NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779]

Contents:

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

Alirocumab 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 from the ERG before the company has checked the ERG report for factual inaccuracies.

This document does not include the ERG's comments about the company's response to the request for additional sensitivity analyses about the applicability of the Patient Access Scheme (PAS) [redacted] in primary care.

Key issues for consideration

- In the absence of final outcomes data from the ODYSSEY trial, the effect of alirocumab on LDL-c was translated into a reduction in cardiovascular (CV) event risk using pooled hazard ratios for cardiovascular events from a meta-analysis of PCSK9 inhibitors (Navarese et al).
  - The ERG stated that LDL-c reduction has a greater impact on cardiovascular events using the Navarese meta-analysis compared with the meta-analysis of statins (Cholesterol Treatment Trialists' Collaboration [CTTC]). Using Navarese the risk reduction per 1 mmol/L reduction in LDL-c was 0.64 for non-fatal

myocardial infarction (MI), coronary revascularisation, ischaemic stroke and any vascular death (95% CI 0.43 to 0.96 for all except vascular death which was 0.40 to 1.04). Using CTTC, the risk reductions per 1 mmol/L reduction in LDL-c were 0.74 (95% CI 0.71 to 0.77) for non-fatal MI, 0.76 (95% CI 0.73 to 0.78) for coronary revascularisation,, 0.79 (95% CI 0.74 to 0.85) for ischaemic stroke and 0.88 (95% CI 0.84 to 0.91) for vascular death.

  - ◊ Does the accepted link between LDL-c reduction and reduction in CV events based on statins hold true for PCSK9 inhibitors?
  - ◊ If so, which source of relative risk reductions should be used to link LDL-c to cardiovascular events for alirocumab?

- Evolocumab (subject to ongoing NICE appraisal) and ezetimibe were included as comparators in the final NICE scope.
  - ◊ What are the most appropriate comparators for the appraisal of alirocumab in the statin tolerant and statin intolerant populations?
- The Department of Health's Patient Access Scheme (PAS) approval letter noted that "there may be a potential transition of patients from secondary to primary care after 2 to 3 years. This has potential implications for the [redacted] patient access scheme. As [redacted] cannot be realised when drugs are prescribed through FP10 prescriptions, the actual [redacted] received by the NHS may be less than the [redacted] offered in the scheme."
  - What proportion of patients receiving alirocumab will, if any, transition into primary care and after how many months/years?

- The company used a baseline low-density lipoprotein cholesterol (LDL-c) ≥3.36 mmol/L on maximally tolerated statins for people with high risk cardiovascular disease (CVD)**.** The ERG stated that a low proportion of high risk cardiovascular disease population would meet these criteria.
  - Has the company used an appropriate baseline LDL-c level for people with high risk CVD?
- The ERG noted that some of the company's costs were inconsistent with previous technology appraisals. The ERG believed that the company's model:
  - underestimated costs for stroke and the post-stroke health states

  - applied follow–up costs following a cardiovascular events (such as stroke) for only up to 3 years
  - did not apply costs for the second half of the first year following a cardiovascular event
    - ◊ Are all of the ERG's changes to the costs appropriate?
- The company assumed a 100% treatment continuation and compliance with alirocumab in its base-case. The ERG suggested that an 8% discontinuation rate was observed in ODYSSEY and LONG-TERM.
  - Is it appropriate to assume that the benefit of treatment with alirocumab persists over a lifetime treatment duration?
  - What is the appropriate discontinuation rate with alirocumab?
- The marketing authorisation includes people with mixed dyslipidaemia, however this population has not been separately considered within the company's submission.
  - Can a recommendation be made for this group?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal is: to appraise the clinical and cost effectiveness of alirocumab 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	As per final scope	The company stated that population in the submission was in line with the scope	The ERG agreed with the company's comments
Intervention	Alirocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe	Alirocumab in combination with maximal tolerated dose of statins, with or without ezetimibe, or alirocumab on a background of no statins, with or without ezetimibe	In line with the scope but adjusted to reflect current NHS usage of ezetimibe	The ERG agreed with the company's comments and stated that the company's specification of the intervention was appropriate and clinically relevant
Comparators	• Optimised statin therapy • When LDL-c is not adequately controlled with optimised statin therapy: ○ Ezetimibe in combination with optimised statin therapy	When LDL-c is not adequately controlled with optimised (maximal tolerated dose) statin therapy: • Optimised statin therapy alone (i.e. no additional	The company anticipate that alirocumab will be used in patients who are not adequately controlled on all maximally used existing therapy	The ERG noted that the company did not include evolocumab as a comparator because it is not standard care in the NHS The ERG agreed with the company's choice.

	○ Evolocumab in combination with optimised statin therapy (subject to NICE guidance) • When LDL-c is not adequately controlled with optimised statin therapy in combination with ezetimibe: ○ Evolocumab in combination with ezetimibe and a statin (subject to NICE guidance) • When statins are contraindicated or not tolerated: ○ Ezetimibe ○ Evolocumab (subject to NICE guidance) ○ Evolocumab in combination with ezetimibe(subject to NICE guidance)	comparator) • Optimised statin therapy plus ezetimibe When LDL-c is not adequately controlled with optimised statin therapy in combination with ezetimibe: • Optimised statin therapy plus ezetimibe (i.e. no additional comparator) When statins are contraindicated or not tolerated: • No additional therapy (on background of ezetimibe) As a base case, the company consider alirocumab as an adjunctive agent to current maximal therapy (maximal tolerated dose statins with or without ezetimibe, or a background of no statins with or without ezetimibe) The comparison is therefore versus no active		

		comparator The company present scenario comparisons versus ezetimibe The company did not conduct formal economic comparison versus evolocumab as NICE have not yet issued guidance and it is not NHS standard of care		
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	As per final scope	n/a	The ERG stated that the outcomes were in line with the final NICE scope

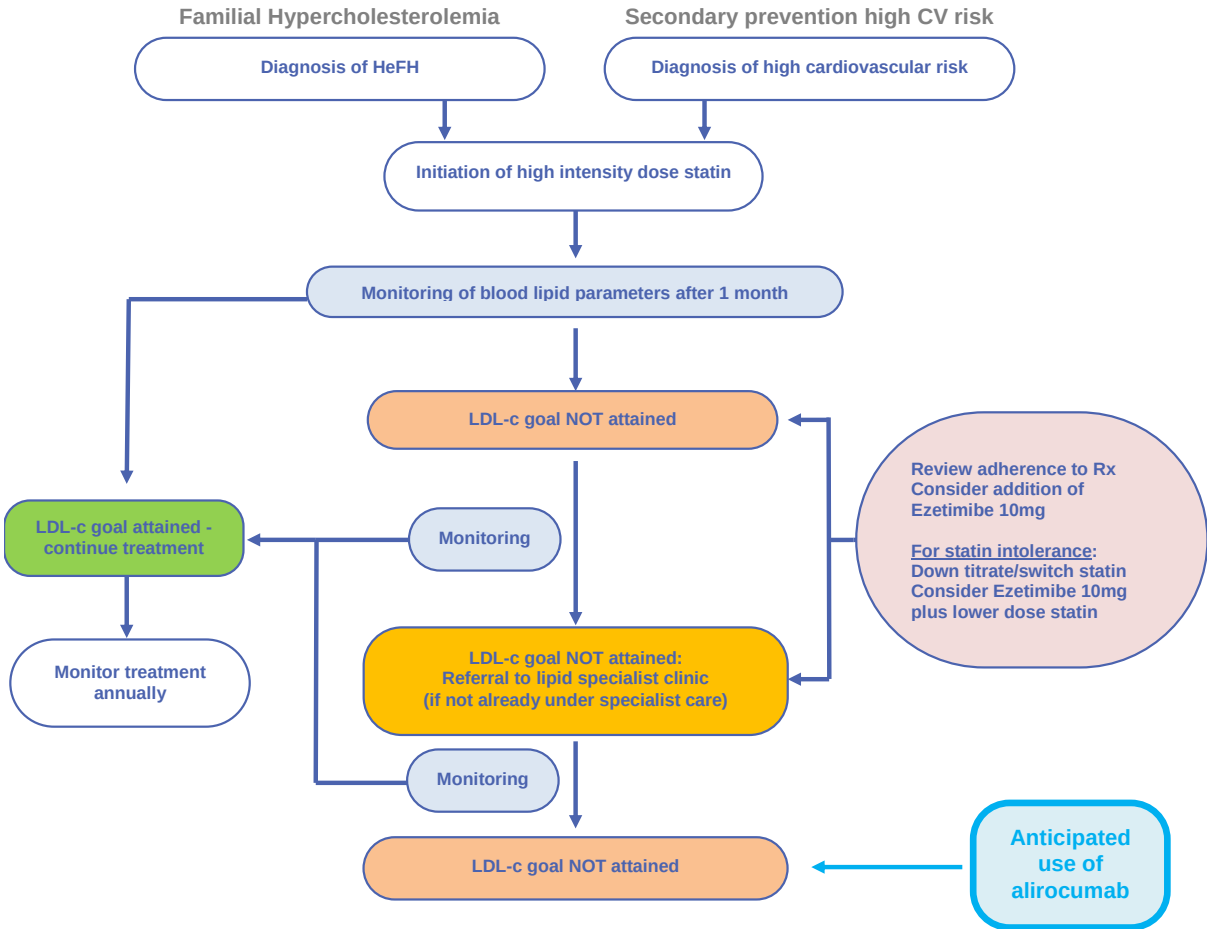
2 The technology and the treatment pathway

