.06	-0.39	0.40	100%

ACS, acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; IS, ischaemic stroke

Disaggregated results – QALY gains by health state

Disaggregated QALYs for ezetimibe alone and evolocumab alone are presented in Table 11. This indicates a total QALY gain of 0.37 for evolocumab alone compared with ezetimibe alone.

Table 11 Analysis D: Base case summary of QALYs by health state

Health state	QALY: No lipid-lowering therapy	QALY: Ezetimibe alone (comparator)	QALY: Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.30	0.24	0.15	-0.09	0.09	16%
IS	0.04	0.03	0.02	-0.01	0.01	2%
HF	0.08	0.08	0.07	-0.01	0.01	1%
ECVD	3.04	3.25	3.63	0.38	0.38	64%
Post-acute	4.15	4.22	4.32	0.10	0.10	17%
No CVD	0.00	0.00	0.00	0.00	0.00	0%
Total	7.61	7.81	8.18	0.37	0.59	100%

ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke

Disaggregated results – costs by health state

The base case disaggregated costs show that there is an anticipated saving of £ [REDACTED] associated with evolocumab alone versus ezetimibe alone. These savings are attributable to a reduction in ACS, IS, HF, CHD death and revascularisation costs (Table 12).

Table 12 Analysis D: Base case summary of costs by health state

Health state	Cost: No lipid-lowering therapy	Cost: Ezetimibe alone (comparator)	Cost: Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	£1,780	£1,427	██████	██████	██████	██████
IS	£304	£243	██████	██████	██████	██████
HF	£505	£472	██████	██████	██████	██████
CHD death	£172	£152	██████	██████	██████	██████
IS death	£91	£94	██████	██████	██████	██████
ECVD	£2,378	£2,543	██████	██████	██████	██████
Post-acute	£5,318	£5,318	██████	██████	██████	██████
Revasc	£6,375	£5,040	██████	██████	██████	██████
Total	£16,923	£15,288	██████	██████	██████	██████
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; Revasc Revascularisation						

Summary of predicted resource use by category of cost

The resource use estimations show increased costs associated with evolocumab alone compared with ezetimibe alone. The summary in Table 13 indicates that these are due to additional costs for medication, and monitoring and training for evolocumab.

Table 13 Analysis D: Base case summary of resource use by health state

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment	Absolute increase	Absolute increment
Medication	£0	£4,354	██████	██████	██████	██████
Monitoring and training	£1,385	£1,415	██████	██████	██████	██████
Health states	£16,923	£15,373	██████	██████	██████	██████
Total	£18,307	£21,143	██████	██████	██████	██████

1.4 Heterozygous familial hypercholesterolaemia

Analysis G: Evolocumab and statin versus ezetimibe and statin

Base case incremental cost-effectiveness results

The incremental cost per QALY gained for evolocumab and statin versus ezetimibe and statin in patients with HeFH is £██████ based on incremental costs of £██████ and incremental QALYs of 0.86 (Table 14).

Table 14 Analysis G: Base case incremental cost, incremental QALYs and ICER for the HeFH population (evolocumab and statin vs. ezetimibe and statin)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£18,589	9.56				
Ezetimibe and statin	£20,672	10.03	£2,083	0.47	£4,398	
Evolocumab and statin		10.89		1.33		
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Clinical outcomes – CV events

The base case undiscounted CV event rates for the HeFH population for evolocumab in combination with statin versus ezetimibe in combination with statin are presented in Table 15. This indicates that evolocumab and statin is anticipated to prevent approximately 0.65 CV events compared with ezetimibe and statin over the lifetime horizon.

Table 15 Analysis G: Base case undiscounted CV event rates

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	1.19	0.90	0.50	-0.39	0.39	55%
IS	0.25	0.19	0.12	-0.08	0.08	11%
HF	0.42	0.38	0.29	-0.09	0.09	12%
CHD death	0.63	0.57	0.45	-0.12	0.12	17%
IS death	0.12	0.13	0.17	0.03	0.03	5%
Total	2.60	2.17	1.53	-0.65	0.71	100%
ACS, acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – QALY gains by health state

Disaggregated QALYs for statin, ezetimibe and statin, and evolocumab and statin are presented in Table 16. This indicates a total QALY gain of 0.86 for evolocumab and statin compared with ezetimibe and statin.

Table 16 Analysis G: Base case summary of QALYs by health state

Health state	QALY: Statin	QALY: Ezetimibe and statin (comparator)	QALY: Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.44	0.33	0.18	-0.15	0.15	7%
IS	0.07	0.05	0.03	-0.02	0.02	1%
HF	0.11	0.10	0.07	-0.03	0.03	1%
ECVD	2.12	2.34	2.68	0.33	0.33	16%
Post-acute	3.48	3.32	2.90	-0.42	0.42	20%
No CVD	3.34	3.89	5.03	1.14	1.14	55%
Total	9.56	10.03	10.89	0.86	2.09	100%
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke						

Disaggregated results – costs by health state

The base case disaggregated costs show that there is an anticipated saving of £ [REDACTED] associated with evolocumab and statin compared with ezetimibe and statin. These savings are attributable to a reduction in ACS, IS, HF, CHD death and revascularisation costs (Table 17).

Table 17 Analysis G: Base case summary of costs by health state

Health state	Cost: Statin	Cost: Ezetimibe and statin (comparator)	Cost: Evolocumab and statin	Increment vs. comparator	Absolute increase vs. comparator	% absolute increment
ACS	£2,439	£1,819	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IS	£593	£451	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HF	£699	£604	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CHD death	£236	£210	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
IS death	£101	£111	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ECVD	£1,566	£1,745	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Post-acute	£3,833	£3,833	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Revasc	£7,109	£5,098	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total	£16,577	£13,870	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; Revasc, revascularisation						

Summary of predicted resource use by category of cost

The resource use estimations show increased costs of £ [REDACTED] associated with evolocumab and statin compared with ezetimibe and statin over the time horizon. The summary in Table 18 indicates that these are due to additional costs for medication, and monitoring and training for evolocumab.

Table 18 Analysis G: Base case summary of resource use by health state

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£487	£5,412	████████	████████	████████	████████
Monitoring and training	£1,525	£1,578	████████	████████	████████	████████
Health states	£16,577	£13,681	████████	████████	████████	████████
Total	£18,589	£20,672	████████	████████	████████	████████

Analysis H: Evolocumab alone versus ezetimibe alone*Base case incremental cost-effectiveness results*

The incremental cost per QALY gained for evolocumab alone versus ezetimibe alone in patients with HeFH is £████████ based on incremental costs of £████████ and incremental QALYs of 0.82 (Table 19).

Table 19 Analysis H: Base case incremental cost, incremental QALYs, and ICER for the HeFH population

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
No lipid-lowering therapy	£18,102	9.56	████████	████████	████████	████████
Ezetimibe alone	£20,472	9.97	£2,370	0.41	£5,733	████████
Evolocumab alone	████████	10.79	████████	1.23	████████	████████

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Clinical outcomes – CV events

The base case undiscounted CV event rates for the HeFH population (statin intolerant or contraindicated) for evolocumab alone compared with ezetimibe alone are presented in Table 20. This indicates that evolocumab alone is anticipated to prevent approximately 0.63 CV events compared with ezetimibe alone.

Table 20 Analysis H: Base case undiscounted CV event rates

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	1.19	0.93	0.54	-0.38	0.38	56%
IS	0.25	0.20	0.12	-0.08	0.08	11%
HF	0.42	0.38	0.30	-0.08	0.08	12%
CHD death	0.63	0.58	0.47	-0.11	0.11	16%
IS death	0.12	0.13	0.16	0.03	0.03	4%
Total	2.60	2.22	1.60	-0.63	0.69	100%

ACS, acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; IS, ischaemic stroke

Disaggregated results – QALY gains by health state

Disaggregated QALYs for statin, ezetimibe and statin, and evolocumab and statin are presented in Table 21. This indicates a total QALY gain of 1.10 for evolocumab alone compared with ezetimibe alone.

Table 21 Analysis H: Base case summary of QALYs by health state

Health state	QALY: No lipid-lowering therapy	QALY: Ezetimibe alone (comparator)	QALY: Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	0.44	0.34	0.20	-0.14	0.14	7%
IS	0.07	0.06	0.03	-0.02	0.02	1%
HF	0.11	0.10	0.07	-0.03	0.03	1%
ECVD	2.12	2.32	2.64	0.33	0.33	17%
Post-acute	3.48	3.35	2.96	-0.39	0.39	20%
No CVD	3.34	3.81	4.88	1.07	1.07	54%
Total	9.56	9.97	10.79	0.82	1.97	100%

ACS, acute coronary syndrome; CVD, cardiovascular disease; ECVD, established CVD; HF, heart failure; IS, ischaemic stroke

Disaggregated results – costs by health state

The base case disaggregated costs show that there is an anticipated saving of £ [REDACTED] associated with evolocumab alone versus ezetimibe alone when considering the health states. These savings are attributable to a reduction in ACS, IS, HF, CHD death and revascularisation costs (Table 22).

Table 22 Analysis H: Base case summary of costs by health state

Health state	Cost: No lipid-lowering therapy	Cost: Ezetimibe alone (comparator)	Cost: Evolocumab alone	Increment vs. comparator	Absolute increase vs. comparator	Absolute increment
ACS	£2,439	£1,890	██████	██████	██████	██████
IS	£593	£468	██████	██████	██████	██████
HF	£699	£616	██████	██████	██████	██████
CHD death	£236	£213	██████	██████	██████	██████
IS death	£101	£110	██████	██████	██████	██████
ECVD	£1,566	£1,723	██████	██████	██████	██████
Post-acute	£3,833	£3,833	██████	██████	██████	██████
Revasc	£7,109	£5,326	██████	██████	██████	██████
Total	£16,577	£14,178	██████	██████	██████	██████
ACS, acute coronary syndrome; CHD, coronary heart disease; ECVD, established; CHF, heart failure; IS, ischaemic stroke; Revasc, Revascularisation						

Summary of predicted resource use by category of cost

The resource use estimations show increased costs associated with evolocumab alone compared with ezetimibe alone (£██████). The summary in Table 23 indicates that these are due to additional costs for medication, and monitoring and training for evolocumab.

Table 23 Analysis H: Base case summary of resource use by health state

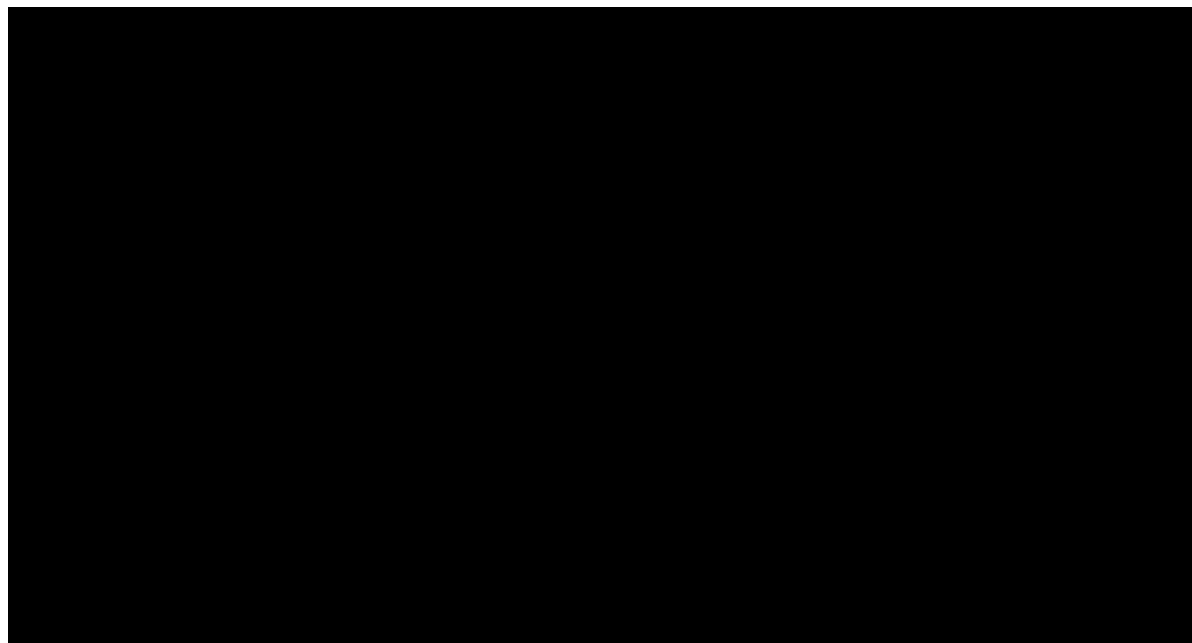
Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment vs. comparator	Absolute increase	Absolute increment
Medication	£0	£4,884	██████	██████	██████	██████
Monitoring and training	£1,525	£1,572	██████	██████	██████	██████
Health states	£16,577	£14,016	██████	██████	██████	██████
Total	£18,102	£20,472	██████	██████	██████	██████

1.5 Sensitivity analyses

Probabilistic sensitivity analysis

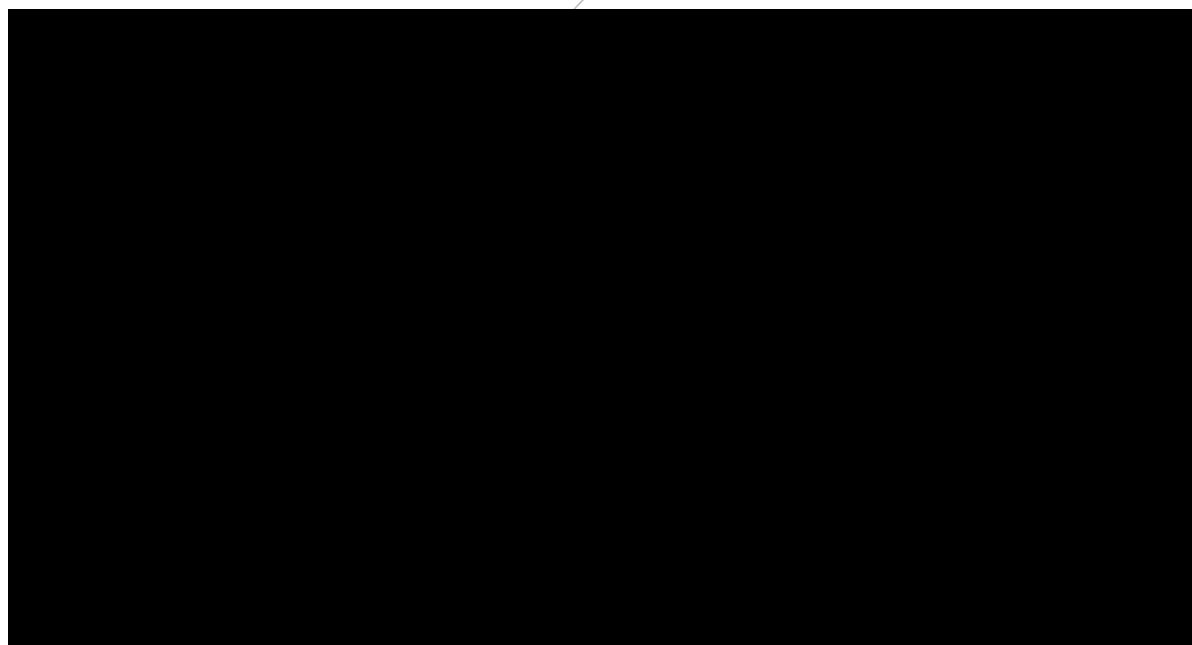
The probabilistic sensitivity analysis was run with 1,000 simulations. Probabilistic sensitivity analysis outputs are represented graphically by plotting incremental cost and effectiveness pairs on the cost-effectiveness plane and presenting the likelihood of evolocumab being the optimal strategy across different maximum willingness-to-pay thresholds. The results of the probabilistic sensitivity analysis depicted as scatter plots are presented in the figures below for patients with existing CVD and HeFH based on scenarios 1 and 2 (Figure 1 to Figure 4). The ellipses represent the 95% CI and the gradients represent £20,000 and £30,000 incremental cost per QALY gained on the scatterplots.

Figure 1 Scatterplot for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1]



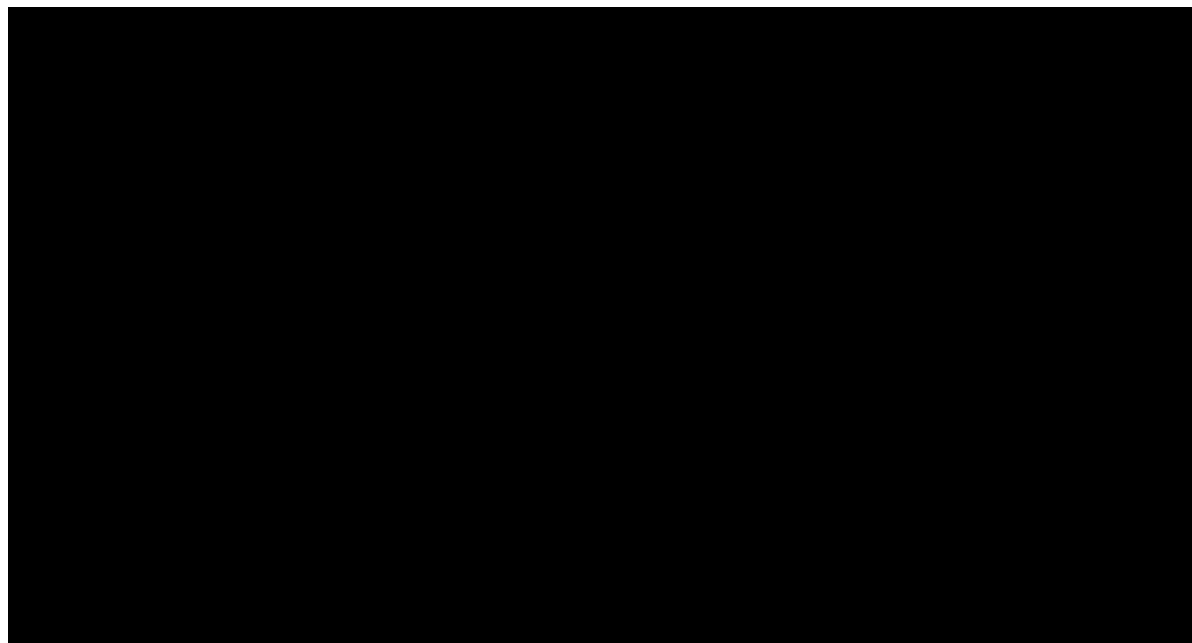
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention

Figure 2 Scatterplot for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2]



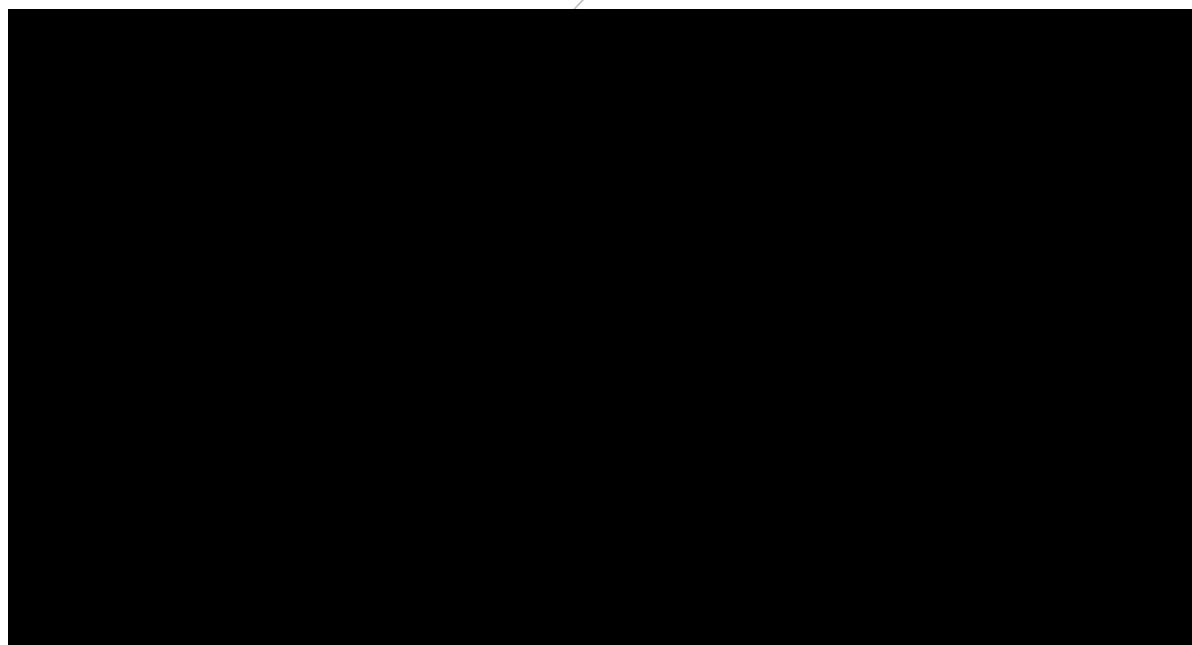
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention

Figure 3 Scatterplot for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

Figure 4 Scatterplot for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2]

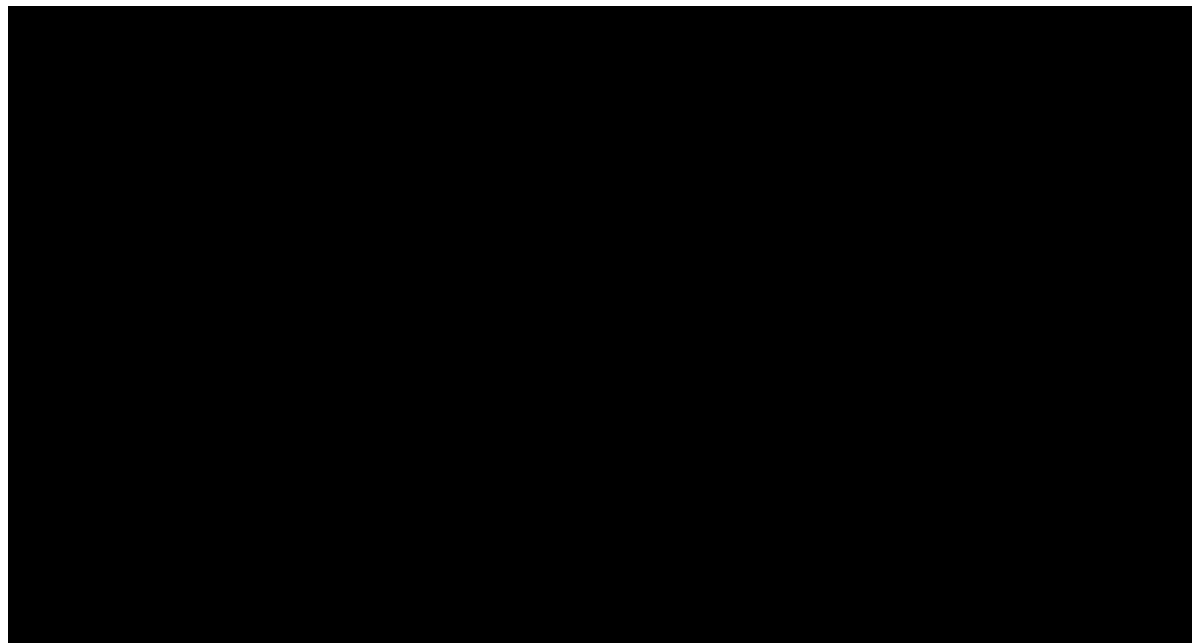


HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

In addition, cost-effectiveness acceptability curves were used to assess the proportion of simulations whereby the different treatment strategies for specific maximum acceptable ICERs. These are presented in Figure 5 to Figure 8 and summarised in Table 24. Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

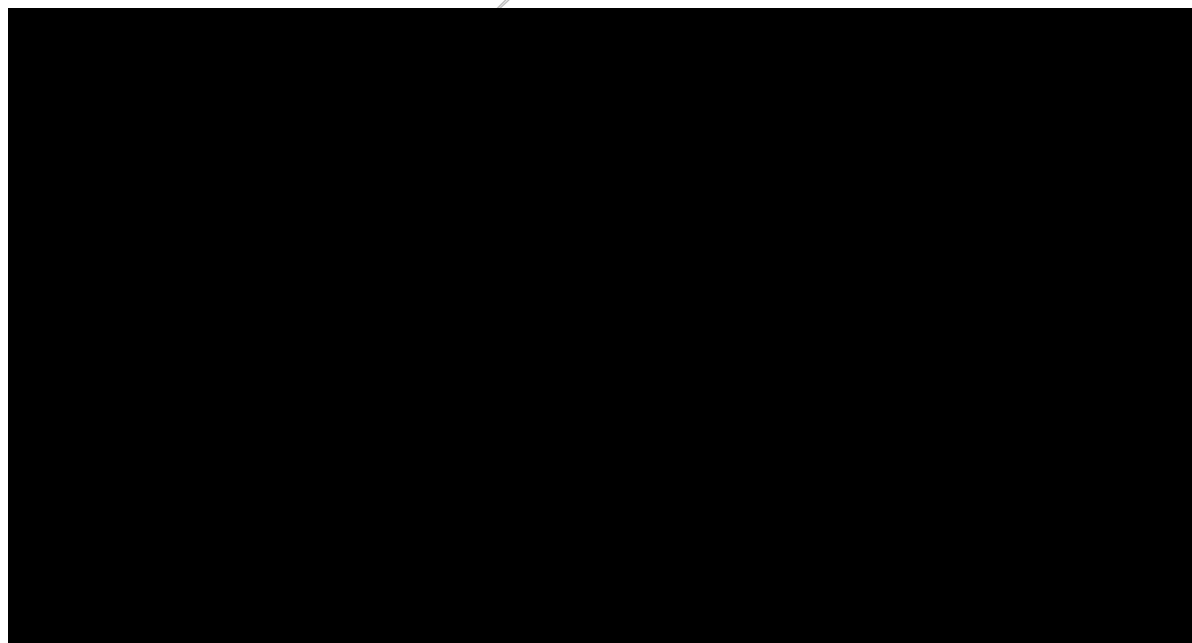
Furthermore, a comparison of the base case results for the deterministic and probabilistic analyses are presented in Table 25.

Figure 5 Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1]



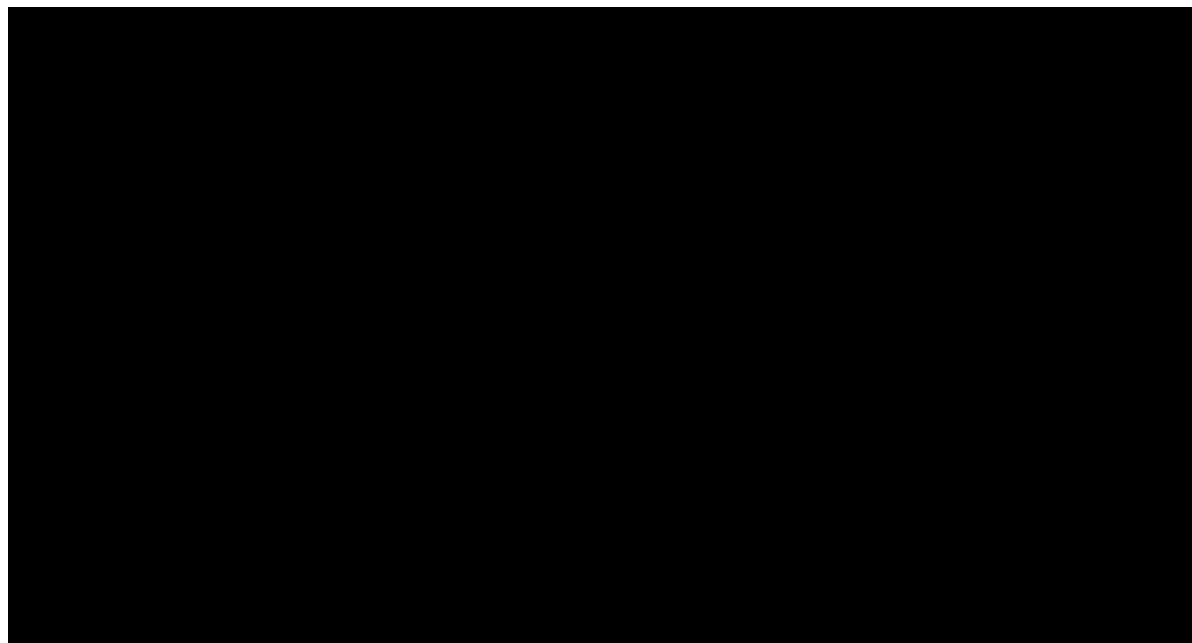
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 6 Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2]



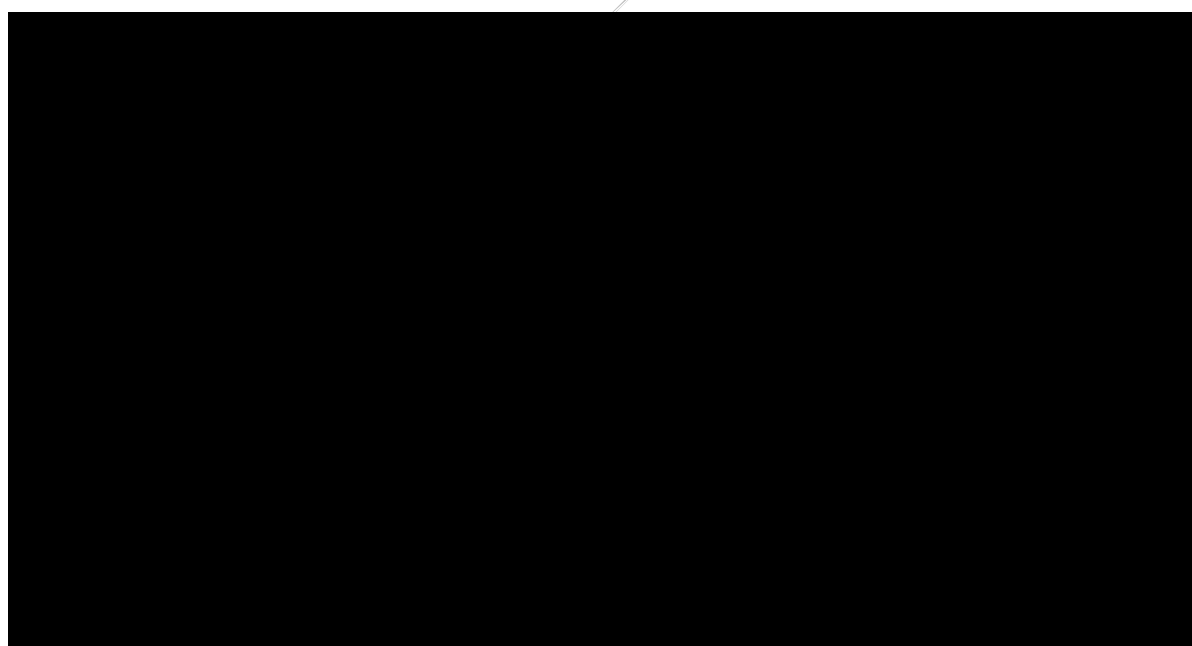
LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 7 Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol

Figure 8 Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol

Table 24 Probability of cost-effectiveness for evolocumab in different populations and maximum acceptable incremental cost-effectiveness ratios [scenarios 1 and 2]

Population	Intervention	Comparator	MAICER	
			£20,000 per QALY	£30,000 per QALY
Existing CVD	Evolocumab and statin	Ezetimibe and statin	██████	██████
	Evolocumab alone	Ezetimibe alone	██████	██████
HeFH	Evolocumab and statin	Ezetimibe and statin	██████	██████
	Evolocumab alone	Ezetimibe alone	██████	██████
HeFH; heterozygous familial hypercholesterolaemia; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year				

Table 25 Deterministic and probabilistic incremental cost-effectiveness ratios

Pop.	Intervention	Comparator	ICER	
			Deterministic	Probabilistic
Existing CVD	Evolocumab and statin	Ezetimibe and statin	██████	██████
	Evolocumab alone	Ezetimibe alone	██████	██████
HeFH	Evolocumab and statin	Ezetimibe and statin	██████	██████
	Evolocumab alone	Ezetimibe alone	██████	██████
HeFH; heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; Pop., population; QALY, quality-adjusted life-year				

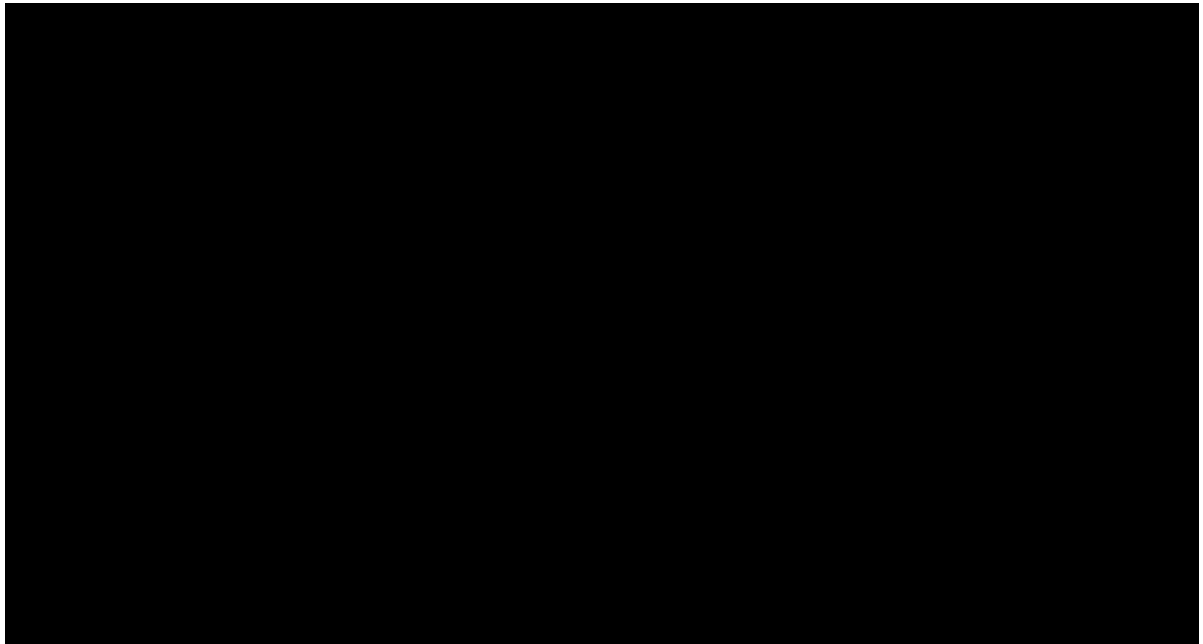
Deterministic sensitivity analysis

Deterministic sensitivity analyses were performed by means of one-way sensitivity analyses, where one parameter was varied relative to its base case value. A summary of the results is presented below for patients with existing CVD and patients with HeFH for evolocumab and statin versus ezetimibe and statin. The additional scenarios are not presented as the results were not sensitive to the different treatment strategies covered in scenarios 2 to 4. All parameters where the incremental cost per QALY gained was sensitive by > 1% are presented in Tornado plots (Figure 9 to Figure 10).

The Tornado plots that indicate the most sensitive parameters for cost-effectiveness of evolocumab versus ezetimibe were:

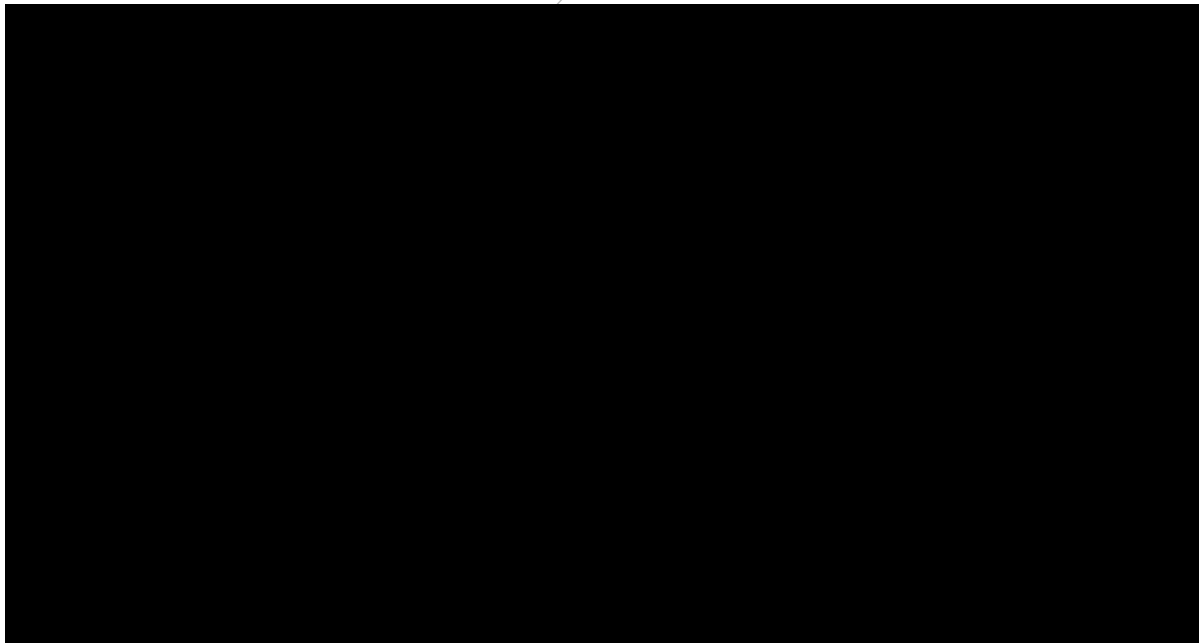
- CV event rate ratio (HeFH alone)
- CPRD ratio ratios (secondary prevention alone)
- treatment duration
- effect of LDL-C reduction on CV events
- ezetimibe treatment effect
- evolocumab treatment effect
- 'ECVD' and 'post-ACS' health state utility multiplier.

Figure 9 Tornado plot: evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1]



ACS, acute coronary syndrome; CI, confidence interval; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 10 Tornado plot: evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]



ACS, acute coronary syndrome; CI, confidence interval; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol

1.6 Scenario analysis

Existing CVD and severity of hypercholesterolaemia

For the existing CVD population, the impact of severity of hypercholesterolaemia has been assessed on the basis of the baseline LDL-C level when treatment with evolocumab or ezetimibe would be initiated. Results from scenario 1 (evolocumab and statin vs. ezetimibe and statin) is presented in Table 26 indicate that the incremental cost per QALY gained is £[REDACTED] to £[REDACTED] based on a baseline LDL-C range of 3.0 mmol/L to 6.0 mmol/L. Additional analyses for scenarios 2 to 4 have not been presented given the same anticipated trend with respect to cost-effectiveness and severity of hypercholesterolaemia.

Table 26 Scenario analyses: Existing CVD and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Baseline LDL-C	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
3.0 mmol/L	[REDACTED]	£21,639	[REDACTED]	8.15	7.80	0.35	[REDACTED]
3.5 mmol/L	[REDACTED]	£21,442	[REDACTED]	8.22	7.84	0.39	[REDACTED]
4.0 mmol/L	[REDACTED]	£21,253	[REDACTED]	8.29	7.87	0.42	[REDACTED]
4.5 mmol/L	[REDACTED]	£21,071	[REDACTED]	8.35	7.89	0.45	[REDACTED]
5.0 mmol/L	[REDACTED]	£20,897	[REDACTED]	8.41	7.92	0.48	[REDACTED]
5.5 mmol/L	[REDACTED]	£20,729	[REDACTED]	8.46	7.95	0.51	[REDACTED]
6.0 mmol/L	[REDACTED]	£20,569	[REDACTED]	8.51	7.98	0.53	[REDACTED]
CVD, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year							

HeFH and severity of hypercholesterolaemia

For the HeFH population, the impact of severity of hypercholesterolaemia has been assessed on the basis of the baseline LDL-C level when treatment with evolocumab or ezetimibe would be initiated (scenario 1 modelled). As for patients with existing CVD, scenarios 2 to 4 have not been presented based on severity of hypercholesterolaemia.

Table 27 Scenario analyses: HeFH and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Baseline LDL-C	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
3.0 mmol/L	[REDACTED]	£21,270	[REDACTED]	10.59	9.92	0.67	[REDACTED]
3.5 mmol/L	[REDACTED]	£20,971	[REDACTED]	10.74	9.98	0.77	[REDACTED]
4.0 mmol/L	[REDACTED]	£20,683	[REDACTED]	10.89	10.03	0.86	[REDACTED]
4.5 mmol/L	[REDACTED]	£20,406	[REDACTED]	11.03	10.09	0.94	[REDACTED]
5.0 mmol/L	[REDACTED]	£20,138	[REDACTED]	11.16	10.14	1.02	[REDACTED]
5.5 mmol/L	[REDACTED]	£19,881	[REDACTED]	11.29	10.20	1.09	[REDACTED]
6.0 mmol/L	[REDACTED]	£19,633	[REDACTED]	11.41	10.26	1.16	[REDACTED]

Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

Additional scenario analyses

The following scenario analyses were performed for patients without existing CVD, patients with existing CVD and patients with HeFH.

Treatment scenarios for evolocumab: In the base case, it is assumed that evolocumab will be used either in combination with statin or alone in patients who are statin intolerant or contraindicated. In these scenarios the cost-effectiveness of evolocumab and ezetimibe versus ezetimibe alone (scenario 3), and evolocumab, statin and ezetimibe versus statin and ezetimibe (scenario 4) are assessed.

Treatment duration: In the base case analysis, a lifetime treatment duration (to a maximum age of 100 years) is assumed. In these scenario analyses the treatment duration is shortened to 5, 10, and 20 years.

Discounting: In the base case, discount rates of 3.5% were applied to both costs and health effects. Here the discount rates are changed to (1) 0% for both costs and health effects, and (2) 0% for costs and 6% for health effects.

Risk capping at age 75 years: As CVD patients age, the risk of CV events increases. In this scenario it is assumed that the risk of CV events does not increase any more after patients have reached the age of 75 years (versus 85 years assumed in the base case).

CV cost data based on NICE CG181: In the base case CV, costs were based on the CPRD study. In this scenario the costs for CV events as presented in NICE CG181 are used.

Utilities based on TTO study: In the base case, utilities as presented in NICE CG181 were used. In this scenario analysis, utilities from the TTO study are used. This analysis uses the absolute utility modelling approach, not the multiplicative approach applied in the base case.

Nursing time evolocumab self-administration training: In the base case it is assumed that 1 hour of nurse time will be needed for evolocumab self-administration training. As this is an assumption, the impact of using half and double the time is investigated.

Analysis E: Evolocumab and ezetimibe versus ezetimibe alone in secondary prevention

The incremental cost per QALY for evolocumab and ezetimibe versus ezetimibe alone in patients with existing CVD is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 0.42 (Table 28).

Table 28 Analysis E: Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab and ezetimibe versus ezetimibe alone)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Ezetimibe	£21,143	7.81			
Evolocumab and ezetimibe		8.24		0.42	
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Analysis F: Evolocumab, statin and ezetimibe versus statin and ezetimibe in secondary prevention

The incremental cost per QALY for evolocumab, statin, and ezetimibe versus statin and ezetimibe in patients with existing CVD is £ based on incremental costs of £ and incremental QALYs of 0.44 (Table 29).

Table 29 Analysis F: Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab, statin and ezetimibe versus statin and ezetimibe)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Statin and ezetimibe	£21,408	7.84			
Evolocumab, statin and ezetimibe		8.28		0.44	
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Analysis I: Evolocumab and ezetimibe versus ezetimibe alone in HeFH

The incremental cost per QALY for evolocumab and ezetimibe versus ezetimibe alone in patients with HeFH is £ based on incremental costs of £ and incremental QALYs of 0.96 (Table 30).

Table 30 Analysis I: Base case incremental cost, incremental QALYs and ICER for patients with HeFH (evolocumab and ezetimibe versus ezetimibe alone)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Ezetimibe	£20,472	9.97			
Evolocumab and ezetimibe		10.93		0.96	

Evolocumab for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Analysis J: Evolocumab, statin, and ezetimibe versus statin and ezetimibe in HeFH

The incremental cost per QALY for evolocumab, statin, and ezetimibe versus statin and ezetimibe in patients with HeFH is £[REDACTED] based on incremental costs of £[REDACTED] and incremental QALYs of 1.00 (Table 31).

Table 31 Analysis J: Base case incremental cost, incremental QALYs, and ICER for patients with HeFH (evolocumab, statin and ezetimibe vs. statin and ezetimibe)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Statin and ezetimibe	£20,672	10.03			
Evolocumab, statin and ezetimibe	[REDACTED]	11.03	[REDACTED]	1.00	[REDACTED]
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Table 32 Scenario analyses – existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
Base case	██████	£21,408	██████	8.23	7.84	0.39	██████
Evolocumab QM PFP	██████	£21,408	██████	8.24	7.84	0.40	██████
5-year treatment duration	██████	£17,968	██████	7.78	7.67	0.10	██████
10-year treatment duration	██████	£19,289	██████	7.93	7.73	0.20	██████
20-year treatment duration	██████	£20,849	██████	8.15	7.81	0.34	██████
Discounting: 0% costs, 0% effects	██████	£31,674	██████	12.07	11.31	0.76	██████
Discounting: 0% costs, 6% effects	██████	£31,674	██████	6.57	6.31	0.26	██████
Risk capping 75 years	██████	£21,417	██████	8.29	7.91	0.38	██████
NICE CG181 CV costs	██████	£24,966	██████	8.23	7.84	0.39	██████
TTO study utilities	██████	£21,408	██████	10.00	9.47	0.52	██████
Nurse training 30 minutes	██████	£21,408	██████	8.23	7.84	0.39	██████
Nurse training 2 hours	██████	£21,408	██████	8.23	7.84	0.39	██████
CV, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

Table 33 Scenario analyses – HeFH population (evolocumab and statin versus ezetimibe and statin) [scenario 1]

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
Base case	██████	£20,672	██████	10.89	10.03	0.86	██████
Evolocumab QM PFP	██████	£20,672	██████	10.93	10.03	0.90	██████
5-year treatment duration	██████	£17,198	██████	9.87	9.68	0.19	██████
10-year treatment duration	██████	£18,191	██████	10.15	9.79	0.36	██████
20-year treatment duration	██████	£19,818	██████	10.61	9.95	0.66	██████
Discounting: 0% costs, 0% effects	██████	£34,004	██████	16.86	15.05	1.81	██████
Discounting: 0% costs, 6% effects	██████	£34,004	██████	8.48	7.93	0.55	██████
Risk capping 75 years	██████	£20,699	██████	10.94	10.07	0.87	██████
NICE CG181 CV costs	██████	£21,943	██████	10.89	10.03	0.86	██████
TTO study utilities	██████	£20,672	██████	11.90	11.02	0.88	██████
Nurse training 30 minutes	██████	£20,672	██████	10.89	10.03	0.86	██████
Nurse training 2 hours	██████	£20,672	██████	10.89	10.03	0.86	██████
CV, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

1.7 Subgroup analysis

Existing CVD and additional risk factors

Table 34 Cost-effectiveness analysis of evolocumab and statin versus ezetimibe and statin in patients with existing CVD and additional risk factors

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER	Difference
Base case		£21,408		8.23	7.84	0.39		0
Baseline LDL-C								
3.0 mmol/L		£21,639		8.15	7.80	0.35		
3.5 mmol/L		£21,442		8.22	7.84	0.39		
4.0 mmol/L		£21,253		8.29	7.87	0.42		
4.5 mmol/L		£21,071		8.35	7.89	0.45		
5.0 mmol/L		£20,897		8.41	7.92	0.48		
5.5 mmol/L		£20,729		8.46	7.95	0.51		
6.0 mmol/L		£20,569		8.51	7.98	0.53		
Gender								
Male		£21,104		8.07	7.69	0.39		
Female		£22,069		8.58	8.18	0.41		
Diabetes mellitus = Yes		£21,795		7.88	7.40	0.48		
Vascular beds = 2		£21,709		7.95	7.49	0.46		
Vascular beds = 3		£22,207		7.54	6.99	0.55		
AF = Yes		£21,704		7.96	7.50	0.46		
CV event in the past year								
ECVD		£17,648		8.99	8.61	0.38		
ACS		£28,294		8.68	8.23	0.46		
Post-ACS		£24,010		8.79	8.35	0.44		
IS		£22,144		6.10	5.91	0.19		
Post-IS		£20,188		6.08	5.89	0.20		
HF		£25,267		6.22	5.77	0.44		
Post-HF		£24,601		6.33	5.92	0.41		
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; ECVD, established cardiovascular disease; EvoMab; evolocumab; EZE, ezetimibe; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TTO, time trade off								

Combination of risk factors with baseline LDL-C, age, and gender

Secondly, the impact of combining one of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 35).

Table 35 Cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin with specific CV risk factors

Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
3.5 mmol/L	Cohort	Cohort												
		+5												
		+10												
	Male	Cohort												
		+5												
		+10												
	Female	Cohort												
		+5												
		+10												
Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
4.0 mmol/L	Cohort	Cohort												
		+5												
		+10												
	Male	Cohort												
		+5												
		+10												
	Female	Cohort												
		+5												

		+10												
Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
4.5 mmol/L	Cohort	Cohort												
		+5												
		+10												
	Male	Cohort												
		+5												
		+10												
	Female	Cohort												
		+5												
		+10												
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; PACS, post-acute coronary syndrome; PHF, post-heart failure; PIS, post-IS; QALY, quality-adjusted life year; SP, secondary prevention; VB, vascular beds														

Combination of two risk factors with baseline LDL-C, age, and gender

Thirdly, the impact of combining two of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 36).