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: figure 4, page 46 of company's submission

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 Alirocumab (Praluent, Sanofi/Regeneron) is a fully-human monoclonal antibody that targets proprotein convertase subtilisin/kextin type 9 (PCSK9). It prevents degradation of LDL receptors in the liver, thereby facilitating LDL clearance from circulation and lowering LDL-C levels in

the blood. It is self-administered subcutaneously. Alirocumab has a marketing authorisation in the UK (received September 2015) for '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 modification therapies (LMTs) in patients unable to reach LDL-c goals with the maximal tolerated dose of statin (when used as recommended by treatment guidelines) or,
- alone or in combination with other LMTs in patients who are statin intolerant or for whom a statin is contraindicated.

2.6 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-c. A technology appraisal review of this guidance is underway to allow new data to be taken into account. In the final appraisal determination (FAD), ezetimibe is 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-c. Final guidance is due to be published in early 2016.

2.7 A technology appraisal of evolocumab, another PCSK9 is currently underway. In the appraisal consultation document (ACD), evolocumab alone or in combination alone with lipid-lowering therapies, is not recommended within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia in adults. Final guidance is due to be published early 2016.

Table 2 Technologies

	Alirocumab	Ezetimibe	Atorvastatin (used in the company's submission as a weighted comparator)	Rosuvastatin (used in the company's submission as a weighted comparator)
Marketing authorisation	Alirocumab 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 The effect of alirocumab on cardiovascular morbidity and mortality has not yet been determined	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 Ezetrol 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 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	Treatment of hypercholesterolaemia Adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate 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

			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	
Administration method	a single-use, pre-filled auto-injector pen in either one pen or two pen packs Dose frequency: 1 injection (75 mg or 150 mg) every 2 weeks	Oral Dosing frequency: 1 tablet (10 mg) daily	Oral Dosing frequency: 1 tablet (10 mg, 40 mg, or 80 g) daily	Oral Dosing frequency: 1 tablet (5 mg, 10 mg, 20 mg, or 40 mg) daily
Cost information	A confidential patient access scheme (PAS) was agreed with the Department of Health Without the PAS, a pen of alirocumab 75 mg and 150 mg costs £168	A 28-tab pack of ezetimibe 10 mg costs £26.31 (BNF, accessed October 2015)	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, accessed October 2015). See the BNF for prices of the other statins	A 28-tab pack of rosuvastatin costs £18.03 for 5 mg and 10 mg tablets; £26.02 for 20 mg tablets and £29.69 for 40 mg tablets. (BNF, accessed October 2015). See the BNF for prices of the other statins

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

3 Comments from consultees

3.1 Comments from patient and profession groups were received from HEART UK, the British Cardiovascular Society and the Royal College of Pathologists. A clinical expert nominated by Sanofi submitted comments.

3.2 The patient expert stated that patients want their cholesterol levels to be normal to reduce cardiac risk and increase life-expectancy. Patients were concerned about the life-long financial consequences associated with routine prescriptions.

3.3 The patient and professional organisations stated that hypercholesterolaemia can be treated with lifestyle changes (such as exercise and diet) and using medication (such as statins, ezetimibe and emerging PCSK9 inhibitors.) or by using LDL-apheresis. The clinical expert stated that although there are guidelines for the management of familial hypercholesterolaemia there is some controversy about the appropriate LDL-c target and the use of cardiovascular risk to treat primary hypercholesterolaemia. The patient and profession groups stated that statins are the main treatment for hypercholesterolaemia and are generally well tolerated. They stated that for some people for whom statins are not tolerated, the alternative treatments such as bile acid sequestrants and fibrates may not be efficacious and have side effects. A professional organisation stated that ezetimibe was safe and efficacious. Comments stated that LDL-apheresis are invasive, time consuming and not available in some parts of the country.

3.4 The professional organisations stated that LDL-c levels are a risk factor for cardiovascular events. The patient organisation noted that alirocumab can reduce cholesterol concentrations by 60% on top of current standard of care for people with familial hypercholesterolaemia. The clinical expert also said that the LDL-c reduction is sustained during treatment. Generally, the professional and clinical experts said that alirocumab has a good safety profile. They stated that people with HeFH and people who

have an increased cardiovascular risk might benefit most from alirocumab.

3.5 The clinical expert and a professional organisation stated that alirocumab would be used in secondary care or specialist clinics (such as lipid clinics). The clinical expert stated that the care of patients could be transferred to primary care, but that most would remain secondary care. The clinical expert and a patient and professional group stated that training for patients to use injections would be needed. The clinical expert stated that injections might be more difficult to use than current tablet therapies.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company carried out a systematic literature review that identified 32 studies of lipid modification therapies for treating hypercholesterolaemia in adults at high cardiovascular risk. The company also undertook another systematic literature review identifying 20 studies of lipid modification therapies for treating hypercholesterolaemia in adults at moderate or high cardiovascular risk. The company included the10 trials of alirocumab identified from the searches: ODYSSEY HIGH FH, FH I and II, LONG TERM, COMBO I and II, OPTIONS I and II, MONO, ALTERNATIVE.

Clinical trials

4.2 The company provided results for 10 ODYSSEY trials for the primary outcomes of percentage change in baseline LDL-c at 24 weeks, and various secondary outcomes. At baseline 5,296 patients were randomised across all the phase III studies the company included. Approximately 26% of study participants had heterozygous familial hypercholesterolaemia, 97% had high or very high cardiovascular risk, 64% had a history of CHD, 34% had a prior myocardial infarction, 8% had a prior ischaemic stroke, and 31% had type 2 diabetes.

See pages 99 to 104 of the company's submission for more information about the patient characteristics for each trial).

4.3 ODYSSEY HIGH FH was a randomised, double-blind study in 107 people with heterozygous familial hypercholesterolaemia who were not adequately controlled with a maximally tolerated, stable, daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab 150 mg or placebo. The difference in mean percent change from baseline in LDL-c level at 12 weeks was -40.3% ($p<0.0001$) and at 24 weeks was -39.1% ($p<0.0001$) with alirocumab compared with placebo. At week 24, 41% of patients with very high cardiovascular risk on alirocumab had LDL-c levels below 1.81 mmol/L or for patients with high cardiovascular risk below 2.59 mmol/L compared with 5.7% for placebo ($p=0.016$).