Table 36 Cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin with two specific CV risk factors

Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB	DM:HF	HF:2VB	HF:3VB
3.0 mmol/L	Cohort	Cohort										
		+5										
		+10										
	Male	Cohort										
		+5										
		+10										
	Female	Cohort										
		+5										
		+10										
Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB	DM:HF	HF:2VB	HF:3VB
3.5 mmol/L	Cohort	Cohort										
		+5										
		+10										
	Male	Cohort										
		+5										
		+10										
	Female	Cohort										
		+5										
		+10										

Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB	DM:HF	HF:2VB	HF:3VB
4.0 mmol/L	Cohort	Cohort										
		+5										
		+10										
	Male	Cohort										
		+5										
		+10										
	Female	Cohort										
		+5										
		+10										
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention; VB, vascular beds Note: heart failure population based on post-health failure health state												

1.8 Validation

Validation of cost-effectiveness analysis

Table 37 Model validation: Predicted rate ratio by CVD event for evolocumab versus high-intensity statin

	Rate ratio per mmol/L reduction, CTTC 2010 (5 years)	Rate ratio per mmol/L reduction, predicted (1 year)	Rate ratio per mmol/L reduction, predicted (5 years)	Rate ratio per mmol/L reduction, predicted (lifetime)	Rate ratio per mmol/L reduction, CTTC 2010 (5 years)	Rate ratio per mmol/L reduction, predicted (1 year)	Rate ratio per mmol/L reduction, predicted (5 years)	Rate ratio per mmol/L reduction, predicted (lifetime)
	Existing CVD				HeFH			
Any major event	0.72	0.72	0.72	0.75	0.72	0.72	0.71	0.75
ACS	0.71	0.71	0.70	0.71	0.71	0.71	0.70	0.71
IS	0.69	0.69	0.68	0.71	0.69	0.69	0.68	0.71
HF*	0.71	0.92	0.92	0.92	0.71	0.80	0.79	0.92
CHD death	0.80	0.80	0.80	0.83	0.80	0.80	0.81	0.83
IS death	1.00	1.00	0.99	1.06	1.00	1.00	0.99	1.06
Revascularisation	0.66	0.69	0.69	0.69	0.66	0.70	0.68	0.69
ACS, acute coronary syndrome; CHD, coronary heart disease; CTTC, Cholesterol Treatment Trialists' Collaboration; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; IS, ischaemic stroke *Assumed equivalent to ACS								

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia

Patient access scheme submission template

October 2015

File name	Version	Contains confidential information	Date
		Yes CIC: Redacted	November 2015

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalalpriceregulationscheme/2009PPRS).

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
(<http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmq9>)
- 'Specification for manufacturer/sponsor submission of evidence'
(<http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologypappraisalsubmissiontemplates.jsp>) and
- Pharmaceutical Price Regulation Scheme 2009
(www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process'
(http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

'Specification for manufacturer/sponsor submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal' (<http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmq9>).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Technology: Evolocumab (brand name: Repatha)

Disease area: Hypercholesterolaemia and mixed dyslipidaemia

3.2 Please outline the rationale for developing the patient access scheme.

The patient access scheme (simple scheme) has been developed in order to allow demonstration of cost-effectiveness for the technology versus the comparator in the relevant populations in accordance with the Institute's reference case.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The patient access scheme is a simple scheme (confidential discount).

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

The proposed patient access scheme applies to the full indication.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections?

Not applicable.

3.6 *What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?*

Not applicable.

3.7 *Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?*

Not applicable.

3.8 *Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.*

The price (including the patient access scheme confidential discount) will be demonstrated to NHS organisations on the original invoice.

3.9 *Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.*

See above.

3.10 *Please provide details of the duration of the scheme.*

The patient access scheme will remain in place until NICE next reviews the product under the technology appraisals programme and a final decision has been published by NICE (as per the declaration signed by Amgen in the patient access scheme proposal template).

3.11 *Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?*

None.

3.12 *If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for*

pharmacists and physicians and patient information documents.
Please include copies in the appendices.

None.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

4 Cost effectiveness

- 4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also *complete the rest of this template.*

The patient access scheme applies to the entire licensed population.

- 4.2 *If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.*

Patient access scheme approved prior to Appraisal Committee meeting. No changes have been made to the model except that identified by the Evidence Review Group (summarised in Addendum dated 4/10/2015).

- 4.3 *Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.*

The patient access scheme is incorporated into the economic model through an effective change in the acquisition price. The list-price of evolocumab is £170.10 per 140mg prefilled pen or syringe. The patient access scheme is a fixed price of £[REDACTED] per 140mg prefilled pen or syringe.

The patient access scheme (evolocumab drug cost) has been implemented in the economic model in the 'Parameters List' worksheet and descriptively in the 'Costs & CVD Utilities' worksheet.

4.4 *Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.*

Not applicable.

4.5 *Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.*

Not applicable.

4.6 *Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.*

Not applicable.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.¹

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

The analyses detailed in Table 1 are presented with and without the patient access scheme (PAS) in this section. Only the summary of resource use (medication, monitoring and health state costs) results tables have been included in this section.

Table 1 Modelled intervention and comparator for patients with and without existing CVD, and patients with HeFH

Pop.	Intervention	Comparator	Analysis, Section, Tables
Without existing CVD	Evolocumab and statin	Ezetimibe and statin	Analysis A
	Evolocumab alone	Ezetimibe alone	Analysis B
	Evolocumab and ezetimibe	Ezetimibe alone	Not conducted
	Evolocumab, statin, and ezetimibe	Ezetimibe and statin	Not conducted
Existing CVD	Evolocumab and statin	Ezetimibe and statin	Analysis C
	Evolocumab alone	Ezetimibe alone	Analysis D
	Evolocumab and ezetimibe	Ezetimibe alone	Analysis E
	Evolocumab, statin, and ezetimibe	Ezetimibe and statin	Analysis F
HeFH	Evolocumab and statin	Ezetimibe and statin	Analysis G
	Evolocumab alone	Ezetimibe alone	Analysis H
	Evolocumab and ezetimibe	Ezetimibe alone	Analysis I
	Evolocumab, statin, and ezetimibe	Ezetimibe and statin	Analysis J
CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia			

¹ For outcome-based schemes, please see section 5.2.8 in appendix B.

Without existing CVD

Analysis A: Evolocumab and statin versus ezetimibe and statin

Table 2 Base case summary of resource use by health state [without PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£287	£5,724	██████	██████	██████	██████
Monitoring and training	£1,712	£1,734	██████	██████	██████	██████
Health states	£3,313	£2,521	██████	██████	██████	██████
Total	£5,313	£9,979	██████	██████	██████	██████

Table 3 Base case summary of resource use by health state [with PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£287	£5,724	██████	██████	██████	██████
Monitoring and training	£1,712	£1,734	██████	██████	██████	██████
Health states	£3,313	£2,521	██████	██████	██████	██████
Total	£5,313	£9,979	██████	██████	██████	██████

Analysis B: Evolocumab alone versus ezetimibe alone

Table 4 Base case summary of resource use by health state [without PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£0	£5,424	██████	██████	██████	██████
Monitoring and training	£1,712	£1,731	██████	██████	██████	██████
Health states	£3,313	£2,612	██████	██████	██████	██████
Total	£5,025	£9,767	██████	██████	██████	██████

Table 5 Base case summary of resource use by health state [with PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£0	£5,424	██████	██████	██████	██████

Monitoring and training	£1,712	£1,731	██████	██████	██████	██████
Health states	£3,313	£2,612	██████	██████	██████	██████
Total	£5,025	£9,767	██████	██████	██████	██████

Existing CVD

Analysis C: Evolocumab and statin versus ezetimibe and statin

Table 6 Base case summary of resource use by health state [without PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£438	£4,819	██████	██████	██████	██████
Monitoring and training	£1,385	£1,420	██████	██████	██████	██████
Health states	£16,923	£15,169	██████	██████	██████	██████
Total	£18,745	£21,408	██████	██████	██████	██████

Table 7 Base case summary of resource use by health state [with PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£438	£4,819	██████	██████	██████	██████
Monitoring and training	£1,385	£1,420	██████	██████	██████	██████
Health states	£16,923	£15,169	██████	██████	██████	██████
Total	£18,745	£21,408	██████	██████	██████	██████

Analysis D: Evolocumab alone versus ezetimibe alone

Table 8 Base case summary of resource use by health state [without PAS]

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment	Absolute increase	Absolute increment
Medication	£0	£4,354	██████	██████	██████	██████
Monitoring and training	£1,385	£1,415	██████	██████	██████	██████
Health states	£16,923	£15,373	██████	██████	██████	██████

Total	£18,307	£21,143				

Table 9 Base case summary of resource use by health state [with PAS]

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment	Absolute increase	Absolute increment
Medication	£0	£4,354				
Monitoring and training	£1,385	£1,415				
Health states	£16,923	£15,373				
Total	£18,307	£21,143				

Analysis E: Evolocumab and ezetimibe versus ezetimibe alone

Table 10 Base case summary of resource use by health state [without PAS]

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment	Absolute increase	Absolute increment
Medication	£0	£4,354				
Monitoring and training	£1,385	£1,415				
Health states	£16,923	£15,373				
Total	£18,307	£21,143				

Table 11 Base case summary of resource use by health state [with PAS]

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment	Absolute increase	Absolute increment
Medication	£0	£4,354				
Monitoring and training	£1,385	£1,415				
Health states	£16,923	£15,373				
Total	£18,307	£21,143				

Analysis F: Evolocumab, statin and ezetimibe versus statin and ezetimibe

Table 12 Base case summary of resource use by health state [without PAS]

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment	Absolute increase	Absolute increment
Medication	£438	£4,819	██████	██████	██████	██████
Monitoring and training	£1,385	£1,420	██████	██████	██████	██████
Health states	£16,923	£15,169	██████	██████	██████	██████
Total	£18,745	£21,408	██████	██████	██████	██████

Table 13 Base case summary of resource use by health state [with PAS]

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment	Absolute increase	Absolute increment
Medication	£438	£4,819	██████	██████	██████	██████
Monitoring and training	£1,385	£1,420	██████	██████	██████	██████
Health states	£16,923	£15,169	██████	██████	██████	██████
Total	£18,745	£21,408	██████	██████	██████	██████

Heterozygous familial hypercholesterolaemia

Analysis G: Evolocumab and statin versus ezetimibe and statin

Table 14 Base case summary of resource use by health state [without PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£487	£5,412	██████	██████	██████	██████
Monitoring and training	£1,525	£1,578	██████	██████	██████	██████
Health states	£16,577	£13,681	██████	██████	██████	██████
Total	£18,589	£20,672	██████	██████	██████	██████

Table 15 Base case summary of resource use by health state [with PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£487	£5,412	██████	██████	██████	██████
Monitoring and training	£1,525	£1,578	██████	██████	██████	██████
Health states	£16,577	£13,681	██████	██████	██████	██████
Total	£18,589	£20,672	██████	██████	██████	██████

Analysis H: Evolocumab alone versus ezetimibe alone**Table 16 Base case summary of resource use by health state [without PAS]**

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment vs. comparator	Absolute increase	Absolute increment
Medication	£0	£4,884	██████	██████	██████	██████
Monitoring and training	£1,525	£1,572	██████	██████	██████	██████
Health states	£16,577	£14,016	██████	██████	██████	██████
Total	£18,102	£20,472	██████	██████	██████	██████

Table 17 Base case summary of resource use by health state [with PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£0	£4,884	██████	██████	██████	██████
Monitoring and training	£1,525	£1,572	██████	██████	██████	██████
Health states	£16,577	£14,016	██████	██████	██████	██████
Total	£18,102	£20,472	██████	██████	██████	██████

Analysis I: Evolocumab and ezetimibe versus ezetimibe alone**Table 18 Base case summary of resource use by health state [without PAS]**

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment	Absolute increase	Absolute increment
Medication	£0	£4,884	██████	██████	██████	██████
Monitoring and training	£1,525	£1,572	██████	██████	██████	██████

Health states	£16,577	£14,016	██████	██████	██████	██████
Total	£18,102	£20,472	██████	██████	██████	██████

Table 19 Base case summary of resource use by health state [with PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£0	£4,884	██████	██████	██████	██████
Monitoring and training	£1,525	£1,572	██████	██████	██████	██████
Health states	£16,577	£14,016	██████	██████	██████	██████
Total	£18,102	£20,472	██████	██████	██████	██████

Analysis J: Evolocumab, statin, and ezetimibe versus statin and ezetimibe

Table 20 Base case summary of resource use by health state [without PAS]

Health state	No lipid-lowering therapy	Ezetimibe alone (comparator)	Evolocumab alone	Increment	Absolute increase	Absolute increment
Medication	£487	£5,412	██████	██████	██████	██████
Monitoring and training	£1,525	£1,578	██████	██████	██████	██████
Health states	£16,577	£13,681	██████	██████	██████	██████
Total	£18,589	£20,672	██████	██████	██████	██████

Table 21 Base case summary of resource use by health state [with PAS]

Health state	Statin	Ezetimibe and statin (comparator)	Evolocumab and statin	Increment	Absolute increase	Absolute increment
Medication	£487	£5,412	██████	██████	██████	██████
Monitoring and training	£1,525	£1,578	██████	██████	██████	██████
Health states	£16,577	£13,681	██████	██████	██████	██████
Total	£18,589	£20,672	██████	██████	██████	██████

4.8 Please present in separate tables the incremental results as follows.²

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

Without existing CVD

Analysis A: Evolocumab and statin versus ezetimibe and statin

Table 22 Base case incremental cost, incremental QALYs, and ICER for patients without existing CVD (evolocumab and statin versus ezetimibe and statin) [without PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£5,313	11.62				
Ezetimibe and statin	£9,979	11.83	£4,667	0.20	£22,896	
Evolocumab and statin		12.14		0.52		

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 23 Base case incremental cost, incremental QALYs, and ICER for patients without existing CVD (evolocumab and statin versus ezetimibe and statin) [with PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£5,313	11.62				
Ezetimibe and statin	£9,979	11.83	£4,667	0.20	£22,896	
Evolocumab and statin		12.14		0.52		£74,331

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Analysis B: Evolocumab alone versus ezetimibe alone

Table 24 Base case incremental cost, incremental QALYs, and ICER for patients without existing CVD (evolocumab alone versus ezetimibe alone) [without PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£5,025	11.62				
Ezetimibe and statin	£9,767	11.80	£4,742	0.18	£26,434	

² For outcome-based schemes, please see section 5.2.9 in appendix B.

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Evolocumab and statin	██████	12.10	██████	0.48	██████	██████
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Table 25 Base case incremental cost, incremental QALYs, and ICER for patients without existing CVD (evolocumab alone versus ezetimibe alone) [with PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£5,025	11.62	██████	██████	██████	██████
Ezetimibe and statin	£9,767	11.80	£4,742	0.18	£26,434	██████
Evolocumab and statin	██████	12.10	██████	0.48	██████	£78,879
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Existing CVD

Analysis C: Evolocumab and statin versus ezetimibe and statin

Table 26 Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab and statin versus ezetimibe and statin) [without PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£18,745	7.61	██████	██████	██████	██████
Ezetimibe and statin	£21,408	7.84	£2,663	0.23	£11,412	██████
Evolocumab and statin	██████	8.23	██████	0.63	██████	██████
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Table 27 Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab and statin versus ezetimibe and statin) [with PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£18,745	7.61	██████	██████	██████	██████
Ezetimibe and statin	£21,408	7.84	£2,663	0.23	£11,412	██████
Evolocumab and statin	██████	8.23	██████	0.63	██████	£46,005
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Analysis D: Evolocumab alone versus ezetimibe alone

Table 28 Base case incremental cost, incremental QALYs and ICER for patients with existing CVD [without PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
No lipid-lowering therapy	£18,307	7.61				
Ezetimibe alone	£21,143	7.81	£2,835	0.20	£13,853	
Evolocumab alone		8.18		0.57		
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Table 29 Base case incremental cost, incremental QALYs and ICER for patients with existing CVD [with PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
No lipid-lowering therapy	£18,307	7.61				
Ezetimibe alone	£21,143	7.81	£2,835	0.20	£13,853	
Evolocumab alone		8.18		0.57		£49,278
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Analysis E: Evolocumab and ezetimibe versus ezetimibe alone

Table 30 Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab and ezetimibe versus ezetimibe alone) [without PAS]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Ezetimibe	£21,143	7.81			
Evolocumab and ezetimibe		8.24		0.42	
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Table 31 Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab and ezetimibe versus ezetimibe alone) [with PAS]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Ezetimibe	£21,143	7.81			
Evolocumab and ezetimibe		8.24		0.42	£52,811
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Analysis F: Evolocumab, statin and ezetimibe versus statin and ezetimibe

Table 32 Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab, statin and ezetimibe versus statin and ezetimibe) [without PAS]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Statin and ezetimibe	£21,408	7.84			
Evolocumab, statin and ezetimibe		8.28		0.44	
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Table 33 Base case incremental cost, incremental QALYs, and ICER for patients with existing CVD (evolocumab, statin, and ezetimibe versus statin and ezetimibe) [with PAS]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Statin and ezetimibe	£21,408	7.84			
Evolocumab, statin and ezetimibe		8.28		0.44	£50,880
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Heterozygous familial hypercholesterolaemia

Analysis G: Evolocumab and statin versus ezetimibe and statin

Table 34 Analysis G: Base case incremental cost, incremental QALYs and ICER for the HeFH population (evolocumab and statin vs. ezetimibe and statin) [without PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£18,589	9.56				
Ezetimibe and statin	£20,672	10.03	£2,083	0.47	£4,398	
Evolocumab and statin		10.89		1.33		
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Table 35 Analysis G: Base case incremental cost, incremental QALYs and ICER for the HeFH population (evolocumab and statin vs. ezetimibe and statin) [with PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
Statin	£18,589	9.56				
Ezetimibe and statin	£20,672	10.03	£2,083	0.47	£4,398	
Evolocumab and statin		10.89		1.33		£22,902
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Analysis H: Evolocumab alone versus ezetimibe alone

Table 36 Analysis H: Base case incremental cost, incremental QALYs, and ICER for the HeFH population [without PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
No lipid-lowering therapy	£18,102	9.56				
Ezetimibe alone	£20,472	9.97	£2,370	0.41	£5,733	
Evolocumab alone		10.79		1.23		
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Table 37 Analysis H: Base case incremental cost, incremental QALYs, and ICER for the HeFH population [with PAS]

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER incremental (QALYs) vs. baseline	ICER incremental (QALYs) vs. comparator
No lipid-lowering therapy	£18,102	9.56				
Ezetimibe alone	£20,472	9.97	£2,370	0.41	£5,733	
Evolocumab alone		10.79		1.23		£23,927
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

Analysis I: Evolocumab and ezetimibe versus ezetimibe alone

Table 38 Analysis I: Base case incremental cost, incremental QALYs and ICER for patients with HeFH (evolocumab and ezetimibe versus ezetimibe alone) [without PAS]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Ezetimibe	£20,472	9.97			
Evolocumab and ezetimibe		10.93		0.96	

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Table 39 Analysis I: Base case incremental cost, incremental QALYs and ICER for patients with HeFH (evolocumab and ezetimibe versus ezetimibe alone) [with PAS]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Ezetimibe	£20,472	9.97			
Evolocumab and ezetimibe		10.93		0.96	£25,609
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Analysis J: Evolocumab, statin, and ezetimibe versus statin and ezetimibe

Table 40 Analysis J: Base case incremental cost, incremental QALYs, and ICER for patients with HeFH (evolocumab, statin and ezetimibe vs. statin and ezetimibe) [without PAS]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Statin and ezetimibe	£20,672	10.03			
Evolocumab, statin and ezetimibe		11.03		1.00	
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Table 41 Analysis J: Base case incremental cost, incremental QALYs, and ICER for patients with HeFH (evolocumab, statin and ezetimibe vs. statin and ezetimibe) [with PAS]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (QALYs) vs. baseline
Statin and ezetimibe	£20,672	10.03			
Evolocumab, statin and ezetimibe		11.03		1.00	£24,826
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Subgroup analysis

Existing CVD and additional risk factors [without PAS]

Table 42 Cost-effectiveness analysis of evolocumab and statin versus ezetimibe and statin in patients with existing CVD and additional risk factors

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER	Difference
Base case		£21,408		8.23	7.84	0.39		0
Baseline LDL-C (mmol/L)								
3.0		£21,639		8.15	7.80	0.35		
3.5		£21,442		8.22	7.84	0.39		
4.0		£21,253		8.29	7.87	0.42		
4.5		£21,071		8.35	7.89	0.45		
5.0		£20,897		8.41	7.92	0.48		
5.5		£20,729		8.46	7.95	0.51		
6.0		£20,569		8.51	7.98	0.53		
Gender								
Male		£21,104		8.07	7.69	0.39		
Female		£22,069		8.58	8.18	0.41		
Diabetes mellitus = Yes		£21,795		7.88	7.40	0.48		
Vascular beds = 2		£21,709		7.95	7.49	0.46		
Vascular beds = 3		£22,207		7.54	6.99	0.55		
AF = Yes		£21,704		7.96	7.50	0.46		
CV event in the past year								
ECVD		£17,648		8.99	8.61	0.38		
ACS		£28,294		8.68	8.23	0.46		
Post-ACS		£24,010		8.79	8.35	0.44		
IS		£22,144		6.10	5.91	0.19		
Post-IS		£20,188		6.08	5.89	0.20		
HF		£25,267		6.22	5.77	0.44		
Post-HF		£24,601		6.33	5.92	0.41		
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; ECVD, established cardiovascular disease; EvoMab; evolocumab; EZE, ezetimibe; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TTO, time trade off								

Combination of risk factors with baseline LDL-C, age, and gender [without PAS]

Secondly, the impact of combining one of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 43).

Table 43 Cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin with specific CV risk factors [without PAS]

Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
3.5 mmol/L	Cohort	Cohort												
		+5												
		+10												
	Male	Cohort												
		+5												
		+10												
	Female	Cohort												
		+5												
		+10												
Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
4.0 mmol/L	Cohort	Cohort												
		+5												
		+10												
	Male	Cohort												
		+5												
		+10												
	Female	Cohort												
		+5												
		+10												

Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
4.5 mmol/L	Cohort	Cohort												
		+5												
		+10												
	Male	Cohort												
		+5												
		+10												
	Female	Cohort												
		+5												
		+10												
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; PACS, post-acute coronary syndrome; PHF, post-heart failure; PIS, post-IS; QALY, quality-adjusted life year; SP, secondary prevention; VB, vascular beds														

Combination of two risk factors with baseline LDL-C, age, and gender [without PAS]

Thirdly, the impact of combining two of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 44).

Table 44 Cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin with two specific CV risk factors [without PAS]

Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB	DM:HF	HF:2VB	HF:3VB
3.0 mmol/L	Cohort	Cohort										
		+5										
		+10										
	Male	Cohort										
		+5										
		+10										
	Female	Cohort										
		+5										
		+10										
Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB	DM:HF	HF:2VB	HF:3VB
3.5 mmol/L	Cohort	Cohort										
		+5										
		+10										
	Male	Cohort										
		+5										
		+10										
	Female	Cohort										
		+5										
		+10										
Baseline	Gender	Age (years)	SP	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB	DM:HF	HF:2VB	HF:3VB

LDL-C			cohort										
4.0 mmol/L	Cohort	Cohort											
		+5											
		+10											
	Male	Cohort											
		+5											
		+10											
	Female	Cohort											
		+5											
		+10											
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention; VB, vascular beds Note: heart failure population based on post-health failure health state													

Existing CVD and additional risk factors [with PAS]

Table 45 Cost-effectiveness analysis of evolocumab and statin versus ezetimibe and statin in patients with existing CVD and additional risk factors

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER	Difference
Base case	██████	£21,408	██████	8.23	7.84	0.39	£46,005	0
Baseline LDL-C (mmol/L)								
3.0	██████	£21,639	██████	8.15	7.80	0.35	£52,222	6,217
3.5	██████	£21,442	██████	8.22	7.84	0.39	£46,795	790
4.0	██████	£21,253	██████	8.29	7.87	0.42	£42,870	-3,135
4.5	██████	£21,071	██████	8.35	7.89	0.45	£39,946	-6,059
5.0	██████	£20,897	██████	8.41	7.92	0.48	£37,724	-8,281
5.5	██████	£20,729	██████	8.46	7.95	0.51	£36,012	-9,993
6.0	██████	£20,569	██████	8.51	7.98	0.53	£34,685	-11,320
Gender								
Male	██████	£21,104	██████	8.07	7.69	0.39	£45,692	-313
Female	██████	£22,069	██████	8.58	8.18	0.41	£46,636	631
Diabetes mellitus = Yes	██████	£21,795	██████	7.88	7.40	0.48	£35,252	-10,753
Vascular beds = 2	██████	£21,709	██████	7.95	7.49	0.46	£37,133	-8,872
Vascular beds = 3	██████	£22,207	██████	7.54	6.99	0.55	£28,550	-17,455
AF = Yes	██████	£21,704	██████	7.96	7.50	0.46	£37,240	-8,765
CV event in the past year								
ECVD	██████	£17,648	██████	8.99	8.61	0.38	£50,673	4,668
ACS	██████	£28,294	██████	8.68	8.23	0.46	£35,586	-10,419
Post-ACS	██████	£24,010	██████	8.79	8.35	0.44	£37,843	-8,162
IS	██████	£22,144	██████	6.10	5.91	0.19	£98,139	52,134
Post-IS	██████	£20,188	██████	6.08	5.89	0.20	£95,268	49,264
HF	██████	£25,267	██████	6.22	5.77	0.44	£39,402	-6,603
Post-HF	██████	£24,601	██████	6.33	5.92	0.41	£43,197	-2,808
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; ECVD, established cardiovascular disease; EvoMab; evolocumab; EZE, ezetimibe; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TTO, time trade off								

Combination of risk factors with baseline LDL-C, age, and gender [with PAS]

Secondly, the impact of combining one of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 46). The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000.