4.4 ODYSSEY FH I was a randomised, double-blind, study in 486 people with heterozygous familial hypercholesterolaemia who were not adequately controlled with a maximally tolerated, stable, daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) or placebo. The difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was -42.9% ($p<0.0001$) and at 24 weeks (with possible up-titration) was -57.9% ($p<0.0001$) with alirocumab compared with placebo. At week 24, 72.2% of patients with very high cardiovascular risk on alirocumab had LDL-c levels below 1.81 mmol/L or for patients with high cardiovascular risk below 2.59 mmol/L compared with 2.4% for placebo ($p<0.0001$).

4.5 ODYSSEY FH II was a randomised, double-blind study in 249 people with heterozygous familial hypercholesterolaemia who were not adequately controlled with a maximally tolerated, stable, daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) or placebo. The difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was -48.4% ($p<0.0001$) and at 24

weeks (with possible up-titration) was -51.4% (p<0.0001) with alirocumab compared with placebo. At week 24, 81.4% of patients had LDL-c levels below 1.81 mmol/L (for patients with very high cardiovascular risk) or below 2.59 mmol/L (for patients with high cardiovascular risk) with alirocumab compared with 11.3% for placebo (p<0.0001)

4.6 ODYSSEY COMBO I was a randomised, double-blind study in 316 people with hypercholesterolaemia and established coronary heart disease or coronary heart disease risk equivalents (see page 74 of the company's submission for definition) that were not adequately controlled with a maximally tolerated daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) or placebo. The difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was -47.4% (p<0.0001) and at 24 weeks was -45.9% (p<0.0001) with alirocumab compared with placebo. At week 24, 75% of patients had LDL-c levels below 1.81 mmol/L with alirocumab compared with 9% for placebo (p<0.0001).

4.7 ODYSSEY COMBO II was a randomised, double-blind, ezetimibe-controlled, double-dummy study in 720 people with hypercholesterolaemia and established coronary heart disease or coronary heart disease risk equivalents who were not adequately controlled with a maximally tolerated daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) or ezetimibe 10 mg. The difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was −29.4% (p<0.0001) and at 24 weeks was -29.8% (p<0.0001) with alirocumab compared with ezetimibe. At week 24, 77% of patients had LDL-c levels below 1.81 mmol/L with alirocumab compared with 46.6% for ezetimibe (p<0.0001).

4.8 ODYSSEY LONG TERM was a randomised, double-blind study in 2341 people with non-familial hypercholesterolaemia or and established

coronary heart disease/coronary heart disease risk equivalent or people with heterozygous familial hypercholesterolaemia with or without coronary heart disease/coronary heart disease risk equivalents who were not adequately controlled with a maximally tolerated daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab 150 mg or placebo. The difference in mean percent change from baseline in LDL-c level at 12 weeks was −64.8% (p<0.0001) and at 24 weeks was -61.9% (p<0.0001) with alirocumab compared with placebo. At week 24, 79.3% of patients had LDL-c levels below 1.81 mmol/L with alirocumab compared with 8% for placebo (p<0.0001).

4.9 ODYSSEY OPTIONS I was a randomised, double-blind study in 355 people with non-familial hypercholesterolaemia or heterozygous familial hypercholesterolaemia and a history of coronary heart disease, risk of cardiovascular disease or diabetes with target organ damage who were not adequately controlled with atorvastatin 20 to 40 mg. Patients on a atorvastatin 20 mg baseline regimen were randomised in a 1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) with atorvastatin 20 mg, atorvastatin 40 mg or atorvastatin 20 mg with ezetimibe 10 mg. Patients on a atorvastatin 40 mg baseline regimen were randomised in a 1:1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) with atorvastatin 40 mg, atorvastatin 80 mg, atorvastatin 40 mg with ezetimibe 10 mg or rosuvastatin 40 mg. For patients on atorvastatin 20 mg, the difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was -39.9% (p<0.0001) and at 24 weeks (with possible up-titration) was -39.1% (p<0.0001) with alirocumab with statin (atorvastatin 20 mg) compared with statin (atorvastatin 40 mg) alone. The difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was -25.8% (p<0.0001) and at 24 weeks (with possible up-titration) was -23.6% (p<0.0001) with alirocumab with statin (atorvastatin 20 mg) compared with ezetimibe with statin (atorvastatin 20 mg). For patients on atorvastatin

40 mg at baseline, the difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was -36% (p<0.0001) and at 24 weeks (with possible up-titration) was -39.2% (p<0.0001) with alirocumab with statin (atorvastatin 40 mg) compared with statin (atorvastatin 80 mg) alone. The difference in mean percent change from baseline in LDL-c leveldifference in mean percent change from baseline in LDL-c level level at 12 weeks (before up-titration) was -27.2% (p<0.0001) and at 24 weeks (with possible up-titration) was -32.6% (p<0.0001) with alirocumab with statin (atorvastatin 40 mg) compared with statin alone (rosuvastatin 40 mg). The difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was -20.8% (p<0.0001) and at 24 weeks (with possible up-titration) was -31.4% (p<0.0001) with alirocumab with statin (atorvastatin 40 mg) compared with ezetimibe with statin (atorvastatin 40 mg). At all time points a higher proportion of patients reached a pre-specified LDL-c target with alirocumab compared with statin or ezetimibe.

4.10 ODYSSEY OPTIONS II was a randomised, double-blind study in 305 people with non-familial hypercholesterolaemia or heterozygous familial hypercholesterolaemia and a history of coronary heart disease, risk of cardiovascular disease or diabetes with target organ damage who were not adequately controlled with rosuvastatin 10 to 20 mg. Patients on a rosuvastatin 10 mg baseline regimen were randomised in a 1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) with rosuvastatin 10 mg, rosuvastatin 20 mg or rosuvastatin 10 mg with ezetimibe 10 mg. Patients on a rosuvastatin 20 mg baseline regimen were randomised in a 1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) with rosuvastatin 20 mg, rosuvastatin 40 mg or rosuvastatin 20 mg with ezetimibe 10 mg. For patients on rosuvastatin 10 mg at baseline, the difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was -32.5% (p<0.0001) and at 24 weeks (with possible up-titration) was -34.2%

(p<0.0001) with alirocumab with statin (rosuvastatin 10 mg) compared with statin (rosuvastatin 20 mg) alone. The difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was 32.2% (p<0.0001) and at 24 weeks (with possible up-titration) was 36.2% (p<0.0001) with alirocumab with statin (rosuvastatin 10 mg) compared with ezetimibe with statin (rosuvastatin 10 mg). For patients on rosuvastatin 20 mg at baseline, the difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was -10.2% (p=0.1747) and at 24 weeks (with possible up-titration) was -20.3% (p=0.0453) with alirocumab with statin (rosuvastatin 20 mg) compared with statin (rosuvastatin 40 mg) alone. The difference in mean percent change from baseline in LDL-c level at 12 weeks (before up-titration) was −13% (p=0.0861) and at 24 weeks (with possible up-titration) was −25.3% (p=0.0136) with alirocumab with statin (rosuvastatin 20 mg) compared with ezetimibe with statin (rosuvastatin 20 mg). At all time points a higher proportion of patients reached a pre-specified LDL-c target with alirocumab compared with statin or ezetimibe.

4.11 ODYSSEY ALTERNATIVE was a randomised, double-blind, ezetimibe controlled, double-dummy study in 361 people with people with non-familial hypercholesterolaemia or heterozygous familial hypercholesterolaemia with a moderate, high or very high cardiovascular risk and a history of intolerance to statin. Patients were randomised in a 2:2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels), ezetimibe 10 mg or atorvastatin 20 mg. The difference in mean percent change from baseline in LDL-c level at 12 weeks was -31.5% (p<0.0001) and at 24 weeks was −30.4% (p<0.0001) with alirocumab compared with ezetimibe.