Table 46 Cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin with specific CV risk factors [with PAS]

Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
3.5 mmol/L	Cohort	Cohort	£46,795	£35,868	£37,888	£37,779	£29,058	£51,463	£36,250	£38,551	£99,700	£38,551	£40,112	£43,989
		+5	£43,566	£33,450	£35,318	£35,218	£27,159	£48,636	£32,393	£35,197	£92,865	£35,197	£37,160	£40,679
		+10	£41,799	£32,132	£33,916	£33,820	£26,134	£47,596	£29,417	£32,929	£88,517	£32,929	£35,424	£38,713
	Male	Cohort	£46,478	£35,790	£37,597	£37,489	£28,791	£51,099	£35,887	£38,248	£99,258	£38,248	£39,811	£43,766
		+5	£43,305	£33,438	£35,081	£34,981	£26,942	£48,330	£32,068	£34,946	£92,465	£34,946	£36,918	£40,513
		+10	£41,574	£32,257	£33,717	£33,621	£25,957	£47,322	£29,111	£32,712	£88,101	£32,712	£35,225	£38,589
	Female	Cohort	£47,435	£35,811	£38,468	£38,359	£29,590	£52,209	£36,976	£39,153	£100,609	£39,153	£40,714	£44,430
		+5	£44,108	£33,344	£35,803	£35,702	£27,596	£49,288	£33,052	£35,708	£93,726	£35,708	£37,650	£41,014
		+10	£42,286	£31,990	£34,341	£34,244	£26,502	£48,207	£30,051	£33,385	£89,452	£33,385	£35,838	£38,977
Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
4.0 mmol/L	Cohort	Cohort	£42,870	£32,815	£34,674	£34,574	£26,540	£47,547	£32,956	£35,042	£91,938	£89,218	£36,577	£40,041
		+5	£39,938	£30,633	£32,353	£32,260	£24,838	£44,961	£29,463	£32,004	£85,778	£84,030	£33,939	£37,089
		+10	£38,344	£29,456	£31,098	£31,009	£23,933	£44,023	£26,776	£29,957	£81,883	£81,717	£32,403	£35,357
	Male	Cohort	£42,575	£32,751	£34,404	£34,304	£26,290	£47,208	£32,621	£34,762	£91,521	£88,739	£36,297	£39,829
		+5	£39,694	£30,634	£32,130	£32,038	£24,633	£44,674	£29,161	£31,770	£85,400	£83,621	£33,711	£36,929
		+10	£38,133	£29,591	£30,909	£30,821	£23,764	£43,766	£26,490	£29,754	£81,492	£81,345	£32,215	£35,234
	Female	Cohort	£43,466	£32,770	£35,217	£35,116	£27,038	£48,245	£33,628	£35,600	£92,799	£90,205	£37,139	£40,461
		+5	£40,445	£30,545	£32,808	£32,715	£25,250	£45,572	£30,075	£32,480	£86,589	£84,904	£34,400	£37,413
		+10	£38,801	£29,336	£31,499	£31,410	£24,283	£44,597	£27,365	£30,384	£82,761	£82,559	£32,796	£35,616

Baseline LDL-C	Gender	Age (years)	SP cohort	DM	AF	2VB	3VB	ECVD	ACS	PACS	IS	PIS	HF	PHF
4.5 mmol/L	Cohort	Cohort	£39,946	£30,547	£32,286	£32,193	£24,675	£44,648	£30,517	£32,442	£86,129	£83,539	£33,920	£37,072
		+5	£37,233	£28,539	£30,147	£30,060	£23,117	£42,237	£27,292	£29,636	£80,480	£78,778	£31,517	£34,388
		+10	£35,765	£27,465	£28,999	£28,916	£22,299	£41,371	£24,818	£27,752	£76,930	£76,693	£30,132	£32,830
	Male	Cohort	£39,669	£30,496	£32,031	£31,938	£24,439	£44,328	£30,203	£32,180	£85,731	£83,083	£33,656	£36,869
		+5	£37,003	£28,552	£29,936	£29,850	£22,923	£41,965	£27,008	£29,416	£80,121	£78,390	£31,302	£34,234
		+10	£35,565	£27,609	£28,819	£28,737	£22,138	£41,127	£24,549	£27,559	£76,559	£76,339	£29,952	£32,710
	Female	Cohort	£40,507	£30,510	£32,798	£32,704	£25,146	£45,309	£31,146	£32,965	£86,951	£84,479	£34,450	£37,473
		+5	£37,712	£28,463	£30,579	£30,492	£23,509	£42,816	£27,867	£30,084	£81,253	£79,611	£31,955	£34,702
		+10	£36,200	£27,360	£29,381	£29,298	£22,635	£41,916	£25,373	£28,156	£77,761	£77,494	£30,508	£33,085
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; PACS, post-acute coronary syndrome; PHF, post-heart failure; PIS, post-IS; QALY, quality-adjusted life year; SP, secondary prevention; VB, vascular beds														

Combination of two risk factors with baseline LDL-C, age, and gender [with PAS]

Thirdly, the impact of combining two of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 47). The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000.

Table 47 Cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin with two specific CV risk factors [with PAS]

Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB	DM:HF	HF:2VB	HF:3VB
3.0 mmol/L	Cohort	Cohort	£52,222	£31,071	£32,790	£32,701	£25,517	£34,462	£26,824	£40,381	£41,970	£34,665
		+5	£48,578	£27,776	£30,596	£30,514	£23,907	£32,139	£25,105	£37,387	£38,831	£32,205
		+10	£46,568	£25,220	£29,392	£29,313	£23,047	£30,861	£24,179	£35,572	£36,930	£30,714
	Male	Cohort	£51,876	£30,969	£32,756	£32,667	£25,433	£34,167	£26,548	£40,398	£41,742	£34,443
		+5	£48,295	£27,688	£30,599	£30,516	£23,862	£31,902	£24,884	£37,443	£38,664	£32,040
		+10	£46,326	£25,137	£29,428	£29,349	£23,039	£30,668	£24,005	£35,663	£36,811	£30,596
	Female	Cohort	£52,920	£31,235	£32,820	£30,480	£25,657	£35,046	£27,374	£40,308	£42,418	£35,104
		+5	£49,165	£27,923	£30,561	£30,480	£23,973	£32,616	£25,548	£37,245	£39,162	£32,531
		+10	£47,093	£25,369	£29,302	£29,225	£23,047	£31,262	£24,536	£35,371	£37,175	£30,950
Baseline LDL-C	Gender	Age (years)	SP cohort	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB	DM:HF	HF:2VB	HF:3VB
3.5 mmol/L	Cohort	Cohort	£46,795	£27,509	£29,269	£29,188	£22,686	£30,779	£23,871	£35,860	£37,292	£30,708
		+5	£43,566	£24,614	£27,353	£27,279	£21,299	£28,746	£22,385	£33,278	£34,579	£28,605
		+10	£41,799	£22,377	£26,319	£26,248	£20,577	£27,646	£21,604	£31,737	£32,961	£27,355
	Male	Cohort	£46,478	£27,412	£29,232	£29,151	£22,604	£30,507	£23,615	£35,866	£37,077	£30,498
		+5	£43,305	£24,528	£27,349	£27,274	£21,251	£28,526	£22,178	£33,318	£34,419	£28,446
		+10	£41,574	£22,294	£26,344	£26,273	£20,562	£27,465	£21,438	£31,808	£32,843	£27,238
	Female	Cohort	£47,435	£27,670	£29,308	£29,228	£22,826	£31,319	£24,382	£35,814	£37,715	£31,123
		+5	£44,108	£24,760	£27,335	£27,262	£21,374	£29,192	£22,801	£33,171	£34,898	£28,920
		+10	£42,286	£22,527	£26,254	£26,185	£20,594	£28,024	£21,944	£31,578	£33,204	£27,590
Baseline	Gender	Age (years)	SP	DM:ACS	DM:AF	DM:2VB	DM:3VB	AF:2VB	AF:3VB	DM:HF	HF:2VB	HF:3VB

LDL-C			cohort									
4.0 mmol/L	Cohort	Cohort	£42,870	£24,947	£26,734	£26,660	£20,658	£28,126	£21,753	£32,576	£33,891	£27,840
		+5	£39,938	£22,337	£25,017	£24,948	£19,428	£26,301	£20,432	£30,291	£31,487	£25,995
		+10	£38,344	£20,330	£24,103	£24,038	£18,803	£25,326	£19,753	£28,948	£30,073	£24,919
	Male	Cohort	£42,575	£24,854	£26,697	£26,622	£20,578	£27,872	£21,512	£32,575	£33,686	£27,641
		+5	£39,694	£22,253	£25,009	£24,940	£19,379	£26,094	£20,236	£30,321	£31,332	£25,842
		+10	£38,133	£20,248	£24,121	£24,056	£18,784	£25,154	£19,593	£29,006	£29,957	£24,804
	Female	Cohort	£43,466	£25,102	£26,778	£26,705	£20,794	£28,632	£22,232	£32,547	£34,294	£28,235
		+5	£40,445	£22,482	£25,010	£24,943	£19,507	£26,721	£20,825	£30,208	£31,795	£26,299
		+10	£38,801	£20,479	£24,055	£23,991	£18,831	£25,686	£20,078	£28,819	£30,313	£25,151
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention; VB, vascular beds Note: heart failure population based on post-health failure health state												

Sensitivity analyses

- 4.9 *Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.*

Deterministic sensitivity analysis

Deterministic sensitivity analyses were performed by means of one-way sensitivity analyses, where one parameter was varied relative to its base case value. The method adopted and the parameters tested are described in the evidence submission (Section 5.6). A summary of the results is presented below for patients with existing CVD and patients with HeFH for evolocumab and statin versus ezetimibe and statin (scenario 1). The additional scenarios are not presented as the results were not sensitive to the different treatment strategies covered in scenarios 2 to 4. All parameters where the incremental cost per QALY gained was sensitive by > 1% are presented in Tornado plots (Figure 1 to Figure 2).

The Tornado plots indicate that the most sensitive parameters for cost-effectiveness of evolocumab versus ezetimibe were in patients with existing CVD are:

- effect of LDL-C lowering on CHD death and IS death
- ezetimibe treatment effect
- CPRD ratio ratios
- effect of LDL-C reduction on CV events
- treatment duration.

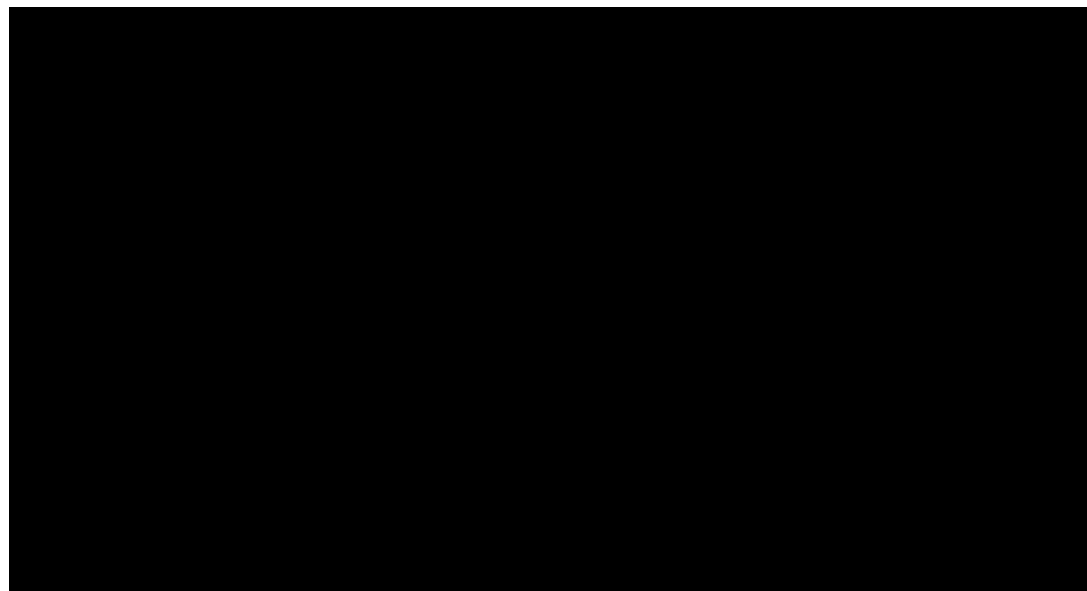
The Tornado plots indicate that the most sensitive parameters for cost-effectiveness of evolocumab versus ezetimibe were in patients with HeFH are:

- effect of LDL-C lowering on CHD death
- CVD event rate ratio (HeFH alone)
- effect of LDL-C reduction on CV events
- ezetimibe treatment effect
- treatment duration
- evolocumab treatment effect.

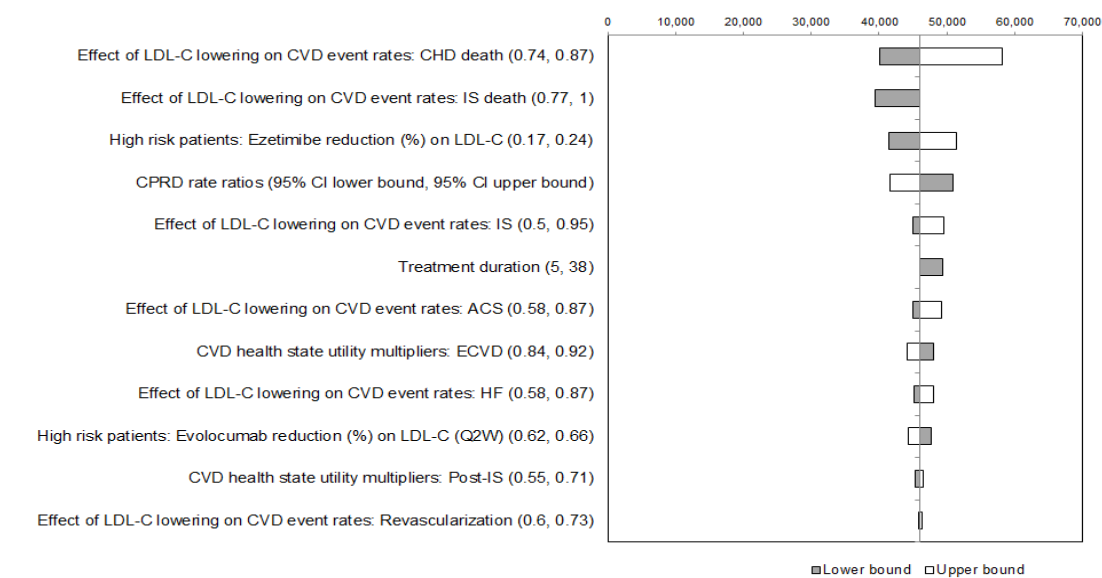
Existing CVD

Figure 1 Tornado plot: evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1]

Without PAS



With PAS

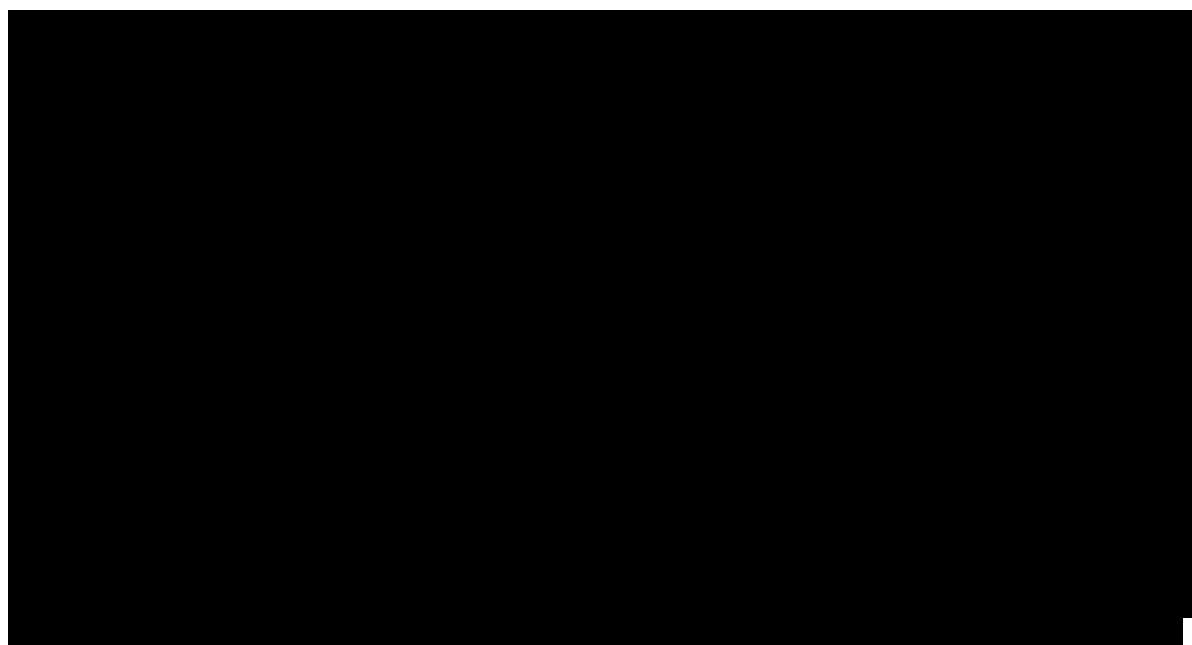


ACS, acute coronary syndrome; CI, confidence interval; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

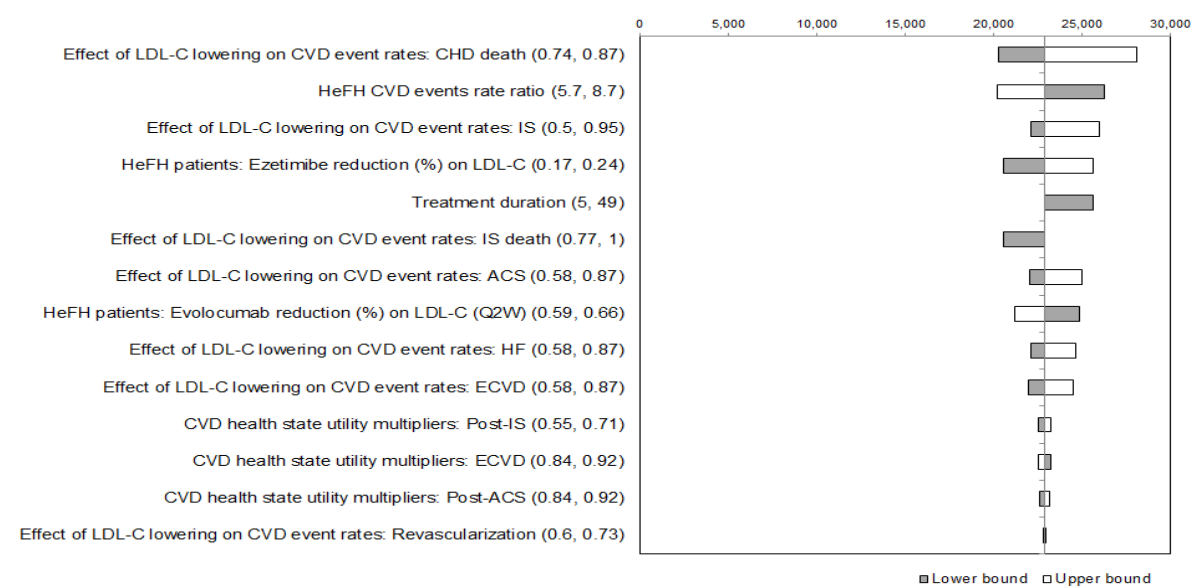
Heterozygous familial hypercholesterolaemia

Figure 2 Tornado plot: evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1]

Without PAS



With PAS

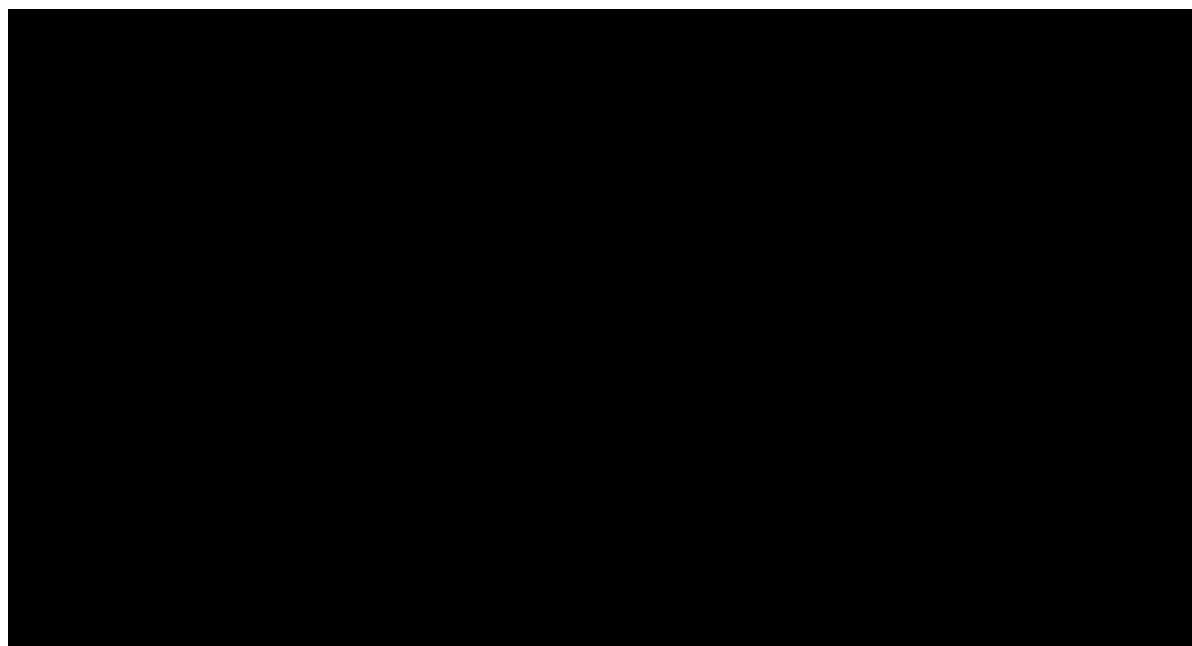


ACS, acute coronary syndrome; CI, confidence interval; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol

- 4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

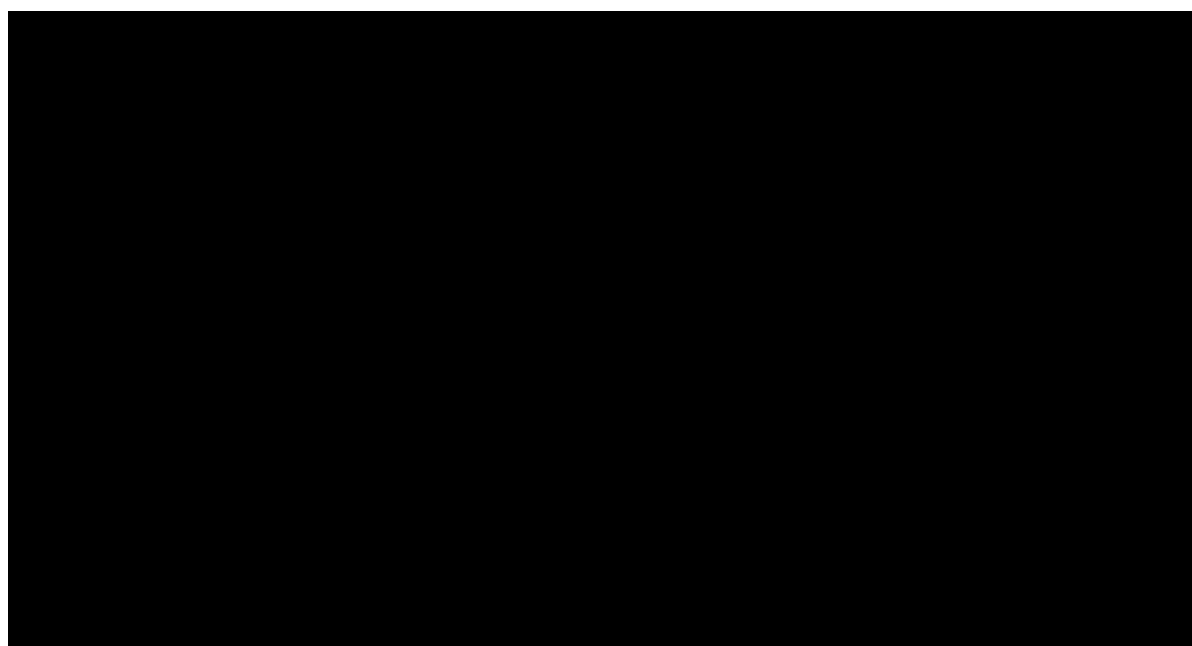
Existing CVD [without PAS]

Figure 3 Scatterplot for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1] [without PAS]



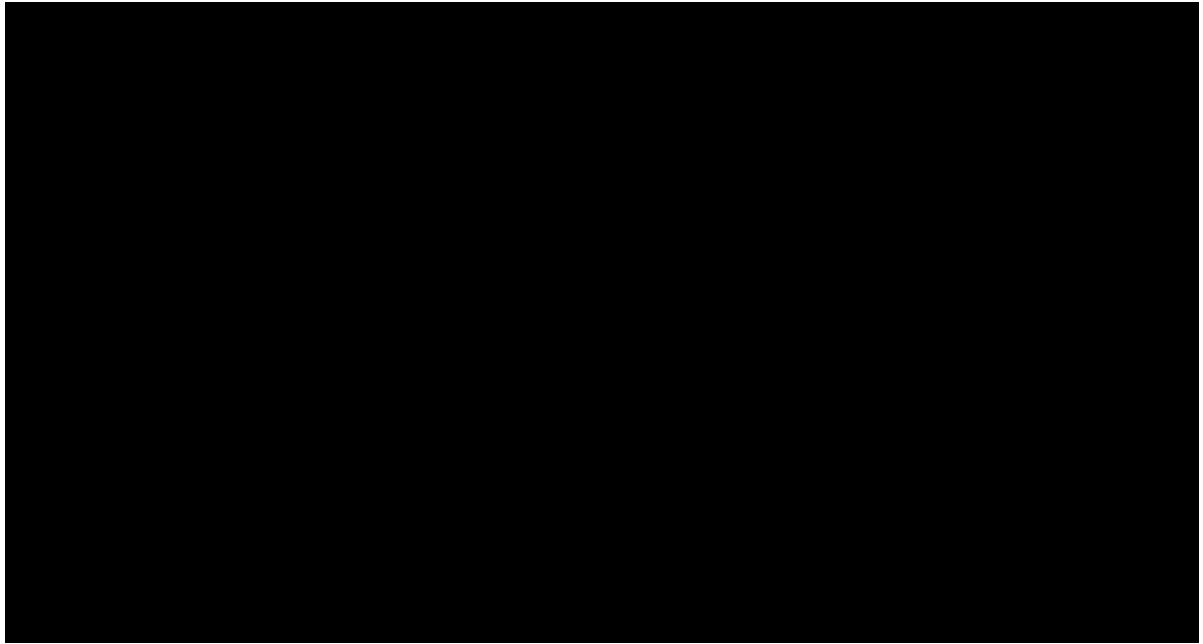
CVD, cardiovascular disease; QALY, quality-adjusted life year;

Figure 4 Scatterplot for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2] [without PAS]



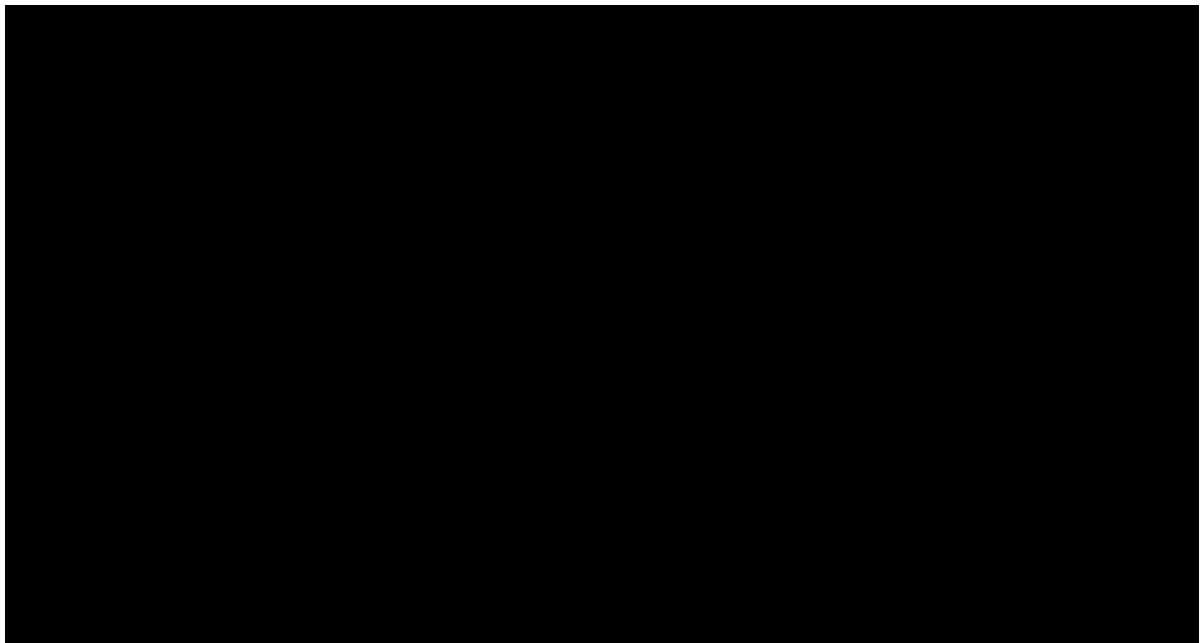
CVD, cardiovascular disease; QALY, quality-adjusted life year

Figure 5 Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1] [without PAS]



CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol

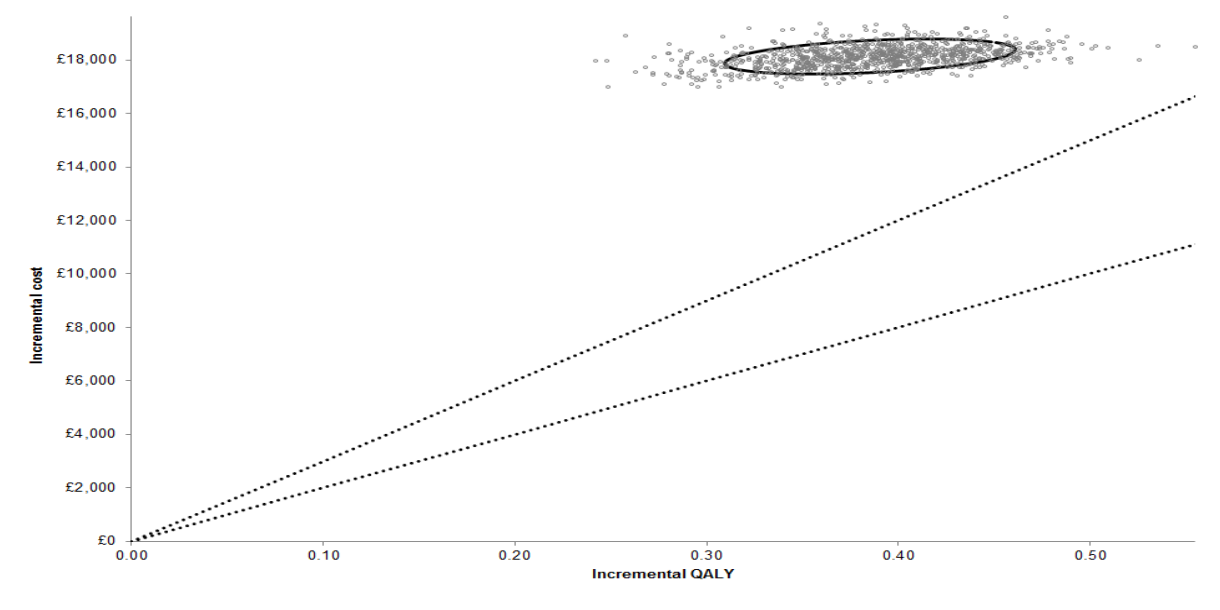
Figure 6 Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2] [without PAS]



CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol

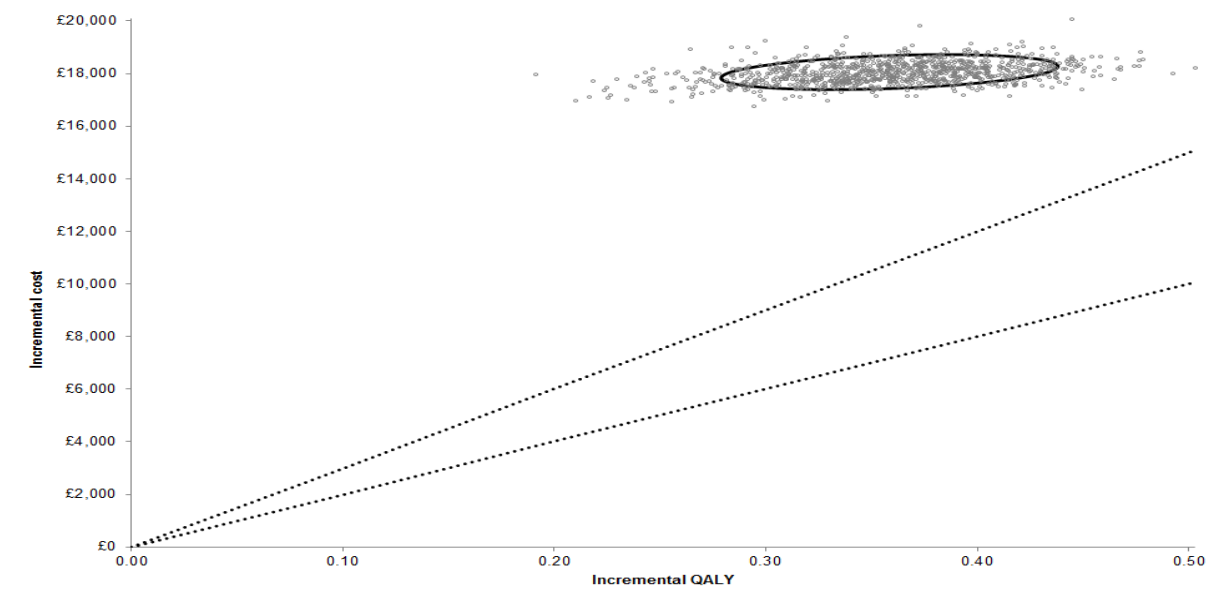
Existing CVD [with PAS]

Figure 7 Scatterplot for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1] [with PAS]



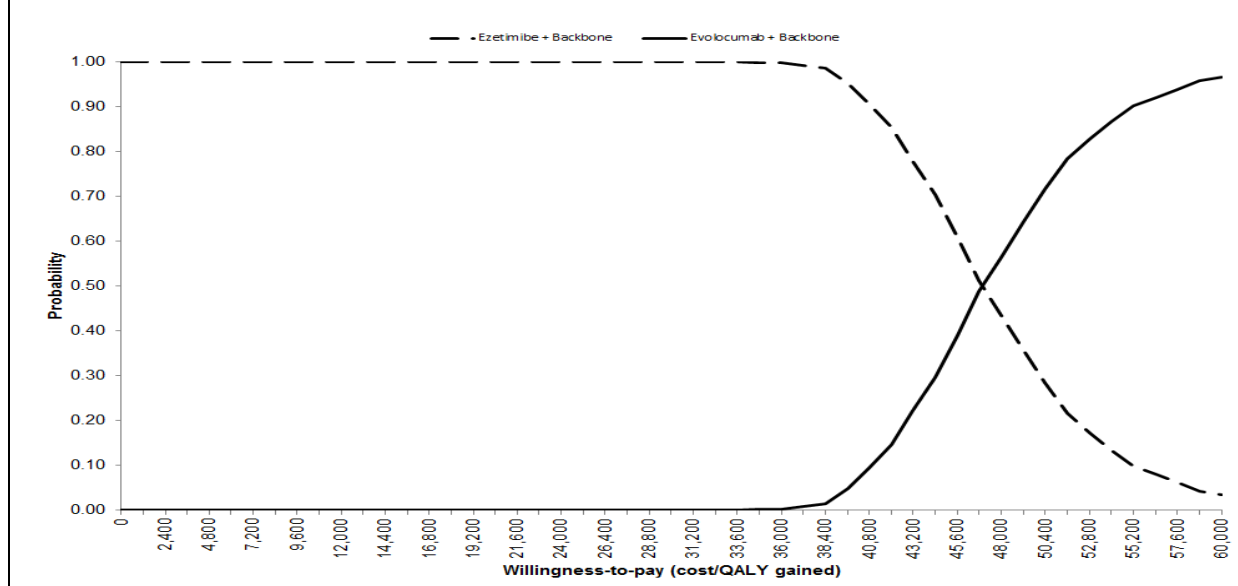
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year;

Figure 8 Scatterplot for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2] [with PAS]



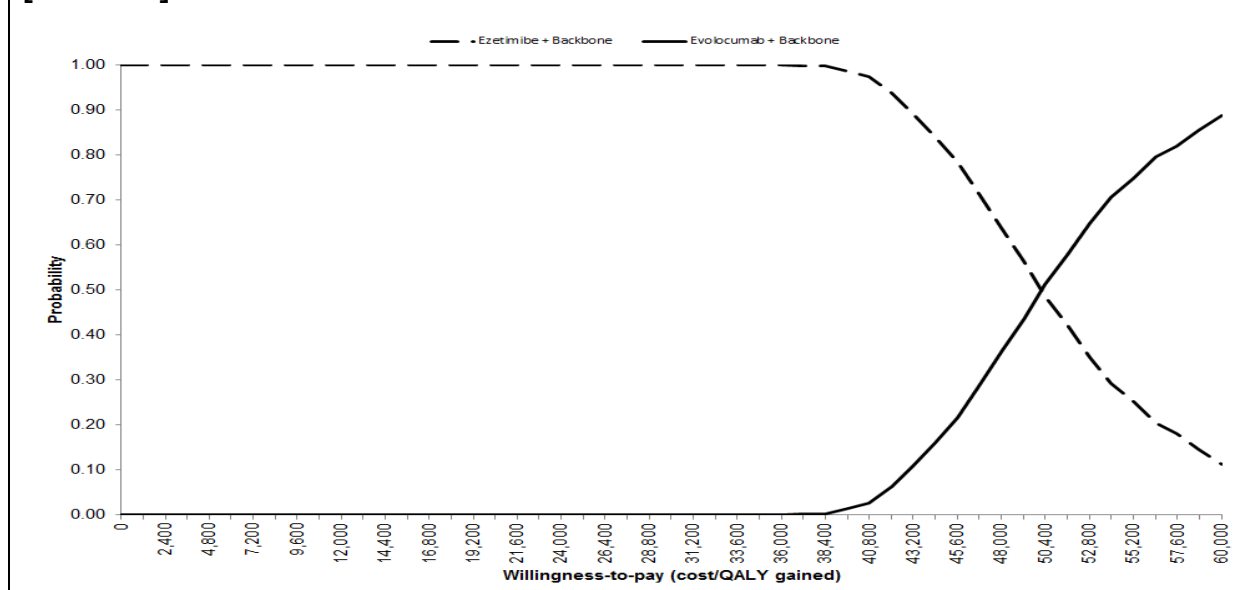
CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year;

Figure 9 Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in patients with existing CVD (based on LAPLACE-2) [scenario 1] [with PAS]



CVD, cardiovascular disease; QALY, quality-adjusted life year;

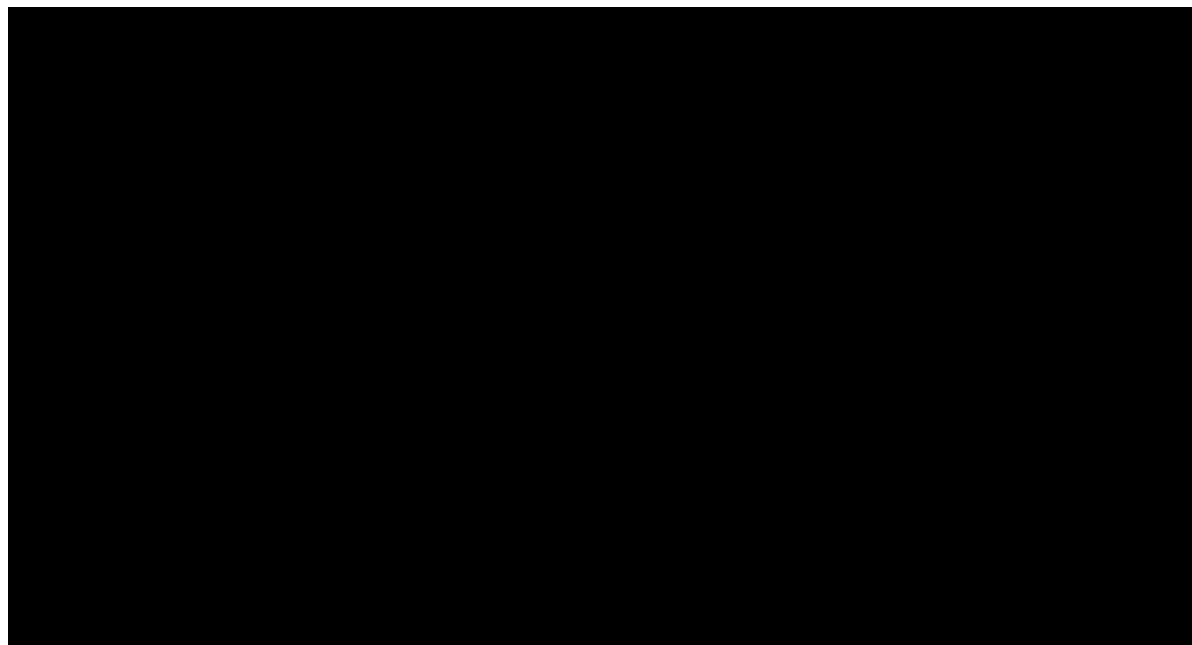
Figure 10 Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in patients with existing CVD (based on LAPLACE-2) [scenario 2] [with PAS]



CVD, cardiovascular disease; QALY, quality-adjusted life year;

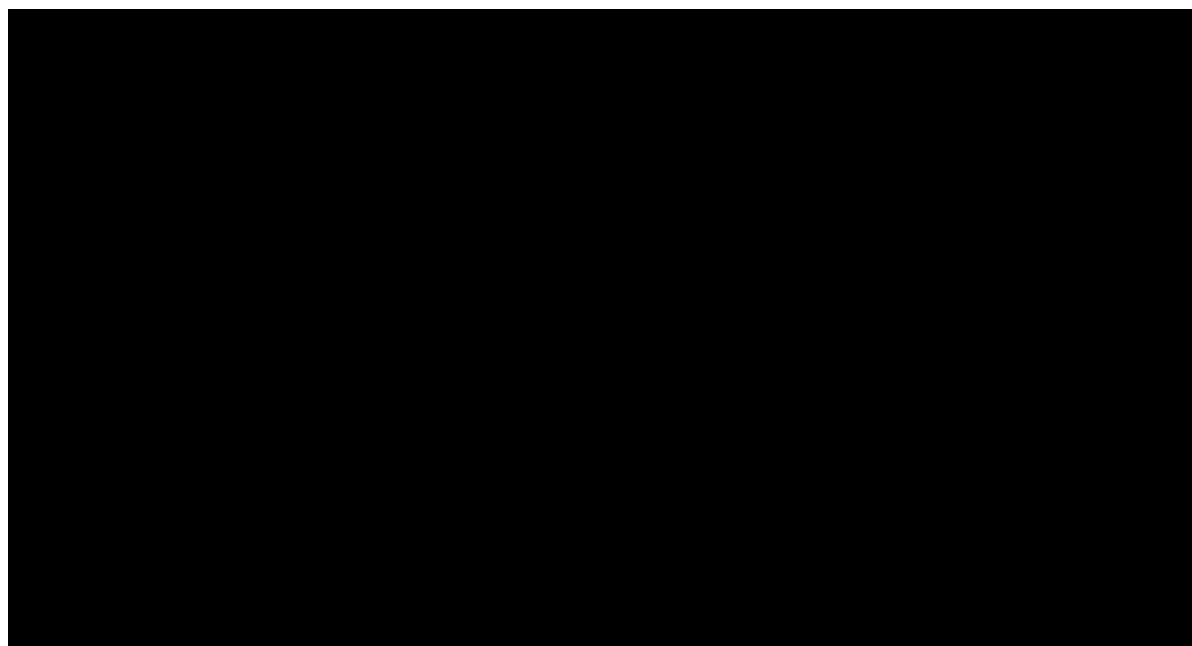
Heterozygous familial hypercholesterolaemia [without PAS]

Figure 14 Scatterplot for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1] [without PAS]



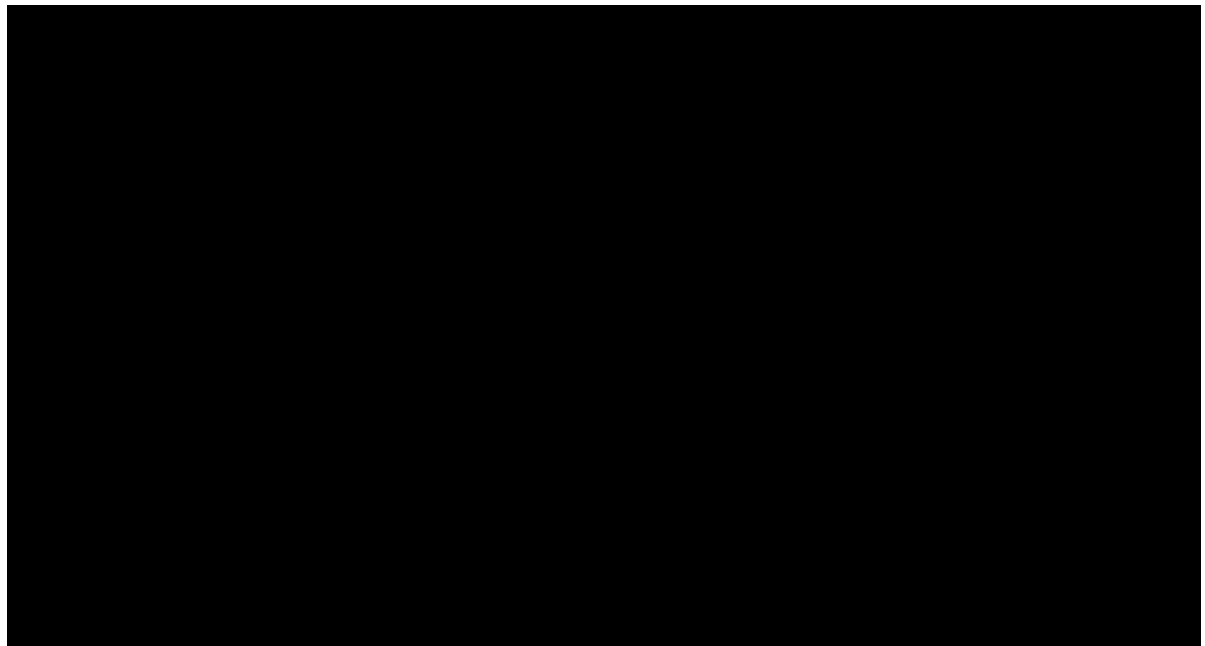
HeFH, heterozygous familial hypercholesterolaemia; QALY, quality-adjusted life year

Figure 15 Scatterplot for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2] [without PAS]



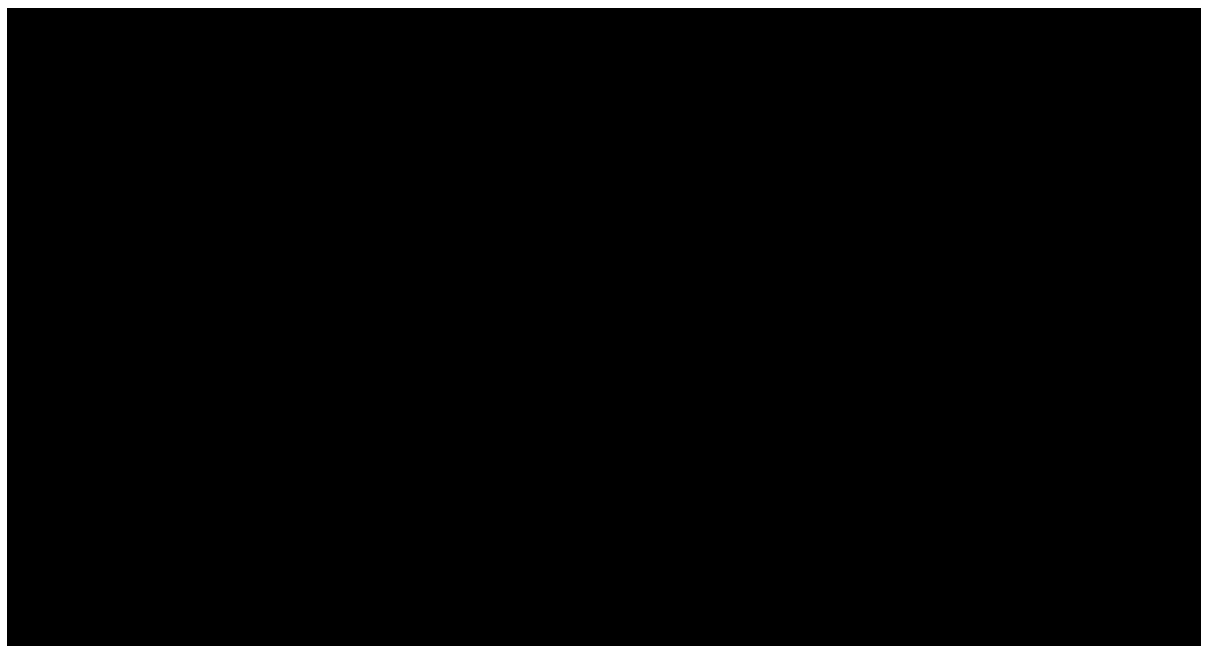
HeFH, heterozygous familial hypercholesterolaemia; QALY, quality-adjusted life year

Figure 18 Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1] [without PAS]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol

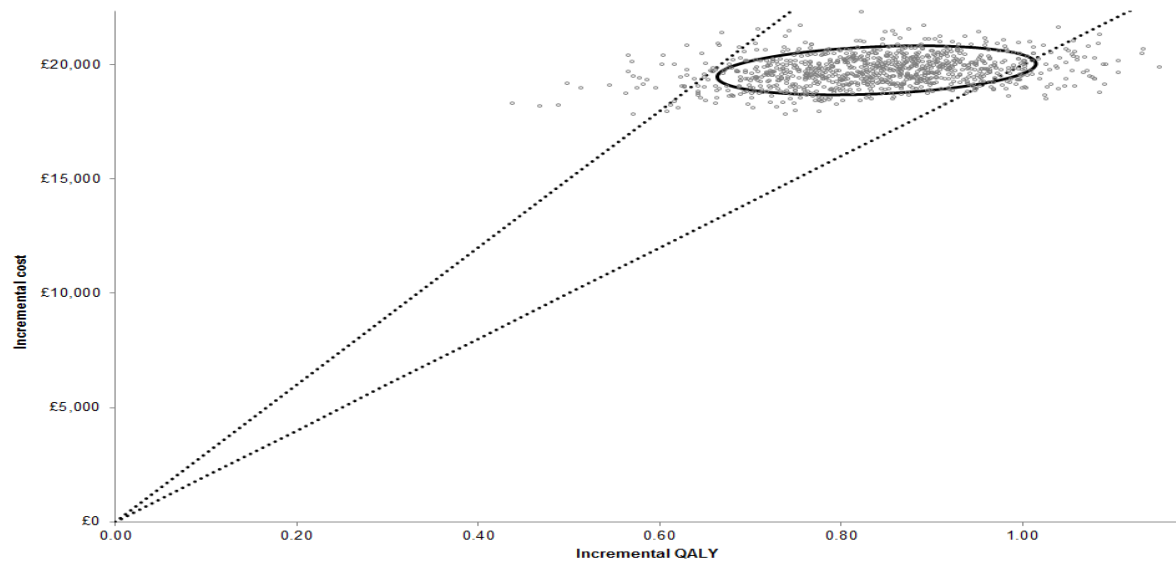
Figure 19 Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2] [without PAS]



HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol

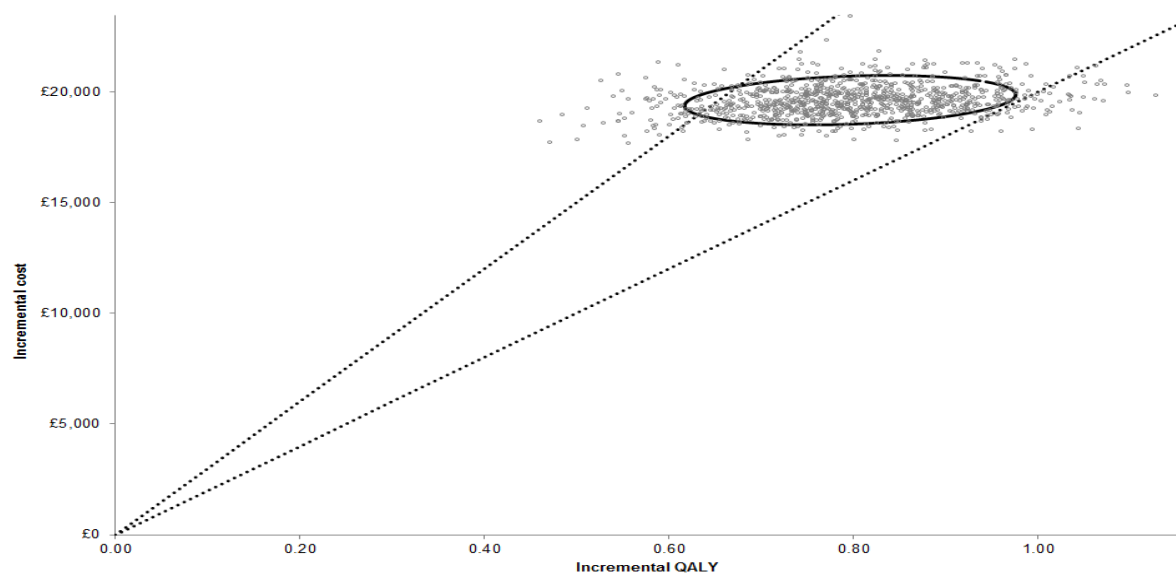
Heterozygous familial hypercholesterolaemia [with PAS]

Figure 14 Scatterplot for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1] [with PAS]



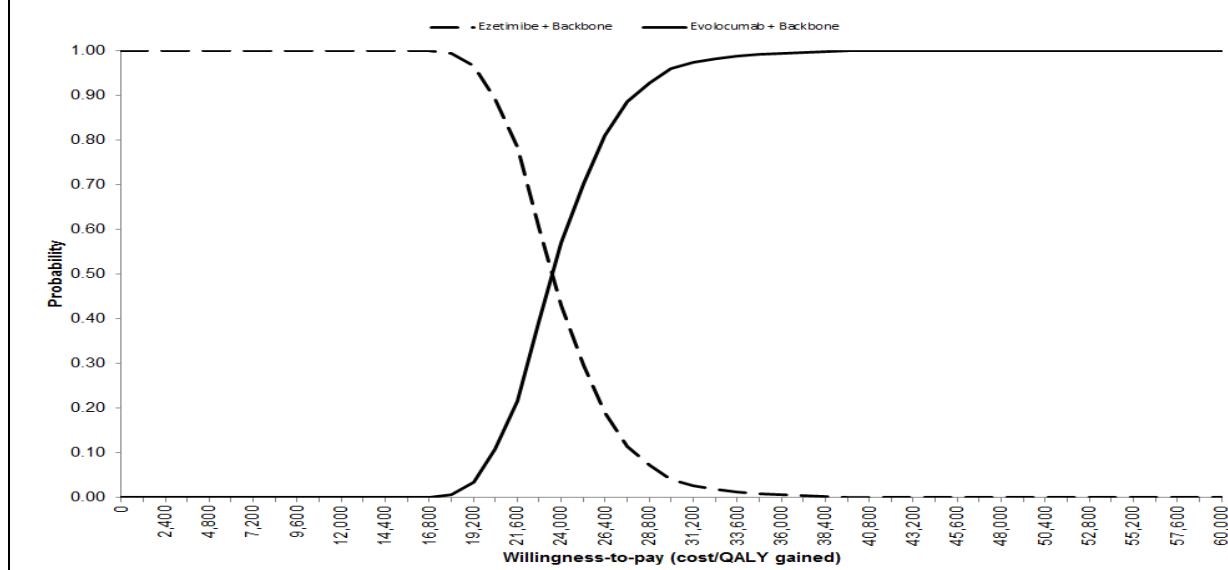
HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

Figure 15 Scatterplot for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2] [with PAS]



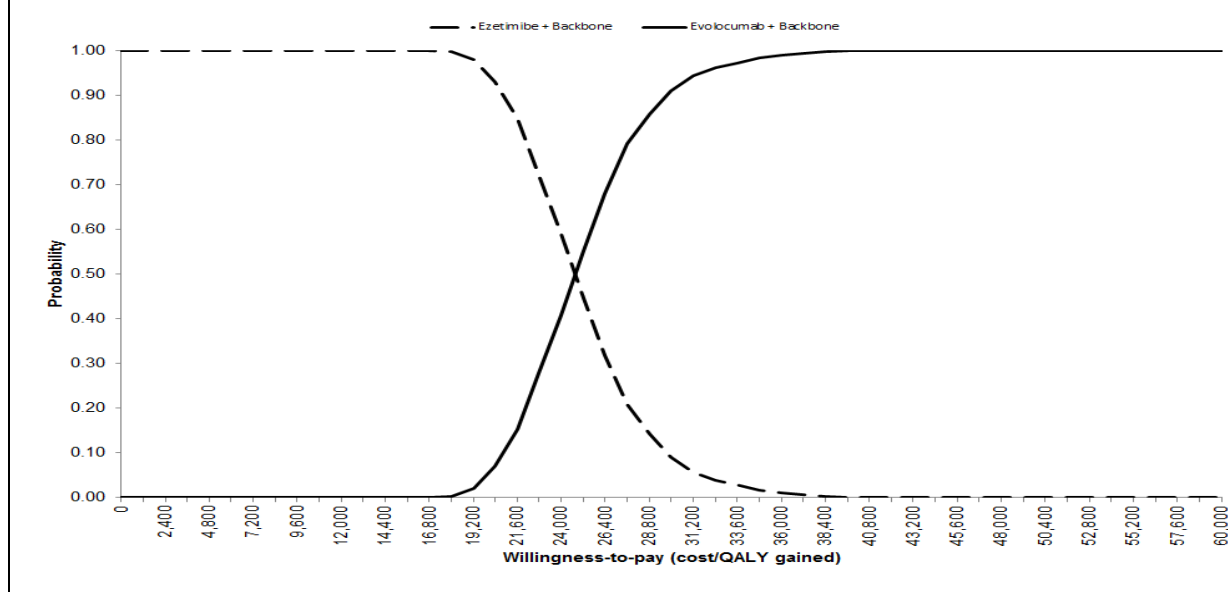
HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year

Figure 18 Cost-effectiveness acceptability curve for evolocumab and statin versus ezetimibe and statin in HeFH (based on RUTHERFORD-2) [scenario 1] [with PAS]



HeFH, heterozygous familial hypercholesterolaemia;

Figure 19 Cost-effectiveness acceptability curve for evolocumab alone versus ezetimibe alone in HeFH (based on RUTHERFORD-2) [scenario 2] [with PAS]



HeFH, heterozygous familial hypercholesterolaemia;

Table 48 Deterministic and probabilistic incremental cost-effectiveness ratios [without PAS]

Pop.	Intervention	Comparator	ICER	
			Deterministic	Probabilistic
Existing CVD	Evolocumab and statin	Ezetimibe and statin		
	Evolocumab alone	Ezetimibe alone		
HeFH	Evolocumab and statin	Ezetimibe and statin		
	Evolocumab alone	Ezetimibe alone		

HeFH; heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; Pop., population; QALY, quality-adjusted life-year

Table 49 Probability of cost-effectiveness for evolocumab in different populations and maximum acceptable incremental cost-effectiveness ratios [without PAS]

Population	Intervention	Comparator	MAICER	
			£20,000 per QALY	£30,000 per QALY
Existing CVD	Evolocumab and statin	Ezetimibe and statin		
	Evolocumab alone	Ezetimibe alone		
HeFH	Evolocumab and statin	Ezetimibe and statin		
	Evolocumab alone	Ezetimibe alone		

HeFH; heterozygous familial hypercholesterolaemia; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Table 50 Deterministic and probabilistic incremental cost-effectiveness ratios [with PAS]

Pop.	Intervention	Comparator	ICER	
			Deterministic	Probabilistic
Existing CVD	Evolocumab and statin	Ezetimibe and statin	£46,005	£47,079
	Evolocumab alone	Ezetimibe alone	£49,278	£50,321
HeFH	Evolocumab and statin	Ezetimibe and statin	£22,902	£23,504
	Evolocumab alone	Ezetimibe alone	£23,927	£24,604

HeFH; heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; Pop., population; QALY, quality-adjusted life-year

Table 51 Probability of cost-effectiveness for evolocumab in different populations and maximum acceptable incremental cost-effectiveness ratios [with PAS]

Population	Intervention	Comparator	MAICER	
			£20,000 per QALY	£30,000 per QALY
Existing CVD	Evolocumab and statin	Ezetimibe and statin	0.0%	0.0%
	Evolocumab alone	Ezetimibe alone	0.0%	0.0%
HeFH	Evolocumab and statin	Ezetimibe and statin	7.8%	95.9%
	Evolocumab alone	Ezetimibe alone	4.7%	91.0%

HeFH; heterozygous familial hypercholesterolaemia; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

- 4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Severity of hypercholesterolaemia

Existing CVD [without PAS]

Table 52 Scenario analyses: Existing CVD and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1] [without PAS]

Baseline LDL-C (mmol/L)	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
3.0	██████	£21,639	██████	8.15	7.80	0.35	██████
3.5	██████	£21,442	██████	8.22	7.84	0.39	██████
4.0	██████	£21,253	██████	8.29	7.87	0.42	██████
4.5	██████	£21,071	██████	8.35	7.89	0.45	██████
5.0	██████	£20,897	██████	8.41	7.92	0.48	██████
5.5	██████	£20,729	██████	8.46	7.95	0.51	██████
6.0	██████	£20,569	██████	8.51	7.98	0.53	██████
CVD, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year							

Existing CVD [with PAS]

Table 53 Scenario analyses: Existing CVD and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1] [with PAS]

Baseline LDL-C (mmol/L)	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
3.0	██████	£21,639	██████	8.15	7.80	0.35	£52,222
3.5	██████	£21,442	██████	8.22	7.84	0.39	£46,795
4.0	██████	£21,253	██████	8.29	7.87	0.42	£42,870
4.5	██████	£21,071	██████	8.35	7.89	0.45	£39,946
5.0	██████	£20,897	██████	8.41	7.92	0.48	£37,724
5.5	██████	£20,729	██████	8.46	7.95	0.51	£36,012
6.0	██████	£20,569	██████	8.51	7.98	0.53	£34,685
CVD, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year							

Heterozygous familial hypercholesterolaemia [without PAS]

Table 5-59 Scenario analyses: HeFH and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1] [without PAS]

Baseline LDL-C (mmol/L)	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
3.0	██████	£21,270	██████	10.59	9.92	0.67	██████
3.5	██████	£20,971	██████	10.74	9.98	0.77	██████
4.0	██████	£20,683	██████	10.89	10.03	0.86	██████
4.5	██████	£20,406	██████	11.03	10.09	0.94	██████
5.0	██████	£20,138	██████	11.16	10.14	1.02	██████
5.5	██████	£19,881	██████	11.29	10.20	1.09	██████
6.0	██████	£19,633	██████	11.41	10.26	1.16	██████
EvoMab; evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year							

Heterozygous familial hypercholesterolaemia [with PAS]

Table 5-59 Scenario analyses: HeFH and severity of hypercholesterolaemia (evolocumab and statin versus ezetimibe and statin) [scenario 1] [with PAS]

Baseline LDL-C (mmol/L)	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
3.0	██████	£21,270	██████	10.59	9.92	0.67	£29,250
3.5	██████	£20,971	██████	10.74	9.98	0.77	£25,629
4.0	██████	£20,683	██████	10.89	10.03	0.86	£22,993
4.5	██████	£20,406	██████	11.03	10.09	0.94	£21,009
5.0	██████	£20,138	██████	11.16	10.14	1.02	£19,480
5.5	██████	£19,881	██████	11.29	10.20	1.09	£18,281
6.0	██████	£19,633	██████	11.41	10.26	1.16	£17,328
EvoMab; evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; QALY, quality-adjusted life year							

Scenario analyses

Existing CVD [without PAS]

Table 54 Scenario analyses – existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1] [without PAS]

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
Base case	██████	£21,408	██████	8.23	7.84	0.39	██████
Evolocumab QM PFP	██████	£21,408	██████	8.24	7.84	0.40	██████
5-year treatment duration	██████	£17,968	██████	7.78	7.67	0.10	██████
10-year treatment duration	██████	£19,289	██████	7.93	7.73	0.20	██████
20-year treatment duration	██████	£20,849	██████	8.15	7.81	0.34	██████
Discounting: 0% costs, 0% effects	██████	£31,674	██████	12.07	11.31	0.76	██████
Discounting: 0% costs, 6% effects	██████	£31,674	██████	6.57	6.31	0.26	██████
Risk capping 75 years	██████	£21,417	██████	8.29	7.91	0.38	██████
NICE CG181 CV costs	██████	£24,966	██████	8.23	7.84	0.39	██████
TTO study utilities	██████	£21,408	██████	10.00	9.47	0.52	██████
Nurse training 30 minutes	██████	£21,408	██████	8.23	7.84	0.39	██████
Nurse training 2 hours	██████	£21,408	██████	8.23	7.84	0.39	██████
CV, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

Existing CVD [with PAS]

Table 55 Scenario analyses – existing CVD (evolocumab and statin versus ezetimibe and statin) [scenario 1] [with PAS]

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
Base case	██████	£21,408	██████	8.23	7.84	0.39	£46,005
Evolocumab QM PFP	██████	£21,408	██████	8.24	7.84	0.40	£69,226
5-year treatment duration	██████	£17,968	██████	7.78	7.67	0.10	£49,363
10-year treatment duration	██████	£19,289	██████	7.93	7.73	0.20	£49,579
20-year treatment duration	██████	£20,849	██████	8.15	7.81	0.34	£46,519
Discounting: 0% costs, 0% effects	██████	£31,674	██████	12.07	11.31	0.76	£35,614
Discounting: 0% costs, 6% effects	██████	£31,674	██████	6.57	6.31	0.26	£104,346
Risk capping 75 years	██████	£21,417	██████	8.29	7.91	0.38	£47,523
NICE CG181 CV costs	██████	£24,966	██████	8.23	7.84	0.39	£46,455
TTO study utilities	██████	£21,408	██████	10.00	9.47	0.52	£34,450

Nurse training 30 minutes	██████	£21,408	██████	8.23	7.84	0.39	£45,902
Nurse training 2 hours	██████	£21,408	██████	8.23	7.84	0.39	£46,210
CV, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; ICER, incremental cost-effectiveness ratio; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

Heterozygous familial hypercholesterolaemia [without PAS]

Table 56 Scenario analyses – HeFH population (evolocumab and statin versus ezetimibe and statin) [scenario 1] [without PAS]

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
Base case	██████	£20,672	██████	10.89	10.03	0.86	██████
Evolocumab QM PFP	██████	£20,672	██████	10.93	10.03	0.90	██████
5-year treatment duration	██████	£17,198	██████	9.87	9.68	0.19	██████
10-year treatment duration	██████	£18,191	██████	10.15	9.79	0.36	██████
20-year treatment duration	██████	£19,818	██████	10.61	9.95	0.66	██████
Discounting: 0% costs, 0% effects	██████	£34,004	██████	16.86	15.05	1.81	██████
Discounting: 0% costs, 6% effects	██████	£34,004	██████	8.48	7.93	0.55	██████
Risk capping 75 years	██████	£20,699	██████	10.94	10.07	0.87	██████
NICE CG181 CV costs	██████	£21,943	██████	10.89	10.03	0.86	██████
TTO study utilities	██████	£20,672	██████	11.90	11.02	0.88	██████
Nurse training 30 minutes	██████	£20,672	██████	10.89	10.03	0.86	██████
Nurse training 2 hours	██████	£20,672	██████	10.89	10.03	0.86	██████
CV, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

Heterozygous familial hypercholesterolaemia [with PAS]

Table 57 Scenario analyses – HeFH population (evolocumab and statin versus ezetimibe and statin) [scenario 1] [with PAS]

Scenario	Cost EvoMab	Cost EZE	ΔCost	QALYs EvoMab	QALYs EZE	Δ QALYs	ICER
Base case	██████	£20,672	██████	10.89	10.03	0.86	£22,902
Evolocumab QM PFP	██████	£20,672	██████	10.93	10.03	0.90	£34,037
5-year treatment duration	██████	£17,198	██████	9.87	9.68	0.19	£25,636
10-year treatment duration	██████	£18,191	██████	10.15	9.79	0.36	£25,547
20-year treatment duration	██████	£19,818	██████	10.61	9.95	0.66	£23,867
Discounting: 0% costs, 0% effects	██████	£34,004	██████	16.86	15.05	1.81	£17,555
Discounting: 0% costs, 6% effects	██████	£34,004	██████	8.48	7.93	0.55	£58,252
Risk capping 75 years	██████	£20,699	██████	10.94	10.07	0.87	£22,812

NICE CG181 CV costs	██████	£21,943	██████	10.89	10.03	0.86	£22,702
TTO study utilities	██████	£20,672	██████	11.90	11.02	0.88	£22,251
Nurse training 30 minutes	██████	£20,672	██████	10.89	10.03	0.86	£22,855
Nurse training 2 hours	██████	£20,672	██████	10.89	10.03	0.86	£22,996
CV, cardiovascular; EvoMab; evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

4.12 *If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.*

Not applicable.

Impact of patient access scheme on ICERs

4.13 *For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses.*

The impact of the patient access scheme on the base-case, subgroup analyses and scenarios analyses for the different populations are presented in Sections 4.8, 4.9 and 4.11. A summary of the ICERs are also available below for the base-case analyses for patients with existing CVD and patients with HeFH.

Table 58 Impact of patient access scheme on ICERs on base-case analyses for patients with existing CVD and patients with HeFH

Pop.	Intervention	Comparator	Analysis, Section, Tables	ICER for intervention versus comparator	
				Without PAS	With PAS
Without existing CVD	Evolocumab and statin	Ezetimibe and statin	Analysis A	██████	£74,331
	Evolocumab alone	Ezetimibe alone	Analysis B	██████	£78,879
	Evolocumab and ezetimibe	Ezetimibe alone	Not conducted	-	-
	Evolocumab, statin, and ezetimibe	Ezetimibe and statin	Not conducted	-	-
Existing CVD	Evolocumab and statin	Ezetimibe and statin	Analysis C	██████	£46,005
	Evolocumab alone	Ezetimibe alone	Analysis D	██████	£49,278
	Evolocumab and ezetimibe	Ezetimibe alone	Analysis E	██████	£52,811
	Evolocumab, statin, and ezetimibe	Ezetimibe and statin	Analysis F	██████	£50,880
HeFH	Evolocumab and statin	Ezetimibe and statin	Analysis G	██████	£22,902
	Evolocumab alone	Ezetimibe alone	Analysis H	██████	£23,927
	Evolocumab and ezetimibe	Ezetimibe alone	Analysis I	██████	£25,609
	Evolocumab, statin, and ezetimibe	Ezetimibe and statin	Analysis J	██████	£24,826
CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio					

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Not applicable.

5.2 *Appendix B: Details of outcome-based schemes*

5.2.1 *If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:*

- *the current price of the intervention*
- *the proposed higher price of the intervention, which will be supported by the collection of new evidence*
- *a suggested date for when NICE should consider the additional evidence.*

Not applicable.

5.2.2 *If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:*

- *the current price of the intervention (the price that will be supported by the collection of new evidence)*
- *the planned lower price of the intervention in the event that the additional evidence does not support the current price*
- *a suggested date for when NICE should consider the additional evidence.*

Not applicable.

5.2.3 *If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:*

- *the current price of the intervention (the price that will be supported by the collection of new evidence)*
- *the proposed relationship between future price changes and the evidence to be collected.*

Not applicable.

5.2.4 *For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:*

- *design of the new study*
- *patient population of the new study*
- *outcomes of the new study*
- *expected duration of data collection*
- *planned statistical analysis, definition of study groups and reporting (including uncertainty)*
- *expected results of the new study*
- *planned evidence synthesis/pooling of data (if applicable)*
- *expected results of the evidence synthesis/pooling of data (if applicable).*

Not applicable.

5.2.5 *If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.*

Not applicable.

5.2.6 *Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.*

Not applicable.

5.2.7 *Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.*

Not applicable.

5.2.8 *Please present the cost-effectiveness results as follows.*

- *For proven value: price increase schemes, please summarise in separate tables:*
 - *the results based on current evidence and current price*
 - *the anticipated results based on the expected new evidence and the proposed higher price.*
- *For expected value: rebate schemes, please summarise in separate tables:*
 - *the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)*
 - *the results based on the current evidence and the lower price (if the new evidence is not forthcoming).*
- *For risk-sharing schemes, please summarise in separate tables:*
 - *the results based on current evidence and current price*
 - *the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)*
 - *the results based on the current evidence and the lower price (if the new evidence is not forthcoming)*
 - *the anticipated results based on the expected new evidence and the proposed higher price.*

A suggested format is shown in table 3, section 4.7.

Not applicable.

5.2.9 *Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.*

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable.

**National Institute for Health and Care Excellence
Centre for Health Technology Evaluation**

Pro-forma Response

ERG report

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia [ID765]

You are asked to check the ERG report from SchARR to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 2 October** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Event rates and risks

Description of problem	Description of proposed amendment	Justification for amendment
The ERG report (page 68-69) states, <i>"It should also be noted that the predicted risks from both the Framingham and REACH equations are actually probabilities which are bounded between 0 to 1, but are not treated as such within the company's model;</i>	We recommend the ERG report is amended with regards this interpretation of event rates and risks.	The economic model is not interpreting Framingham and Wilson risk predictions as rates. They are interpreted as risks and then converted to rates. This can be checked in the patient level data risk predictions. For example, worksheet 'RUTHERFORD-2', cell AA7:

<i>these are instead assumed to be “event rates” (see Figure 5, box 2 “patient-level CV event rate”). This error in logic is discussed in more detail in Section 5.3”.</i>		=IF(\$C7=0,-<u>LN(1-(1-0.88936^EXP(3.06117*LN(\$B7)+((1-\$F7)*1.93303+\$F7*1.99881)*LN(\$H7)+1.1237*LN(\$K7)-0.93263*LN(\$L7)+0.65451*\$D7+0.57367*\$E7-23.9802)))</u>,"") The Framingham risk prediction, which is converted to a rate using an exponential survival function (bold and underlined text): rate = - LN (1 - risk) and then used in the rate predictions by age in the model.



Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: A Single Technology Appraisal

Critique of company's addendum 2 and accompanying PAS application

Mr Rachid Rafia, Research Fellow, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Dr Paul Tappenden, Reader in Health Economic Modelling, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Dr Christopher Carroll, Reader in Health Technology Assessment, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

8th October 2015

1. Introduction

In response to the critique presented in the Evidence Review Group (ERG) report,¹ the company submitted a further amended health economic model at the fact check stage which addresses some of the concerns raised by the ERG. The changes made by the company and their impact upon the economic analyses using the list price for evolocumab are documented within the company's addendum 2.² The impact of the model amendments together with the Patient Access Scheme (PAS) for evolocumab are presented in the company's PAS submission.³ The key changes made by the company relate to:

- (i) The use of the REACH Registry risk equations⁴ within the health economic model (and re-estimation of calibration factors in the CPRD/HES datasets⁵).
- (ii) The addition of constraints which are intended to prevent the model from generating negative transition probabilities.
- (iii) The use of treatment effects calculated from baseline (instead of the treatment differences compared with statins at the mean of week 10/12) and amendments to the treatment effect estimate used for the HeFH population.
- (iv) The inclusion of a PAS for evolocumab.

This document provides a brief summary and critique of the changes made by the company within their model. Owing to time constraints, the ERG advises caution in that this critique is based on the limited information provided by the company within addendum 2 and only a brief examination of the company's revised model.

2. ERG critique of amendments in company's addendum 2

2.1 Model implementation and misspecification of evidence inputs - REACH registry equations

The company appears to have corrected the model implementation error whereby the risk equation for the next cardiovascular (CV) event reported by Wilson *et al*⁴ was interpreted as the risk of the next non-fatal CV event, thereby leading to double counting of fatal CV events in the company's original submitted model. The company's amended model now uses only the risk equation for "next cardiovascular event" from the REACH Registry.⁴

Briefly, this amendment has been implemented as follows. The company's model first estimates the risk (probability) of any CVD event using the REACH equation for next CV event using baseline patient characteristics for the subset of patients within the LAPLACE-2 trial with baseline LDL-C > 2.5 mmol/L (non-familial population) and the modified intention-to-treat (mITT) population from the RUTHERFORD-2 trial (HeFH population). The aggregate risks (probability) are then transformed into aggregate rates and further transformed into age-specific rates for any CV event (according to history of CV events). The resulting CV event rates are then adjusted by a series of calibration factors

estimated from the CPRD/HES data, and transformed back into probabilities which are then separated into fatal (coronary heart disease [CHD] death and ischaemic stroke [IS] death) and non-fatal events (established CVD [ECVD], acute coronary syndromes [ACS], myocardial infarction [MI] and heart failure [HF]).

The ERG is generally satisfied with the company's amendment. The ERG notes however that the description provided in the company's addendum 2 is sometimes misleading and a number of changes to the model structure have been made (notably the addition of a further worksheet named "Calibrated Rates (model)" in the model). Whilst not justified by the company, the ERG notes that the company's amended model uses the risk for post-event states for patients with ECVD rather than the risk associated with the acute event. In the absence of any justification of this within the company's addendum 2, the ERG is unclear whether this assumption was made intentionally or whether this is a programming error.

The ERG reiterates that whilst the company has attempted to resolve this issue within their existing model structure, the overall approach to using calibrated risk equations is convoluted and circular; the ERG would have preferred a model which calculates transition probabilities based on CV events directly observed within the CPRD/HES datasets. This would reduce the number of assumptions and adjustments made by the company. The impact of this alternative approach on the ICER for evolocumab is unclear.

2.2 Model implementation and misspecification of evidence inputs – negative transition probabilities

In response to concerns raised within the ERG report¹ about the presence of negative transition probabilities, the company has added a number of constraints to prevent the model from generating negative values. Some of these constraints appear somewhat arbitrary and the logic underpinning them is difficult to follow from the information provided in the company's addendum 2. Within addendum 2, the company provides only a limited description of the constraints added to the amended model. Following scrutiny of the model, the ERG notes the following changes:

- The adjustment of the probabilities of CV events for all individual event health states (acute and post-acute) for the proportion of patients that die from other causes. The ERG is generally satisfied with this amendment.
- The addition of constraints for all individual event health states (acute and post-acute), such that the estimated risk of an event cannot be greater than the risk of the first CV event in patients without a history of CVD. The ERG believes that these constraints are inappropriate and arbitrary as the model attempts to compare two different risks: (a) the event risk in patients with a history of CVD and (b) the event risk in patients without a history of CVD. This is not described in addendum 2.

- For the composite health states which include one acute event (i.e. whereby patients have experienced an acute event in the previous model cycle), the risk of CV events associated with the previous acute event is used to represent the future risk of the next CV event. The ERG notes that this is different to the approach used in the company's original model, whereby the highest risk was used. The company's addendum 2 states that this approach was used to prevent the sum of probabilities from exceeding 1.0. The ERG considers these adjustments to be arbitrary and notes that the use of composite health states adds complexity to the model and relies on assumptions that are not informed by evidence.
- For the composite health states which do not include an acute event, the highest probability is used. The approach has been slightly amended compared with the original submitted model.

The ERG notes that under the base case assumptions, the transition probabilities remain positive in all three main populations included within the company's model. However, if the user sets the HeFH calibration factors to very high (clinically implausible) values e.g. 1,000, then several transition probabilities in the "Prob_Backbone" (statins/no treatment) worksheet become negative. Correspondence from the company indicates that a possible reason for the occurrence of these negative values is due to software precision limitations within Microsoft Excel. Whilst the ERG cannot verify this without a full check of the amended model, the ERG believes the company's explanation to be reasonable.

2.3 Model implementation and misspecification of evidence inputs – LDL-C treatment effects

In response to comments made within the ERG report (see ERG report, Section 5.3, point 7), the company has amended the treatment effect estimates used in the model. The key changes are as follows:

- For the non-familial population (statin tolerant), use of the treatment effect from the LAPLACE-2 trial for evolocumab and ezetimibe from baseline (rather than the treatment difference compared with statins at the mean of weeks 10/12).
- For the HeFH population (statin tolerant), use of the treatment effect from the RUTHERFORD-2 trial for evolocumab and from the LAPLACE-2 trial for ezetimibe (rather than using the treatment effect from the LAPLACE-2 trial for both arms).

For patients who are unable to take statins, no change has been made and the treatment effect from the GAUSS-2 trial is used.

Overall, the ERG is satisfied with these amendments.

2.4 Additional amendments to the economic model

2.4.1 Implementation of the PAS

The PAS appears to have been implemented correctly within the company's new model. This is applied as a simple price discount per pack of evolocumab. The ERG was able to replicate the summary results presented in Table 58 of the company's PAS submission using the company's new model. The ERG was also able to generate similar probabilistic results to those presented within the PAS submission.³

2.4.2 Inclusion of statin indicator variable

As suggested within the ERG report,¹ the company's amended model includes a statin indicator variable for the REACH registry equations to account for differential CV event risk in patients who are or are not able to take statins. However, as per the company's original analyses, this variable is set to "yes" for all analyses presented using the corrected model. Consequently, this amendment has no impact on the company's new analyses. The ERG considers that this variable should have been set to "no" for all analyses in which patients are unable to take statins.

3. Summary of results presented within the company's PAS submission

3.1 Base case cost-effectiveness results (deterministic)

Table 1 summarises the deterministic cost-effectiveness results presented within the company's addendum 2. For the sake of brevity, and in line with the final NICE scope, results are presented only for the comparison of evolocumab (with or without statins) versus ezetimibe (with or without statins). The ERG notes that whilst the inclusion of the PAS reduces the incremental costs of evolocumab, the amendments to the company's model described above result in a noticeable reduction in the incremental estimates of QALYs gained for evolocumab in most of the company's analyses. All results presented here are based on the PAS submission³ and re-analyses of the company's amended model including the PAS price.

Non-familial primary prevention population (analyses A and B)

As discussed in the ERG report,¹ during the clarification stage of the appraisal, the ERG identified a serious programming error within the company's model whereby it was possible for many of the transition probabilities, and hence the health state populations in the Markov trace, to be negative. Consequently, NICE submitted a request to the company to rectify the error. In response, the company submitted an amended model and an addendum detailing revised results produced using this amended model (company's addendum 1).⁶ Within addendum 1, the company's threshold analyses for evolocumab within the non-familial primary prevention population were considered to be "invalid" and re-analyses within this population using the first corrected model were not presented. The company's addendum 2 and PAS submission do not include any further threshold analyses in the non-

familial primary prevention population. Instead however, the PAS submission, which is based on the second amended version of the model, presents a cohort-based analysis for this population. It should be noted that the company's addendum 2 and PAS submission do not present probabilistic sensitivity analyses for the primary prevention population, hence results presented here are based on re-analyses undertaken by the ERG. All results are presented separately for those patients who are able to take statins (denoted ST) and for those patients in whom statins are contraindicated or not tolerated (denoted SI).

Within the non-familial primary prevention ST population (analysis A), the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.32 QALYs at an additional cost of [REDACTED] compared with ezetimibe plus statins; the resulting ICER is estimated to be £74,331 per QALY gained. The probabilistic ICER is higher at £76,446 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe is approximately zero at a willingness-to-pay (WTP) threshold of £30,000 per QALY gained. Within the non-familial primary prevention SI population (analysis B), the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.30 QALYs at an additional cost of [REDACTED] compared with ezetimibe monotherapy; the resulting ICER is estimated to be £78,879 per QALY gained. The probabilistic ICER is higher at £80,688 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe is approximately zero at a WTP threshold of £30,000 per QALY gained.

Non-familial secondary prevention population (analyses C and D)

Within the non-familial secondary prevention ST population (analysis C), the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.39 QALYs at an additional cost of [REDACTED] compared with ezetimibe plus statins; the resulting ICER is estimated to be £46,005 per QALY gained. The probabilistic ICER is higher at £47,079 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe is approximately zero at a WTP threshold of £30,000 per QALY gained. Within the non-familial secondary prevention SI population (analysis D), the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.37 QALYs at an additional cost of [REDACTED] compared with ezetimibe monotherapy; the resulting ICER is estimated to be £49,278 per QALY gained. The probabilistic ICER is higher at £50,321 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe is approximately zero at a WTP threshold of £30,000 per QALY gained.

HeFH primary/secondary prevention population (analyses G and H)

Within the HeFH primary/secondary prevention ST population (analysis G), the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.86 QALYs at an

additional cost of [REDACTED] compared with ezetimibe plus statins; the resulting ICER is estimated to be £22,902 per QALY gained. The probabilistic ICER is higher at £23,504 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe is approximately 0.08 at a WTP threshold of £20,000 per QALY gained, and approximately 0.96 at a WTP threshold of £30,000 per QALY gained. Within the HeFH primary/secondary prevention SI population (analysis H), evolocumab monotherapy is expected to produce an additional 0.82 QALYs at an additional cost of [REDACTED] as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £23,927 per QALY gained. The probabilistic ICER is higher at £24,604 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe is approximately 0.05 at a WTP threshold of £20,000 per QALY gained, and approximately 0.91 at a WTP threshold of £30,000 per QALY gained.

Table 1: Summary of company's base case cost-effectiveness results (deterministic, corrected model, including PAS)

Analysis	Population characteristics and comparison	Evolocumab		Ezetimibe		Incremental		
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER
Non-familial primary prevention population – cohort analysis								
Analysis A	ST (evo+statins vs eze+statins)	12.14		11.83	£9,979	0.32		£74,331
Analysis B	SI (evo vs eze)	12.10		11.80	£9,767	0.30		£78,879
Non-familial secondary prevention population - cohort analysis								
Analysis C	ST (evo+statins vs eze+statins)	8.23		7.84	£21,408	0.39		£46,005
Analysis D	SI (evo vs eze)	8.18		7.81	£21,143	0.37		£49,278
HeFH primary/secondary prevention population - cohort analysis								
Analysis G	ST (evo+statins vs eze+statins)	10.89		10.03	£20,672	0.86		£22,902
Analysis H	SI (evo vs eze)	10.79		9.97	£20,472	0.82		£23,927

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe; LDL-C - low-density lipoprotein cholesterol

3.2 Scenario analysis results – evolocumab in combination with ezetimibe

Table 2 summarises the results of the company's scenario analyses in which evolocumab is given in combination with ezetimibe (with/without concomitant statins). Probabilistic analyses were not presented for these populations and have not been repeated by the ERG.

Non-familial secondary prevention population (analyses E and F)

Within the non-familial secondary prevention SI population (analysis E), the company's scenario analysis suggests that evolocumab plus ezetimibe is expected to produce an additional 0.42 QALYs at an additional cost of [REDACTED] compared with ezetimibe; the resulting ICER is estimated to be £52,811 per QALY gained. Within the ST population (analysis F), evolocumab plus ezetimibe plus statins is expected to produce an additional 0.44 QALYs at an additional cost of [REDACTED] compared with ezetimibe plus statins; the resulting ICER is estimated to be £50,880 per QALY gained.

HeFH primary/secondary prevention population (analyses I and J)

For the HeFH primary/secondary prevention SI population (analysis I), the company's scenario analysis suggests that evolocumab plus ezetimibe is expected to produce an additional 0.96 QALYs at an additional cost of [REDACTED] compared with ezetimibe monotherapy; the resulting ICER is estimated to be £25,609 per QALY gained. Within the ST population (analysis J), evolocumab plus ezetimibe plus statins is expected to produce an additional 1.00 QALYs at an additional cost of [REDACTED] compared with ezetimibe plus statins; the resulting ICER is estimated to be £24,826 per QALY gained.

3.3 Subgroup analyses

The company's PAS submission also includes the results of a number of subgroup analyses across individual and combinations of CV risk factors. These are reported on pages 28-32 of the PAS submission³ and are not reproduced here. In some subgroups, the ICER for evolocumab is estimated to be below £30,000 per QALY gained. As noted in the ERG report,¹ these analyses employ arbitrary manipulations of the individual patient trial data which will ultimately produce biased risk estimates. The ERG considers that it would have been more appropriate to estimate baseline CVD risk from the CPRD/HES dataset and to subsequently adjust these using relative risks from the published literature to reflect these additional risk factors. Consequently, the ERG would advise caution in the interpretation of all of these analyses.

Table 2: Summary of company's scenario analysis results (evolocumab plus ezetimibe, deterministic, corrected model, including PAS)

Analysis	Population characteristics and comparison	Evolocumab plus ezetimibe		Ezetimibe		Incremental		
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER
Non-familial secondary prevention population – cohort analysis								
Analysis E	SI (evo+eze vs eze)	8.24		7.81	£21,143	0.42		£52,811
Analysis F	ST (evo+eze+statins vs eze+statins)	8.28		7.84	£21,408	0.44		£50,880
HeFH primary/secondary prevention - cohort analysis								
Analysis I	SI (evo+eze vs eze)	10.93		9.97	£20,472	0.96		£25,609
Analysis J	ST (evo+eze+statins vs eze+statins)	11.03		10.03	£20,672	1.00		£24,826

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe; LDL-C - low-density lipoprotein cholesterol

4. Discussion and additional ERG exploratory analyses

Overall, the ERG is generally satisfied with some of the changes made by the company, although some concern remains regarding the apparently arbitrary logic underlying some of the constraints used in the company's amended model. The ERG notes that within their new model, the company have addressed only a selected set of issues raised within the ERG's critique of the company's original model (see ERG report,¹ Table 46, pages 137-138). Whilst the ERG recognises that some of the concerns identified by the ERG are matters of subjective opinion rather than unequivocal errors, the ERG would advise some caution in the interpretation of the company's results due to: (a) the circular approach used by the company using a calibrated risk predictions instead of using directly observed CV events; (b) the selected populations used in the model; (c) the likely overestimation of the risk of CV events in the HeFH population (i.e. the calibration factor of 7.1 based on Benn *et al*); (d) uncertainty regarding the relationship between LDL-C reduction and reductions in CV events, and; (e) the use of a model structure which includes multiple composite event states which are populated using many assumptions and little evidence.

The ERG notes that the most favourable ICERs for evolocumab reported within the company's PAS submission are those for the HeFH population (HeFH ST ICER=£22,902 per QALY gained; HeFH SI ICER=£23,927 per QALY gained, see Table 1). The calibration rate of 7.1 is a key driver of the cost-effectiveness of evolocumab in this population. It is noteworthy that within the company's model, the calibration factor of 7.1 is applied to the modified ITT population recruited into the RUTHERFORD-2 trial; these patients are already, by definition, at an increased risk due to their prior diagnosis of HeFH. The ERG considers that this calibration factor is likely to be an overestimate and notes that the use of a lower calibration factor would produce less favourable ICERs for evolocumab.

In order to explore the extent of this potential bias, the ERG identified a long-term cohort study and Cox regression analysis assessing the efficacy of statins in patients with familial hypercholesterolaemia (FH, without prevalent CHD) reported by Versmissen *et al*.⁷ Figure 1 shows the predicted CVD event-free survival curve for the HeFH primary prevention ST population with a starting age of 49 years, based on the amended company's model. According to the company's model predictions, approximately 50% of HeFH patients on statins would experience an event (which may include death from other causes) by the age of 57-58 years (i.e. after 8 to 9 years). For comparison, Figure 2 shows the risk of CHD within the Versmissen *et al* cohort study.⁷ The Kaplan-Meier curve indicates that the proportion of patients experiencing a CHD event within the same time interval is approximately 10%. Versmissen *et al* report that the risk of MI in statin-treated patients with FH was not significantly greater than that in an age-matched sample from the general population (hazard ratio=1.44, 95% confidence interval 0.80 to 2.60, $p=0.23$). Although the Versmissen *et al* study has potential limitations, in particular its use of an observational design and associated potential for

confounding and the use of CHD rather than CVD as an outcome, this indicates that the company's calibration factor of 7.1 may inflate the risk of CV events and death within the HeFH population within the model.

Figure 1: Predicted event-free survival from company's amended model – HeFH primary prevention population

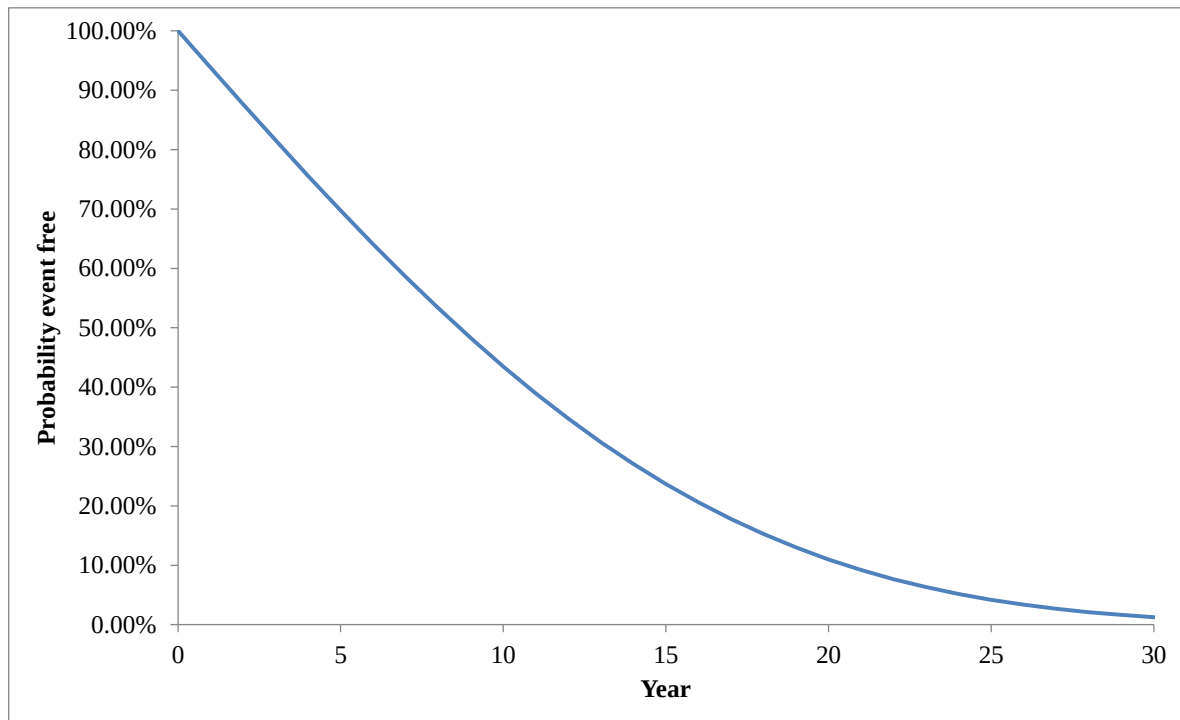
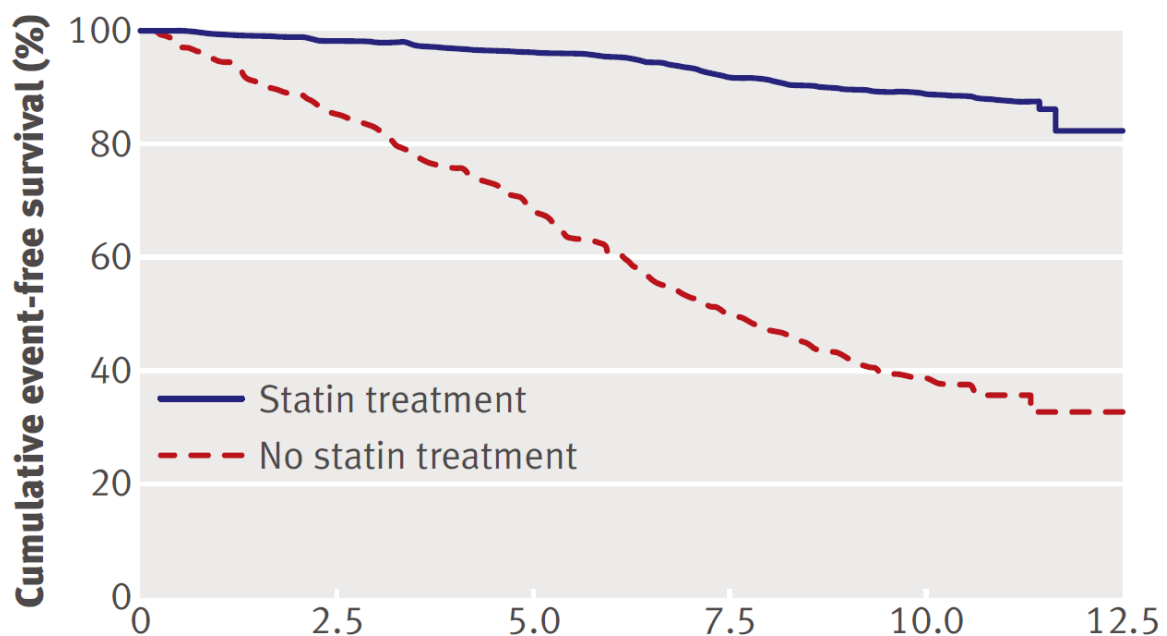


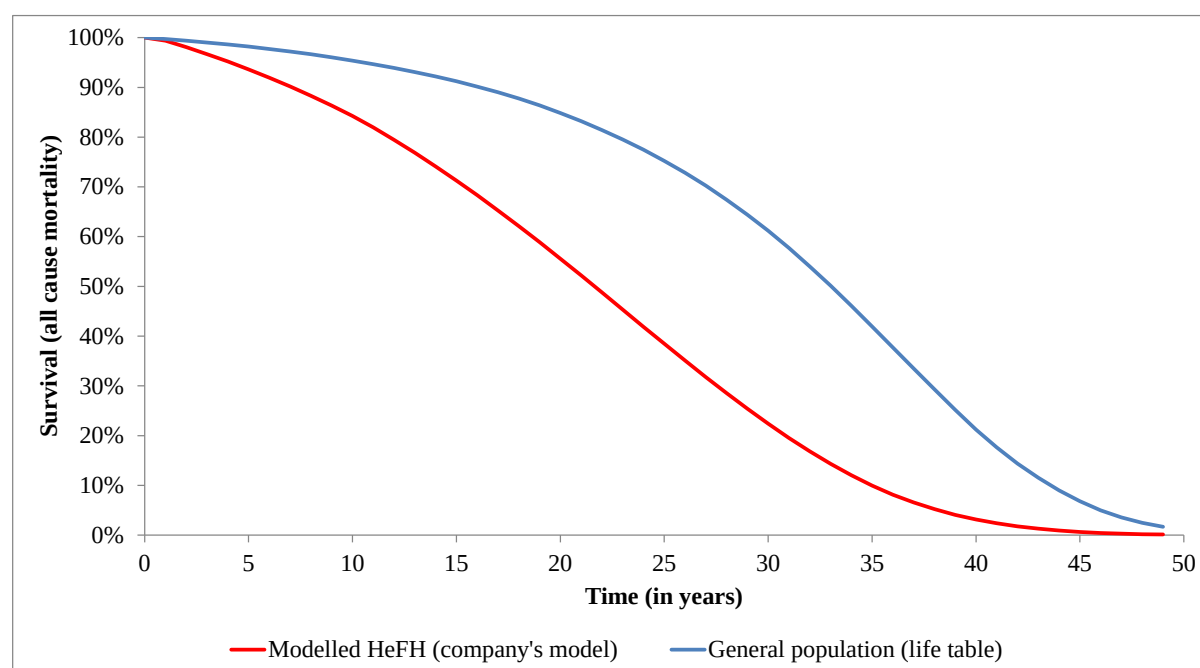
Figure 2: Cumulative CHD-free survival among patients with familial hypercholesterolaemia according to statin treatment



As previously highlighted within the ERG report, the UK study by Neil *et al*⁸ reported a lower standardised mortality ratio (SMR) for CHD in patients with HeFH treated with statins. The SMR for CHD deaths was 1.03 for primary prevention, and 3.88 for secondary prevention in people between 20 and 79 years of age. Within the Neil study, the SMR for all-cause mortality for the period 1992-2006 was not statistically significant (SMR=0.94, 95% CI 0.84 to 1.05, $p=0.31$). A recent Norwegian study has also been published based on registry data from 4,688 male and female individuals from the Unit for Cardiac and Cardiovascular Genetics (UCCG) Registry with verified molecular genetic diagnosis of familial hypercholesterolemia linked to the Norwegian Cause of Death Registry.⁹ Within this study, Mundal *et al* reported that compared with the Norwegian population, CVD mortality was significantly higher in the UCCG Registry in all age groups younger than 70 years (SMR=2.29, 95% CI 1.65 to 3.19 in men and women combined; SMR=2.00, 95% CI 1.32 to 3.04 in men; SMR=3.03, 95% CI 1.76 to 5.21 in women). The SMR for CVD mortality across all ages (including people over the age of 70 years) was 1.56 (1.41 in males and 1.75 in females). This study also reported a non-significant SMR for all-cause mortality (SMR=0.87, 95% CI 0.72 to 1.05, p -value not reported). In summary, these studies indicate that there may be a difference in the rate of CVD/CHD mortality for patients with HeFH (although the company's model appears to overestimate this difference). However, no significant difference has been reported for all-cause mortality.