4.12 ODYSSEY MONO was a randomised, ezetimibe-controlled, double-blind study in 103 people with hypercholesterolaemia with a moderate cardiovascular risk. Patients were randomised in a 1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) or ezetimibe 10 mg. The difference in mean

percent change from baseline in LDL-c level at week 12 (before up-titration) was -28.5% ($p<0.0001$) and at week 24 (with possible up-titration) was -31.6% ($p<0.0001$) with alirocumab compared with ezetimibe.

Table 3 Difference in mean percent change in LDL-c from baseline at 24 weeks for each trial

Trial	Intervention/ Comparator	Population	Primary Outcome – difference in mean percent change in LDL-C from baseline at Week 24	
			vs placebo	vs ezetimibe
FH I N = 486	Alirocumab vs Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs	−57.9% (p<0.0001; 95% CI −63.3 to −52.6)	
FH II N = 249	Alirocumab vs Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs	−51.4% (p<0.0001; 95% CI −58.1 to −44.9)	
HIGH FH N = 107	Alirocumab vs Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs and with LDL-C ≥160 mg/dL (4.14 mmol/L)	−39.1% (p<0.0001; 95% CI −51.1 to −27.1)	
COMBO I N = 316	Alirocumab vs Placebo	Patients at high CV risk with hypercholesterolaemia not adequately controlled with statin ± other LMTs	−45.9% (p<0.0001; 95% CI −52.5 to −39.3)	
COMBO II N = 720	Alirocumab vs Ezetimibe	Patients at high CV risk with hypercholesterolaemia not adequately controlled with statin therapy		−29.8% (p<0.0001; 95% CI −34.4 to −25.3)
LONG TERM N = 2341	Alirocumab vs Placebo	Patients with HeFH or non-FH at high CV risk not adequately controlled with a statin ± other LMTs	−61.9% (p<0.0001; 95% CI −64.3 to −59.4)	
ALTERNATIVE N = 314	Alirocumab vs Ezetimibe, Atorvastatin	Patients with primary hypercholesterolaemia and		−30.4% (p<0.0001; 95% CI −30.6 to −24.2)

		moderate, high, or very high CV risk in whom statins cannot be tolerated		
MONO N =103	Alirocumab vs Ezetimibe	Patients at moderate CV risk with LDL-C ≥100 mg/dL (2.59 mmol/L) and ≤190 mg/dL (4.91 mmol/L)		−31.6% (p<0.0001; 95% CI −40.2 to −23.0)
			vs statin Up-titration	**vs ezetimibe**
OPTIONS I N = 355	Alirocumab + Atorvastatin vs Atorvastatin+Ezetimibe; Atorvastatin (up-titrated); Rosuvastatin (switch)	Patients at high CV risk with non-FH or HeFH not adequately controlled with atorvastatin (20 mg or 40 mg) ± other LMT excluding ezetimibe	1. Atorvastatin 20 mg: −39.1% (p<0.0001; 99% CI −55.9 to −22.2) 2. Atorvastatin 40 mg −49.2% (p<0.0001; 99% CI −65.0 to −33.5); Rosuvastatin switch: −32.6% (p<0.0001; 99% CI −48.4 to −16.9)	1. −23.6% (p<0.0001; 99% CI −40.7 to −6.5) 2. −31.4% (p<0.0001; 99% CI −47.4 to −15.4)
OPTIONS II N = 305	Rosuvastatin+Alirocumab vs Rosuvastatin+Ezetimibe; Rosuvastatin (up-titrated)	Patients at high CV risk with non-FH or HeFH not adequately controlled with rosuvastatin (10 mg or 20 mg) ± other LMT excluding ezetimibe	1. Rosuvastatin 10 mg: −34.2% (p<0.0001; 98.75% CI −49.2 to −19.3); 2. Rosuvastatin 20 mg: −20.3 % (p=0.0453; 98.75% CI −45.8 to 5.1)	1. −36.1% (p<0.0001; 98.75% CI: −51.5 to −20.7) 2. −25.3% (p=0.0136; 98.75% CI −50.9 to 0.3)
HeFH: heterozygous familial hypercholesterolaemia; LMT: Lipid modification therapy; CV: cardiovascular; CI: confidence interval				

Source: Response to A7 in company's clarification letter

ERG comments

4.13 The ERG stated that although it had identified missing search terms in the company's search strategy which may have affected the overall sensitivity of the search strategies, it generally considered the searches as fit for purpose. The ERG noted that several studies were subjectively selected as relevant and may have potentially introduced bias.

4.14 The ERG noted that the LDL-c reduction with alirocumab compared with control was rapid and persistent throughout follow-up. It stated that the data provides strong evidence that alirocumab is clinically effective.

Meta-analyses

4.15 The company undertook pairwise meta-analyses of individual patient data for the mean percent change from baseline in calculated LDL-c levels (on-treatment) using a fixed-effects model. The company compared alirocumab (with or without statin) with statin or ezetimibe (with or without statin) (Table 4 and Table 5). The meta-analyses showed:

- The difference in mean percent change from baseline in LDL-c level at 12 weeks was approximately −49.3% with alirocumab 75 mg with statin compared with placebo with statin.
- The difference in mean percent change from baseline in LDL-c level at 24 weeks ranged from −54.1% to −56.1% with alirocumab 75 mg (with possible up-titration to 150 mg) with statin compared with placebo with statin.
- The difference in mean percent change from baseline in LDL-c level at 24 weeks was −62.5% with alirocumab 150 mg with statin compared with placebo with statin.
- The difference in mean percent change from baseline in LDL-c level at 12 weeks was approximately −27.2% to −33.1% with alirocumab 75 mg with or without statin compared with ezetimibe with or without statin.
- The difference in mean percent change from baseline in LDL-c level at 24 weeks was approximately −29.9% to −35.1% with alirocumab 75 mg

(with possible up-titration to 150 mg) with or without statin compared with ezetimibe with or without statin.

The company did not present information on the heterogeneity between trials.

Further details of the company's meta-analyses (for example, why certain studies were pooled and synthesised) can be found on pages 154 to 157 of the company's submission and section A10 of the company's clarification response.

Table 4 Results of company's meta-analyses of placebo-controlled studies

Follow-up period (studies included in pooled analysis)	Mean % difference from baseline (95% CI)
12 weeks follow-up	
Alirocumab 75 mg with statin vs placebo with statin (FH I, FH II, COMBO I)	−49.3% (95% CI −52.5 to −46.1)
Alirocumab 75 mg with statin vs placebo with statin (FH I, FH II)	−49.3% (95% CI −53.1 to −45.5)
24 weeks follow-up	
Alirocumab 75 mg (with possible up-titration to 150 mg) with statin vs placebo with statin (FH I, FH II, COMBO I)	−54.1% (95% CI −57.6 to −50.6)
Alirocumab 150 mg with statin vs placebo with statin (LONG TERM + HIGH FH)	−62.5% (95% CI −64.8 to −60.2)
Alirocumab 75 mg (with possible up-titration to 150 mg) with statin vs placebo with statin (FH I, FH II)	−56.1% (95% CI −60.3 to −51.9)

Source: adapted from table 36, page 156 of company's submission and response to A10 in company's clarification letter

Table 5 Results of company's meta-analyses of ezetimibe-controlled studies

Follow-up period (studies included in pooled analysis)	Mean % difference from baseline (95% CI)
12 weeks follow-up	
Alirocumab 75 mg vs ezetimibe 10 mg (ALTERNATIVE)	−33.1% (95% CI −38.0 to −28.2)
Alirocumab 75 mg with statin vs ezetimibe 10 mg with statin (COMBO II, OPTIONS I, OPTIONS II)	−27.2% (95% CI −30.6 to −23.7)
24 weeks follow-up	
Alirocumab 75 mg (with possible up-titration to 150 mg) vs ezetimibe 10 mg (ALTERNATIVE)	−35.1% (95% CI −40.7 to −29.5)
Alirocumab 75 mg (with possible up-titration to 150 mg) with statin vs ezetimibe 10 mg with statin (COMBO II, OPTIONS I, OPTIONS II)	−29.9% (95% CI: −34.0 to −25.9)

Source: adapted from table 37, page 157 of company's submission

4.16 The company provided information from 3 independent meta-analyses of PCSK9 inhibitors (Li et al; Navarese et al and Zhang et al) showing significant reduction in LDL-c and other atherogenic lipid fractions and no significant difference in adverse events. The Navarese meta-analysis of 24 randomised controlled trials showed a difference in mean percent change from baseline in LDL-c level of −47.49% (95% CI −69.64 to −25.35) and reduced all-cause mortality and cardiovascular mortality with PCSK9 antibodies compared with control.

For further information on these meta-analyses and results, see pages 157 to 161 of the company's submission.

4.17 The company did not provide an indirect or mixed treatment comparison. It stated that direct head to head evidence from ODYSSEY was available for relevant comparisons in the scope. The company identified 7 studies of evolocumab (see table 30, page 162 of the company's submission) but stated that there were differences between ODYSSEY trials (for alirocumab) and PROFICIO trials (for evolocumab) in the primary endpoint, the patient cohort, and intervention dosing. The company also

stated that there were at least 6 ongoing clinical studies of alirocumab. For further details, see pages 162 to 169 of the company's submission.

ERG comments

4.18 The ERG noted that evolocumab was not included as a relevant comparator by the company because it was still under assessment by NICE. It noted that there were no head to head trials of alirocumab compared with evolocumab and a comparison would need to be made using a network meta-analysis. The ERG also noted that Navarese included trials on both alirocumab and evolocumab and in its opinion, the effectiveness of evolcocumab and alirocumab was likely to be similar.

Adverse effects of treatment

4.19 The company provided safety information based on 5234 patients from combined phase II and phase III studies. The company stated that the rate of treatment emergent adverse events (TEAEs), and serious TEAEs was similar between alirocumab and control arms (see tables 47 to 49, pages 171 and 172 of the company's submission). A local injection site reaction was the most common TEAE observed in patients treated with alirocumab. It also stated that discontinuation due to general allergic adverse events was infrequent but occurred in a higher percentage of the people treated with alirocumab. The effect of discontinuation was explored in scenario analyses (see section 5.40).

4.20 The rate of major adverse cardiovascular events (death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation, major adverse cardiac events) was HR 0.81 (95% CI 0.52 to 1.25) with alirocumab compared with control. A post-hoc analysis from LONG TERM showed lower major adverse cardiac events with alirocumab compared with placebo (HR 0.52; 95% CI 0.31 to 0.90; p=0.02).

4.21 The company stated that there was no observed difference in the safety profile observed between alirocumab 75 mg and 150 mg and in TEAEs in patients with very low LDL-c levels.

ERG comments

4.22 The ERG was concerned that the only long-term data was based on a post-hoc analysis from LONG TERM, but noted that an ongoing trial (due January 2018) would provide further long0term data on final cardiovascular outcomes in the future.

5 Cost-effectiveness evidence

5.1 The company did base-case cost-effectiveness analyses of alirocumab as either an adjunct to statin therapy in 4 populations:

- people with heterozygous familial hypercholesterolaemia (HeFH) for primary prevention
- people with heterozygous familial hypercholesterolaemia (HeFH) for secondary prevention
- people with existing high risk cardiovascular disease, coronary revascularisation or other arterial revascularisation procedures
- people with recurrent cardiovascular events or polyvascular disease.

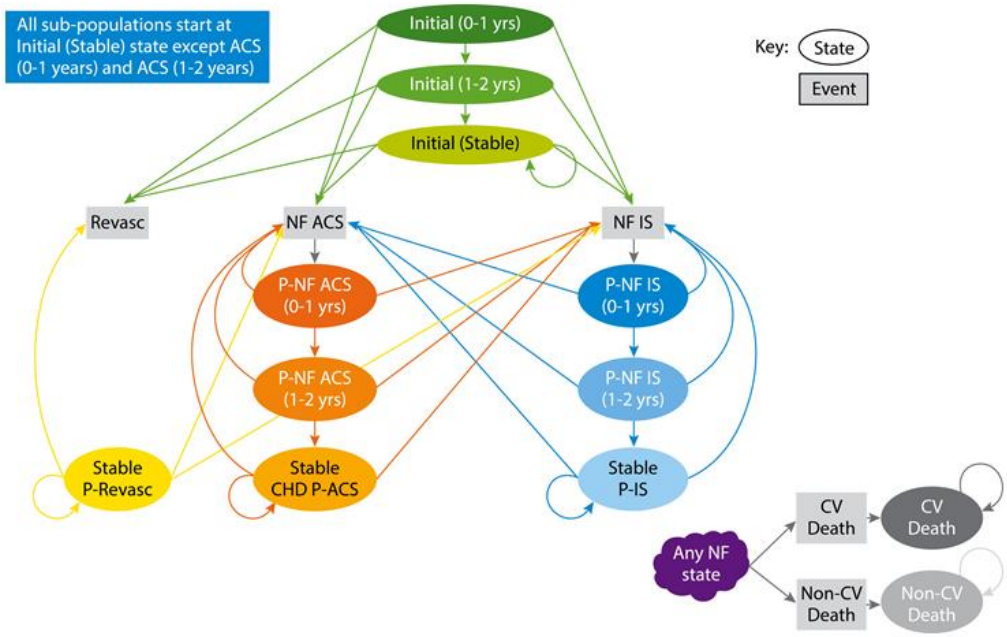
The company also carried out analyses in people with HeFH for whom statins cannot be tolerated, people with a high risk of cardiovascular disease and people with recurrent cardiovascular events or polyvascular disease.

The company compared alirocumab as an adjunct to ezetimibe for people in whom statins cannot be tolerated. It also assumed that for people for whom statin cannot be tolerated have higher baseline LDL-c levels compared with patients who can take statins.

Model structure

5.2 The company submitted a Markov model based on the modelling approaches developed for the NICE guideline's on lipid modification and familial hypercholesterolaemia, and technology appraisals on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia, ticagrelor for the treatment of acute coronary syndromes and rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (Figure 1). The cycle length was 1 year and a half cycle correction was applied. An annual discount rate of 3.5% was applied to costs and health effects. The model had a lifetime time horizon and was conducted from a NHS and personal social services perspective.

Figure 1 Company's model structure



ACS=acute coronary syndrome; IS=ischaemic stroke; NF=non-fatal; P=post-; Revasc=elective revascularisaton that did not occur as a result of an ACS event;. NF ACS is a composite of NF myocardial infarction or NF unstable angina. with hospitalisation. NF IS excludes transient ischaemic attack. CV deaths: death due to any CV event (inclusive of ischaemic and non-ischaemic CV events)

Source: figure 30, page 194 and table 55, page 196 of the company's submission

5.3 The model simulates a cohort of the population which might experience health events over a specified time horizon. The cohort's characteristics

are based on starting age, sex, prevalence of diabetes, LDL-c level and cardiovascular risk. Costs and outcomes are compared between identical cohorts of people on alirocumab and comparators.

5.4 The baseline characteristics (age, sex, percentage of patients with diabetes and minimum LDL-c level) for each population were informed by UK data from The Health Improvement Network (THIN), patient characteristics from ODYSSEY trials and the UK National Familial Hypercholesterolaemia audit. The baseline characteristics for each population are presented in Table 6:

- For heterozygous familial hypercholesteraemia, the starting age was 50 years for primary prevention, and 60 years for secondary prevention. The baseline LDL-c level was 2.59 mmol/L, 50% of the cohort was male and 7% of the cohort had diabetes.
- For high risk cardiovascular disease, the starting age was 65 years and 60% of the cohort was male. The baseline LDL-c level was 3.36 mmol/L and 23% of the cohort had diabetes.
- For recurrent events / polyvascular disease, the starting age was 65 years and 60% of the cohort was male. The baseline LDL-c level was 2.59 mmol/L and 30% of the cohort had diabetes.