Figure 3 compares the modelled survival for the HeFH population from the company's model to the expected survival for the UK general population using life tables for a 51 year old cohort (corresponding to the starting age in the model). The ERG notes that the risk of all-cause mortality for the HeFH population predicted by the company's model is considerably greater (approximately 3 times) than the risk of mortality expected within the UK general population. As noted above, this is not in line with the estimates reported by Neil *et al*⁸ and Mundal *et al*.⁹

Figure 3: Comparison of modelled HeFH all-cause mortality and expected general population all-cause mortality



Whilst there is uncertainty surrounding the rate of CV events in the HeFH population relative to that in the non-familial population, it is likely that the ICERs for evolocumab in the HeFH population are higher than those presented within the company's PAS submission. Figures 4 and 5 present exploratory analyses undertaken by the ERG using the company's model to demonstrate the impact of using alternative HeFH calibration factors on the ICERs for evolocumab versus ezetimibe in patients who are able to take statins (ST) and those who are unable to take statins (SI). Table 3 presents a threshold analysis to determine the minimum HeFH calibration factor required in order for the ICER for evolocumab versus ezetimibe to be below £30,000 per QALY gained. These analyses each indicate that the ICER for evolocumab versus ezetimibe increases considerably as the assumed HeFH calibration factor decreases. The threshold analysis results suggest that the calibration factor must be greater than 4.5 to 5.6 in order for the ICER for evolocumab versus ezetimibe to be below £30,000 per QALY gained. As noted above, the calibration factor is applied to an already high-risk population (high cholesterol) and therefore the minimum calibration factor required for evolocumab to achieve an ICER which is below £30,000 per QALY gained compared with the risk from the general population would be considerably higher.

Figure 4: ERG exploratory analysis - impact of alternative HeFH CV event calibration factors on the ICER for evolocumab plus statins versus ezetimibe plus statins (ST, deterministic, including PAS)

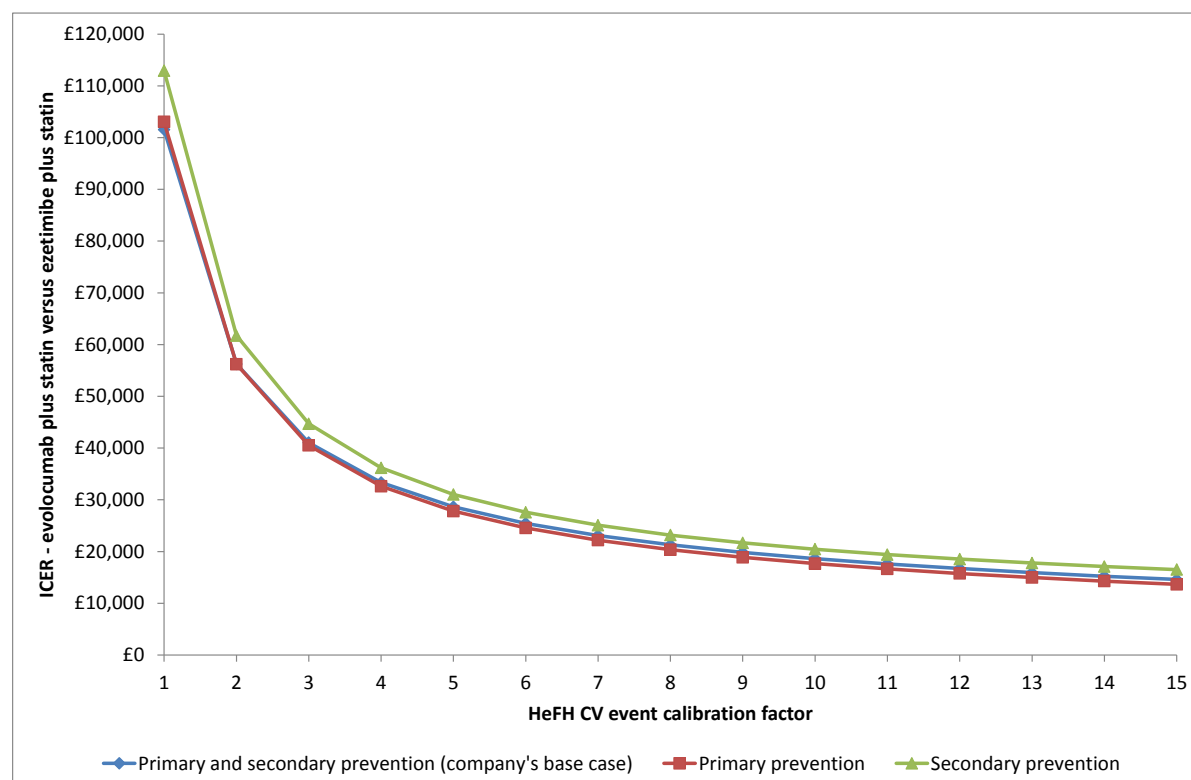


Figure 5: ERG exploratory analysis - impact of alternative HeFH CV event calibration factors on the ICER for evolocumab monotherapy versus ezetimibe monotherapy (SI, deterministic, including PAS)

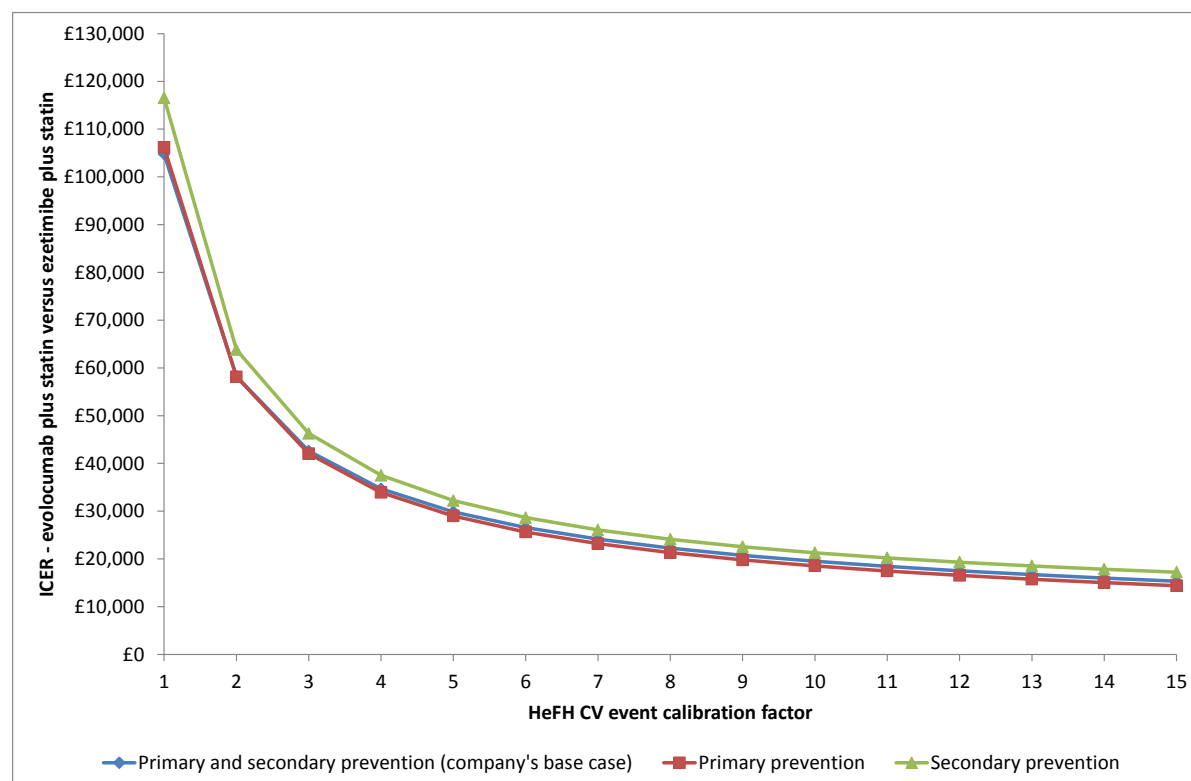


Table 3: Threshold analysis results – minimum HeFH calibration factor required in order for the ICER for evolocumab versus ezetimibe to be £30,000 per QALY gained or less

HeFH population	Statin tolerant	Statin intolerant
Primary and secondary prevention	4.67	4.96
Primary prevention	4.49	4.76
Secondary prevention	5.26	5.58

References

1. Carroll C, Tappenden P, Rafia R, Sanderson J, Chambers D, Clowes M, Durrington P, Qureshi N, and Wierzbicki A. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: A Single Technology Appraisal. School of Health and Related Research (SchARR), 2015.
2. Amgen. Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia: addendum 2; 2015.
3. Amgen. Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia: Patient Access Scheme submission; 2015.
4. Wilson P, D'Agostino RS, Bhatt D, Eagle K, Pencina M, Smith S, *et al.* An international model to predict recurrent cardiovascular disease. *American Journal of Medicine* 2012;125:695-703 e1.
5. Amgen. Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia: Company's submission to the National Institute for Health and Care Excellence (NICE); 2015.
6. Amgen. Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia. Company's addendum 1; 2015.
7. Vermissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DCG, Liem AH, *et al.* Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *British Medical Journal* 2008;337:a2423.
8. Neil A, Cooper J, Betteridge J, Capps N, McDowell I, Durrington P, *et al.* Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *European Heart Journal* 2008;21:2625-33.
9. Mundal L, Sarancic M, Ose L, Iversen PO, Borgan JK, Veierød MB, *et al.* Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992-2010. *Journal of the American Heart Association* 2014;3(6):e001236.



Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: A Single Technology Appraisal

Erratum

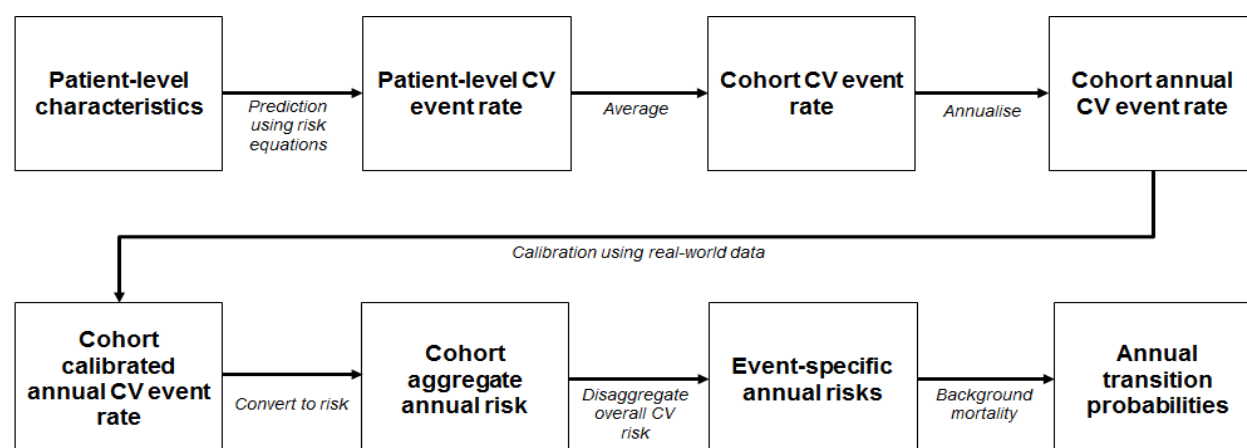
Produced by	School of Health and Related Research (SchARR), The University of Sheffield
Authors	Christopher Carroll, Reader in Health Technology Assessment, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Paul Tappenden, Reader in Health Economic Modelling, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Rachid Rafia, Research Fellow, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Jean Sanderson, Research Associate, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Duncan Chambers, Research Fellow, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Mark Clowes, Information Specialist, SchARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA Paul Durrington, Professor, Cardiovascular Research Group, Core Technology Facility, Manchester, M13 9NT Nadeem Qureshi, Professor, Faculty of Medicine & Health Sciences, Tower Building University Park, Nottingham, NG7 2RD Anthony Wierzbicki, Professor, King's College London, Guy's and St. Thomas' NHS Foundation Trust, Westminster Bridge Road, London, SE1 7EH

- (i) Estimation of transition probabilities for people prior to receiving evolocumab and/or ezetimibe.
- (ii) Estimation of the relative reduction in CVD events associated with the use of evolocumab and/or ezetimibe based on reductions in LDL-C observed in RCTs.^{23,24}
- (iii) Estimation of transition probabilities in patients receiving evolocumab, ezetimibe or evolocumab plus ezetimibe.
- (iv) Estimation of QALYs, costs and cost-effectiveness.

(i) Estimation of transition probabilities for people prior to receiving evolocumab and/or ezetimibe

The steps used by the company to estimate transition probabilities in the absence of evolocumab and/or ezetimibe (referred to as “population CV event rates” in the CS) are described in Figure 5.

Figure 5: Step-wise sequence of estimating event-specific transition probabilities from patient-level characteristics (reproduced from CS,¹³ Figure 5-4 page 182)



CV - cardiovascular

Published risk equations^{53,54} are applied to individual patient data (IPD) from the subgroup of patients enrolled in the LAPLACE-2 trial²³ who had a baseline LDL-C>2.5mmol/L and from the modified ITT population of the RUTHERFORD-2 trial²¹ to estimate the average aggregate risk of the next CVD event for males and females separately. The Framingham equations for males and females⁵³ are used to estimate the risk of a first CVD event in people who do not have a history of CVD. The REDuction of Atherothrombosis for Continued Health (REACH) Registry equations⁵⁴ are used to predict the risk of experiencing a fatal or any CVD event (assumed incorrectly to be non-fatal by the company) in people who have a history of CVD. The company assumes (incorrectly) that the risk predicted for “cardiovascular death” and “next cardiovascular event” from the REACH equations are independent of each other and can be added (effectively producing a total CVD risk). ~~It should also be noted that the predicted risks from both the Framingham and REACH equations are actually probabilities which are bounded between 0 to 1, but are not treated as such within the company’s model; these are instead~~

~~assumed to be “event rates” (see Figure 5, box 2 “patient level CV event rate”). This error in logic is discussed in more detail in Section 5.3.~~

The calculated average aggregate risks of CVD events (10-year risk from Framingham⁵³ and 20-month risk from REACH⁵⁴) are then transformed into annualised rates; these are calculated separately for males and females (using a sex-specific equation from Framingham and a covariate for sex within the REACH equation). Limited details are provided within the CS¹³ regarding this step in the process. From the company’s model, the age coefficients (for males and females separately) from the risk equations are used to obtain annual age- and sex-specific rates under the assumption that the event rate follows an exponential distribution such that the sum of the CVD event risks is equal to the average aggregate 10-year risk of CVD using the following formula:

$$risk(t) = \hat{\phi} \times \exp(\phi) \ln\left(\frac{age(t)}{\rho}\right) \quad [i]$$

Where:

risk(t) = annual risk at a given age

φ̂ = risk prediction by risk equation

φ = age coefficient in the risk equation

age(t) = current age

ρ = mean age

The annual age-specific risks obtained for males and females are then averaged to obtain an average annual age-specific risk; these are capped at a maximum age of 86 years (i.e. the risk is assumed to remain constant after age 85 years) and are subsequently multiplied by either: (a) state-specific calibration factors to reflect the performance of the risk equations in the UK for the non-familial primary hypercholesterolaemia populations (based on the LAPLACE-2 trial²³), or (b) an overall calibration factor to reflect the differences in the risk of CVD events between HeFH and non-HeFH patients (HeFH analyses only). Following this process, the company transform the resulting risks onto the probability scale using the following formula:

$$probability = 1 - \exp(-rate) \quad [ii]$$

The average aggregate annual age-specific probabilities of CVD events are then apportioned according to specific CVD events based on multinomial logistic regression models (see Section 5.2.2). The average aggregate risks for first CVD events derived from the Framingham equations⁵³ after calibration are apportioned into ECVD, ACS, IS, HF, CHD death and stroke death events. The risks for subsequent CVD events derived from the REACH Registry equations⁵⁴ after calibration are

Section 5.2.2). The ERG notes that based on information provided within the CS¹³ and during the clarification process,³⁵ the baseline risk of experiencing CV events could have been estimated directly from the company's CPRD and HES analysis, and that the use of the Framingham and REACH equations is not necessary as it does not appear to provide additional information compared with using the CPRD and HES data. In effect, the company's approach involves estimating CV risk using equations then adjusting these to reflect real-world CPRD/HES data rather than using the CPRD/HES data directly. The ERG sought clarification from the company regarding this matter (see clarification response,³⁵ question B33). The company's response stated that:

"...the economic model could indeed have directly used the CPRD study event rates to model an overall high-risk population as per the study cohort definitions. However, this approach would not have permitted us to assess specific high-risk populations such as those with existing CVD with 1 or 2 additional risk factors who remain at the highest residual risk."

The ERG considers the company's response to be unsatisfactory because: (a) the analyses in individuals with additional risk factors (AF and 2/3 vascular beds) are presented only within the company's subgroup analyses and do not reflect the main population specified in the NICE scope,⁴ and; (b) the company's analysis in patients with existing CVD with one or two additional risk factors employs arbitrary manipulations of the IPD which will ultimately produce biased risk estimates. The ERG considers that it would have been more appropriate to estimate baseline CVD risk from the CPRD/HES data and to subsequently adjust these using relative risks from the published literature to reflect these additional risk factors. It is also noteworthy that the company's process for estimating CVD risk in all populations requires several other assumptions (e.g. removing the effect of age and sex), the validity of which are unclear.

(d) Model implementation and misspecification of evidence inputs

Upon scrutinising the company's model, the ERG identified a number of inconsistencies and errors in the model's implementation and logic, which appear to be due to a misinterpretation or misuse of evidence. These are described in below.

~~Firstly, the company's model treats the predictions from the Framingham⁵³ and REACH Registry⁵⁴ risk equations as event rates (see CS,¹³ Figure 5-4, page 182). However, in response to a request for clarification from the ERG, the company recognised that the risk predicted by these equations are actually probabilities which are bounded between 0 to 1 (see clarification response,³⁵ question B17).~~

~~In addition,~~ The company's model misinterprets what the REACH Registry risk equations⁵⁴ are predicting. As detailed in Section 5.2, the REACH Registry risk equations predict: (i) the risk of any

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia

Supportive Documentation

October 2015

File name	Version	Contains confidential information	Date
		Yes CIC: Redacted	November 2015

Documentation required:

Please find information with regards to the request for additional documentation received on 16th October 2015 for the proposed Patient Access Scheme (PAS) and potential GP prescribing.

- A sensitivity analysis which varies 1) the proportion of patients who would transition from secondary care to primary care and 2) time spent in secondary care before patients move to primary care. These sensitivity analyses should take into account that the PAS price will only apply to patients who are prescribed evolocumab through secondary care. The sensitivity analyses should be undertaken for each of the 3 populations in the model (i.e. patients with primary non-familial hypercholesterolaemia without existing CVD, patients with primary non-familial hypercholesterolaemia with existing CVD and patients with HeFH (with or without existing CVD). Please also provide the rationale for the value of the inputs used.
- Amgen's commitment to providing the acquisition price to the GP prescribing setting for evolocumab in future, including the example of what Amgen have done for denosumab.

1. Sensitivity analysis for prescribing of evolocumab in primary care

We have conducted additional sensitivity analyses whereby we have varied the proportion and time of patients who would transition from secondary care to primary care. We have used the PAS price for secondary care and NHS list price in primary care as per the request for additional documentation.

Notably, we believe prescribing through FP10 prescriptions will only occur with a primary care rebate in operation (Section 2). In the absence of this, we agree patients routine lipid management could transition to primary care; however, prescribing and fulfilment of evolocumab would still remain in secondary care since the technology will only be deemed cost-effective by local NHS commissioners alongside a PAS (if recommended). This was our experience for denosumab; hence the establishment of a primary care rebate model to facilitate transition of care between secondary and primary care.

The incremental cost-effectiveness results of the sensitivity analyses are presented in Table 1 to Table 3 for evolocumab versus ezetimibe (statin tolerant population). The results for patients with statin intolerance have not been presented given the general consistency.

Economic model functionality amends:

The economic model has the following amends marked up in yellow:

- Main worksheet - addition of selectors for:
 - Evolocumab prescribing setting (secondary or secondary/primary)
 - Years to transition to primary care
- Costs and CVD utilities worksheet – addition of inputs for primary care proportions for the three populations.

Table 1 Patients without existing CVD: Incremental cost-effectiveness results (£/QALY gained) for evolocumab versus ezetimibe (statin tolerant)

Years to transition to primary care	Proportion of patients treated with evolocumab in primary care										
	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
2	74,331	████	████	████	████	████	████	████	████	████	████
3	74,331	████	████	████	████	████	████	████	████	████	████

Table 2 Patients with existing CVD: Incremental cost-effectiveness results (£/QALY gained) for evolocumab versus ezetimibe (statin tolerant)

Years to transition to primary care	Proportion of patients treated with evolocumab in primary care										
	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
2	46,005	████	████	████	████	████	████	████	████	████	████
3	46,005	████	████	████	████	████	████	████	████	████	████

Table 3 Patients with heterozygous familial hypercholesterolaemia: Incremental cost-effectiveness results (£/QALY gained) for evolocumab versus ezetimibe (statin tolerant)

Years to transition to primary care	Proportion of patients treated with evolocumab in primary care										
	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
2	22,902										
3	22,902										

2. Patient Access Scheme and confidential commercial discount

We wish to confirm our intention to provide evolocumab to the NHS at the same acquisition cost regardless of the care setting (secondary or primary care). As noted, savings associated with lower acquisition costs for medicines with simple PAS compared to list price cannot be realised by the NHS when prescribed through FP10 prescriptions due to the current financial flows.

We have experience with regards implementation of parallel simple PAS (secondary care) and an equivalent confidential commercial discount (primary care) for an existing medicine that has been recommended through a NICE Technology Appraisal (NICE TA265: Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours). Denosumab was recommended in October 2012 in conjunction with a simple PAS. Whilst the majority of patients with bone metastases are managed in secondary care, primary care prescribing through FP10 prescriptions has occurred in some areas based on localised patient pathways and service re-design opportunities with this medicine. Similarly to evolocumab, we are committed to providing denosumab to the NHS at the same acquisition cost regardless of the care setting (secondary or primary care). As such, this has been referred to as a confidential commercial discount (financially considered as a primary care rebate) since the PAS was only approved in the context of secondary care.

To enable Clinical Commissioning Groups (CCGs) to realise the lower acquisition cost, we have developed a primary care rebate process which has been reviewed and approved by PrescQIPP Governance Review Board (further information available at: <http://www.prescgipp.info/projects/pharmaceutical-industry-scheme-governance-review-board>). CCGs and Amgen follow the process outlined below. This has been in operation with approximately 10 CCGs over the last two years.

- CCG representative signs a single contract agreement with Amgen for primary care rebate for all supplies of denosumab.
- Denosumab is prescribed on a FP10 prescription and dispensed by a community pharmacy at list price.
- List price acquisition cost is paid by relevant CCG based on patient's registered GP.
- CCG pharmacist emails ePACT (NHS Business Services Authority) prescribing data for denosumab to Amgen every three months.
- Amgen issue a single quarterly rebate to each CCG to ensure that the same net acquisition cost for denosumab as per the approved simple PAS.

We acknowledge the feedback that since routine lipid management is an area of standard GP practice, there may be a potential transition of patients from secondary to primary care after 2 to 3 years. We would plan to follow the same process if evolocumab prescribing was to transition to primary care in the future for some patients. The primary care rebate model was designed in collaboration with the NHS to ensure minimal administrative burden for NHS staff. Therefore, CCG representatives (e.g. pharmacist) are only required to complete a single contract agreement at the outset and then provide routinely available ePACT data via email to ensure realisation of the equivalent simple PAS price in primary care. The primary care rebate model has been noted for its ease of administration.