  Other baseline LDL-c levels were applied in the company's scenarios (see section 5.39).

Table 6 Baseline characteristics in the company's model

Population	HeFH (primary prevention)	HeFH (secondary prevention)	High-risk CVD	Recurrent events/ polyvascular disease
Age (years) (justification)	50 (in line with ODYSSEY and with National FH audit)	60 (assumed older than primary prevention but younger than secondary prevention as a whole)	65 (THIN data shows an average age of ~70 years; ODYSSEY had an average age of 60 years)	65 THIN data shows an average age of ~70 years; ODYSSEY had an average age of 60 years)
% males (justification)	50% (in line with ODYSSEY and National FH audit – no gender difference)		60% (based on THIN data)	60% (based on THIN data)
% with diabetes (justification)	7% (observed in THIN data, in line with estimates of prevalence of diabetes in FH patients)[a]		23% (based on prevalence observed in THIN data)	30% (based on prevalence observed in THIN data)
Baseline LDL-c level (minimum)	2.59 mmol/L (represents patients above currently recommended targets despite current therapy)		3.36 mmol/L (represents patients far from currently recommended targets)	2.59 mmol/L (represents patients above currently recommended targets despite current therapy)
[a] Comments provided by the company in its executable model states that 0% of the population had diabetes in the base-case HeFH (secondary prevention) analysis using data from Morschladt 2003 – see section 5.16 for further information.				

Source: adapted from table 58, page 204 of the company's submission

5.5 The baseline probability of cardiovascular death in all post-acute coronary syndrome and post ischaemic stroke health states was multiplied by 1.5 to account for the higher risk of future events associated with recurrence of cardiovascular events.

ERG comments

5.6 The ERG considered the model structure to be generally appropriate. However, it noted that the company used a composite event state for acute coronary syndrome (ACS) includes myocardial infarction (MI) and unstable angina (UA). The ERG commented that the company's model structure made it difficult to simulate different treatment effects on MI and UA events. The ERG also noted that the company's model omitted the

transient ischemic attack and stable angina health states and that it had limited capacity to capture multiple cardiovascular event histories. The ERG stated the company's structural assumptions could underestimate quality adjust life years (QALY) gains and downstream cost savings associated with more effective treatments.

5.7 The ERG stated that the company omitted TEAEs from the model resulting in a potential bias in favour of alirocumab. However, it noted that this was unlikely to have significant impact on cost effectiveness.

Model details

Treatment

5.8 Alirocumab was given in line with its marketing authorisation in the model. Alirocumab was modelled as an adjunctive therapy to existing maximally tolerated current therapy in the company's base case. For those patients for whom statins cannot be tolerated, this can be either maximal tolerated dose of statins or maximal tolerated dose of statins plus ezetimibe. The company assumed that the relative reduction in LDL-c for alirocumab was constant across all subgroups.

5.9 For the HeFH population, alirocumab with statins and ezetimibe was compared with statins with ezetimibe in the company's base-case analysis. The company stated that ezetimibe was recommended by NICE and that people with familial hypercholesterolaemia would already receive ezetimibe in combination with maximally tolerated dose of statins. It further stated that approximately 50% of HeFH patients in ODYSSEY were receiving statins with ezetimibe as background therapy.

5.10 For the high cardiovascular risk population, alirocumab with statins was compared with statins in the company's base-case analysis. The company modelled alirocumab without ezetimibe because information from IMS sales data (see page 209 of the company's submission) showed usage, access and uptake of ezetimibe in the NHS was highly varied. For the high cardiovascular risk population who are. For the high cardiovascular

population for people for whom statins cannot be tolerated, the company compared alirocumab plus ezetimibe with ezetimibe.

Clinical variables and parameters

5.11 The patient population was modelled according to the severity of hypercholesterolaemia (their baseline LDL-c levels) before starting treatment. The average baseline LDL-c levels by LDL-c cut-off for each population are available in table 57, page 203 of the company's submission. The baseline cardiovascular risk (calculated using THIN data) was adjusted by LDL-c level using a log-linear relationship between the absolute LDL-c observed in statin studies and cardiovascular events using the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis.

5.12 LDL-c was used as a surrogate to link to cardiovascular events because the ODYSSEY Outcomes trial (CVOT) is ongoing and does not report until 2018. The company considered alternative data sources to estimate the class and treatment effects of PCSK9 inhibitors on cardiovascular outcomes. The company used the Navarese meta-analysis in its base-case because it preferred estimates from PCSK9 inhibitor studies rather than estimates from statin studies (such as CTTC)) and that it reflected the population who will receive alirocumab. The company did sensitivity analyses using the CTTC meta-analysis, outcome data from LONG-TERM, and pooled trials in sensitivity analyses (see section 5.40).

5.13 The company derived the risk reduction of cardiovascular events using Navarese, a meta-analysis of 24 RCT's (n=10,159). It estimated the risk reduction per 1.0 mmol/L reduction in LDL-c for cardiovascular mortality was Rate ratio (RR) 0.64 (95% CI 0.40 to 1.04) and for myocardial infarction as RR 0.64 (95% CI 0.43 to 0.96) by assuming a log-linear relationship between LDL-c level and cardiovascular event. The risk reduction for coronary revascularisation and ischaemic stroke was assumed to be the same as other non-fatal cardiovascular events (Table 7).

Table 7 Rate ratio (RR) of event per 1 mmol/L reduction in LDL-c based on Navarese meta-analysis

Event type	RR per 1 mmol/L reduction in LDL-c
Non-fatal myocardial infarction	0.64
Coronary revascularisation	No results presented – assumed to be the same as other non-fatal CV events
Ischaemic stroke	No results presented in IS – assumed to be the same as other non-fatal CV events
Vascular death	0.64

Source: table 61, page 211 of the company's submission

5.14 In its response to ERG questions at clarification (see question B19 in the response to clarification), the company provided corrected percentage reduction, standard errors and sources for LDL-c reduction with alirocumab compared placebo or statin from the pooled meta-analyses (Table 8). These were mainly based on the results from the meta-analyses (4.15) or ODYSSEY trials.

For further information about the company's approach to link LDL-c to cardiovascular events, see pages 209 to 212 of the company's submission.

Table 8 Percentage reduction in LDL-c used in company's base-case

			Percent (%) Reduction in LDL-C		
			As Monotherapy (SE)	**As Add-On To Statin (SE)**	**Source**
Comparison vs Placebo	**FH**	Alirocumab (75 mg)	49.3% (1.9)	49.3% (1.9)	Pooled FH I and FH II prior to uptitration (week 12) – values versus placebo
		Alirocumab (150 mg)	59.6% (2.3)	59.6% (2.3)	Pooled High FH and HeFH patients from LONG-TERM – values versus placebo at week 24
	High CV Risk	Alirocumab (75 mg)	49.3% (1.6)	49.3% (1.6)	FH I and FH II and COMBO I pooled prior to up titration (week 12) – values versus placebo
		Alirocumab (150 mg)	62.5% (1.2)	62.5% (1.2)	LONG-TERM – values versus placebo at week 24
Comparison vs Ezetimibe	**FH**	Alirocumab (75 mg)	51.2% (1.7)	51.0% (1.1)	Assumed same as high CV risk.
		Alirocumab (150 mg)	59.6% (2.3)	59.6% (2.3)	Assumed same as vs placebo
	High CV Risk	Alirocumab (75 mg)	51.2% (1.7)	51.0% (1.1)	Values are percent reduction from baseline prior to up-titration (at week 12). For monotherapy, value from ALTERNATIVE was used. For combination therapy, pooled from COMBO II, OPTIONS I and OPTIONS II

		Alirocumab (150 mg)	62.5% (1.2)	62.5% (1.2)	Assumed same as vs placebo
Ezetimibe (10 mg)		-	18.0% (1.8)	23.9% (1.4)	Represents percent reduction from baseline for ezetimibe. For monotherapy, value from ALTERNATIVE; for combination therapy, pooled from COMBO II, OPITIONS I and II

Source: adapted from the company's clarification response to question B19

Transition probabilities

5.15 Transition probabilities were based on Kaplan-Meier analyses from an observational retrospective cohort analysis using the THIN database of people with established cardiovascular disease, diabetes, familial hypercholesterolaemia (HeFH), or chronic kidney disease (CKD). This was used to calculate 1-year cardiovascular risk probabilities. Patients were classified into different cardiovascular risk categories according to their cardiovascular history, and were followed up for the occurrence of major adverse cardiovascular events including MI, unstable angina, coronary revascularisation, ischaemic stroke, and cardiovascular death.

For further information (such as the THIN data analysis), see page 212 to 216 of the company' submission.

5.16 Transition probabilities for the primary prevention of cardiovascular events were based on the Dutch lipid criteria for people with heterozygous familial hypercholesterolaemia because the patient characteristics from THIN were not representative of the FH population. For the secondary prevention of cardiovascular events in heterozygous familial hypocholesterolaemia population, some patient characteristics (such as rate of diabetes and age) remained different from known prevalence. Therefore, the company used data from Morschladt 2003 in its base-case analysis for the secondary prevention of cardiovascular events for people with heterozygous familial hypocholesterolaemia. See pages 213 to 215 of the company's submission for details on the company's rationale for using the Ditch lipid crtieria.

5.17 Non-cardiovascular death probabilities increase in accordance with age and sex using UK life tables. Probability of cardiovascular events increase with age according to published data.

Utility values

5.18 Age-adjusted utilities values for the primary prevention of HeFH model were calculated using Health Survey for England (HSE) data for people with no history of cardiovascular disease multiplied by the disutility associated with cardiovascular events based on Ara et al. The following utility values were used in the 1st year of the model: non-fatal myocardial infarction 0.765; unstable angina 0.765; acute coronary syndrome 0.765; ischaemic stroke 0.775 (Table 9).

Table 9 Cardiovascular event disutility multipliers used in the company's model for the primary prevention of HeFH population analysis

	Mean (SE)		
	First year	**Second year**	**Stable beyond 2 years**
Non-fatal myocardial infarction	0.765 (0.019)	0.906 (0.020)	0.906 (0.020)
Unstable angina	0.765 (0.019)	0.960 (0.015)	0.960 (0.015)
Acute coronary syndrome	0.765 (0.019)	0.924 (0.018)	0.924 (0.018)
Revascularisation	N/A	N/A	1.000
Ischaemic stroke	0.775 (0.038)	0.822 (0.018)	0.822 (0.018)

Source: Table 65, page 222 of the company's submission

5.19 Age-adjusted utility values for the secondary prevention of hypercholesterolemia populations, such as a high risk cardiovascular disease, recurrent events/polyvascular disease and secondary prevention of HeFH were estimated using Health Survey for England (HSE) data for people with no history of cardiovascular disease multiplied by disutility values associated with a chronic cardiovascular health state (cardiovascular event occurring more than 12 months ago) based on Ara et al. The following utilities were used a baseline values for the secondary prevention populations: HeFH (secondary prevention) 0.924, acute coronary syndrome (0 to 12 months) 0.765, history of ischaemic stroke 0.822; acute coronary syndrome (13 to 24 months) 0.924; chronic heart disease 0.924; peripheral arterial disease 0.924 and polyvascular 0.854.

5.20 Disutilities for further cardiovascular events in the model (Table 9) were applied to the secondary prevention population baseline utilities (Table

10). Different utility values were explored in the company's scenario analysis (see section 5.40)

Table 10 Utility multipliers for secondary prevention baseline

Baseline utility multipliers	Multiplier (SE)
HeFH (secondary prevention)	0.924 (0.018)
Acute coronary syndrome (0–12 months)	0.765 (0.019)
History of ischaemic stroke	0.822 (0.018)
Acute Coronary Syndrome (13–24 months)	0.924 (0.018)
Chronic heart disease	0.924 (0.018)
Peripheral arterial disease	0.924 (0.018)
HeFH (primary prevention)	N/ A (1.000)
Polyvascular	0.854 (0.024)

Source: table 66, page 223 of the company's submission

Costs

5.21 Costs of treatment for hypercholesterolaemia and cardiovascular events were based on the cost of hospitalisation, follow-up care and medication. Drug acquisition costs from January 2015 for the intervention and comparator costs were taken from the British National Formulary (BNF). The cost of the background therapy was weighted by the proportion of the cohort using the statin sources from market research data. The cost of alirocumab was based on patient access scheme, in the form of a simple discount.

Table 11 Drug acquisition costs in the company's model

Treatment	Dose	Annual cost (£)
Ezetimibe	10 mg	342.97
Atorvastatin (Lipitor)	10 mg	15.51
	20 mg	18.90
	40 mg	21.77
	80 mg	34.94
Rosuvastatin (Crestor)	5 mg	235.03
	10 mg	235.03
	20 mg	339.19
	40 mg	386.51

Source: table 68, page 228 of the company's submission

5.22 The cost of an acute coronary syndrome was based on a weighted average of one-year event probabilities derived from THIN analyses. The company stated that resource use (such as monitoring) will be identical between arms because alirocumab will be used as an add-on to a maximally tolerated current therapy.

5.23 Costs for the first 3 years after a cardiovascular event were included in the company's model (Table 12). In its response to clarification, the company stated that that it was not certain if modelling ongoing lifetime costs for all patients was appropriate. A company scenario applying lifetime costs for all health states showed a limited impact on the ICERs (see table 20, page 34 of company's response to clarification).

5.24 Health state costs are based on the NICE guideline's on lipid modification. The costs were based on the BNF, the NHS Drug Tariff, NHS reference costs, PSSRU unit costs, and the NICE guideline on stroke rehabilitation in adults. The costs for each health state were: non-fatal myocardial infarction £3337 (incremental 2nd year cost £788, 3rd year cost £788); unstable angina £3313 (incremental 2nd year cost £385, 3rd year cost £385); acute coronary syndrome £3329.00 (incremental 2nd year cost £653.67, 3rd year cost £653.67); revascularisation £3802.32; ischaemic stroke £4092 (incremental 2nd year cost £155, 3rd year cost £155); cardiovascular death £1174; non-cardiovascular death £0.

Table 12 Health state costs in the company's model

Health state	Event cost (£)	Incremental second year costs (£)	Incremental third year costs (£)
Non-fatal myocardial infarction	3337	788	788
Unstable angina	3313	385	385
Acute coronary syndrome	3329	653.67	653.67
Revascularisation	3802.32	-	-
Ischaemic stroke	4092	155.00	155
Cardiovascular death	1174	-	-
Non-cardiovascular death	0.00	-	-

Source: Table 69, page 228 of company's submission

5.25 Costs of adverse events were not modelled because they were similar between alirocumab and the control groups, including placebo.

ERG comments

5.26 The ERG believed that in terms of face validity, the company's model structure and transition probabilities were plausible. It stated that it did not identify any programming errors in the model. The ERG noted that the secondary prevention HeFH population (using Morschladt et al) had a smaller cardiovascular risk compared with data from THIN. The ERG was unable to verify the most appropriate risk without another external data source.

5.27 Although the ERG accepted the company's decision to focus on a threshold of an LDL-c level of 3.36 mmol/L for people with high risk cardiovascular disease, it noted that Jameson et al reported a mean LDL-c of 2.13 mmol/L treated with atorvastatin in UK people with cardiovascular disease in primary care. It also noted that a large proportion of people in THIN were being treated with low intensity statins and may not have been on optimal statin treatment. The ERG stated that the mean baseline LDL-c levels used by the company may not have been applicable to people treated with maximally tolerated statins. Overall, the

ERG considered the company's mean LDL-c levels as uncertain, but was unclear at the direction of the bias.

5.28 For baseline characteristics, the ERG noted that the average age of the cohort in the THIN data was around 70 years old compared with 60 years old in the ODYSSEY. It commented that the company considered that alirocumab might be started in people younger than average. The ERG considered this assumption as reasonable. It also believed that the company's use of THIN for cardiovascular event and transition probabilities was appropriate because using QRISK2 risk estimates were not valid for the high cardiovascular risk population.

5.29 The ERG had several comments about the company's assumptions used to scale the estimated effect of alirocumab to cardiovascular events:

- The ERG was satisfied with company's approach to estimate the LDL-c reduction with alirocumab compared with placebo. It noted that the LDL-c reduction achieved by alirocumab does not different significantly by background lipid therapy.
- The ERG noted that the company assumed there is a linear/log-linear relationship is between LDL-c and cardiovascular events as demonstrated by CTTC. The ERG noted that the estimated relative reduction in cardiovascular events from Navarese were greater than estimates from CTTC. The ERG also noted that the estimates from Navarese were based on a small number of events reported in shorter trials. In contrast the CTTC analysis was based on 26 trials. The ERG explored this issue in its exploratory analyses (see section 5.45).
- The ERG noted that the company used all the trials used to estimate the mean reduction with LDL-c from the Navarese, instead of only the trials used to estimate the hazard ratios for cardiovascular events. In its response to clarification, the company provided estimates of LDL-c reduction using trials only informing the hazard ratios for myocardial infarction and cardiovascular death(LDL-c reduction of 1 mmol/L resulted in a hazard ratio of 0.58 for cardiovascular death and 0.68 for

myocardial infarction). The ERG considered these values as more relevant. The ERG explored this issue in an exploratory analysis (see section 5.45).

- The ERG noted that the company's estimated hazard ratio for myocardial infarction events was used for ischaemic stroke and coronary revascularisation events. The ERG stated that this was a controversial assumption because other studies (such as CTTC) show that effect of LDL-c lowering on ischemic stroke may not be as big as it is for acute coronary syndrome events. It noted that alternative hazard ratios were explored in the company's scenario analyses (see section 5.40).

5.30 The ERG stated that the company assumed 100% treatment continuation and compliance over the time horizon. It noted that the high compliance was in line with ODYSSEY (approximately 98%) and that the assumption was consistentwith the NICE guideline on lipid modification and the technology appraisal on ezetimibe.

5.31 The ERG stated that the company's health statue utility values were estimated and implemented appropriately. However it had had several comments on the company's costs used in the model, the ERG explored some of these issues in exploratory analyses (see section 5.45):

- It noted that the company's model only captured costs for the first 6 months following a cardiovascular event in the first year and therefore did not capture follow-up for the second half of the first year.
- It noted that follow-up costs for cardiovascular events incurred up to 3 years after the event. The ERG considered this assumption as conservative and possibly unrealistic because patients following cardiovascular events (such as stroke) may require ongoing social care and medical attention. The ERG acknowledged that it was difficult to calculate and incorporate these costs into the model, however it believed that costs associated with post-stroke states may be underestimated.

- The ERG was unclear how the cost of revascularisation was estimated.
- The ERG noted that the company's submission mentioned that alirocumab will be continued in secondary care via a sponsored homecare service. The ERG noted that the company provided very little detail about the homecare service, but stated that administration costs associated with this were unlikely to place a significant burden on the NHS.

Company's base-case results and sensitivity analysis (with PAS)

5.32 The company provided incremental cost effectiveness ratios (ICERs) for all comparisons, populations and sensitivity analysis with and without the Patient Access Scheme (PAS) for alirocumab. The ICERs provided in this document include the PAS.

5.33 The company's base-case results for HeFH are presented in Table 13. The company's base-case incremental cost-effectiveness ratios (ICERs) for the HeFH primary prevention were £36,793 per quality-adjusted life year (QALY) gained (incremental costs £52,256; incremental QALYs 1.42) for alirocumab with a statin and ezetimibe compared with statin and ezetimibe alone and £16,896 per quality-adjusted life year (QALY) gained (incremental costs £39,306; incremental QALYs 2.33) for alirocumab with a statin compared with ezetimibe with a statin.

5.34 For the HeFH secondary prevention population the ICERs were £16,896 per QALY gained (incremental costs £39,306; incremental QALYs 2.33) for alirocumab with a statin and ezetimibe compared with statin and ezetimibe and £20,352 per QALY gained (incremental costs £34,632; incremental QALYs 1.70) for alirocumab with a statin compared with ezetimibe with a statin. The company also provided results for the HeFH secondary prevention population using baseline risk data from THIN instead of Morschladt. See table 2a of the company's PAS submission for further information.

Table 13 Company's base-case results for HeFH

	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	ICER
HeFH – primary prevention (baseline LDL-c ≥2.59 mmol/L)						
Alirocumab + statins + ezetimibe	[redacted]	[redacted]	[redacted]	52,256	1.42	36,793
Statins + ezetimibe	[redacted]	[redacted]	[redacted]	-	-	-
HeFH –secondary prevention (baseline LDL-c ≥2.59 mmol/L)						
Alirocumab + statins + ezetimibe	[redacted]	[redacted]	[redacted]	39,306	2.33	16,896
Statins + ezetimibe	[redacted]	[redacted]	[redacted]	-	-	-
HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L) comparison with ezetimibe						
Alirocumab + statins	[redacted]	[redacted]	[redacted]	45,962	0.95	48,193
Ezetimibe + statins	[redacted]	[redacted]	[redacted]	-	-	-
HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L) comparison with ezetimibe						
Alirocumab + statins	[redacted]	[redacted]	[redacted]	34,632	1.70	20,352
Ezetimibe + statins	[redacted]	[redacted]	[redacted]	-	-	-

Source: table 2a of the company's PAS submission

5.35 The company's base-case results for high risk cardiovascular disease are presented in Table 14. The company's base-case ICERS for the high risk cardiovascular disease population were £19,751 per QALY gained (incremental costs £34,684; incremental QALYs 1.76) for alirocumab with a statin compared with statin alone and £24,175 per QALY gained (incremental costs £31,195; incremental QALYs 1.29) for alirocumab with a statin compared with ezetimibe with a statin. For the high risk cardiovascular disease population for whom statins cannot be tolerated, the ICERs were £17,256 per QALY gained (incremental costs £35,146; incremental QALYs 2.04) for alirocumab with ezetimibe compared with ezetimibe alone and £17,295 per QALY gained (incremental costs £30,829; incremental QALYs 1.78) for alirocumab alone compared with ezetimibe alone.

Table 14 Company's base-case results for high risk cardiovascular disease

	Total costs	Total QALYs	Total LYG	Incremental costs	Incremental QALYs	ICER
High-risk CVD (baseline LDL-c ≥3.36 mmol/L)						
Alirocumab + statins	[redacted]	[redacted]	[redacted]	34,684	1.76	19,751
Statins	[redacted]	[redacted]	[redacted]	-	-	-
High-risk CVD (baseline LDL-c ≥3.36 mmol/L) – statin intolerant						
Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	35,146	2.04	17,256
ezetimibe	[redacted]	[redacted]	[redacted]	-	-	-
Additional comparison: High-risk CVD (baseline LDL-c ≥3.36 mmol/L) – comparison with ezetimibe						
Alirocumab + statins	[redacted]	[redacted]	[redacted]	31,195	1.29	24,175
Ezetimibe + statins	[redacted]	[redacted]	[redacted]	-	-	-
Additional comparison: High-risk CVD (baseline LDL-c ≥3.36 mmol/L) – statin intolerant comparison with ezetimibe						
Alirocumab	[redacted]	[redacted]	[redacted]	30,829	1.78	17,295
Ezetimibe	[redacted]	[redacted]	[redacted]	-	-	-

Source: table 2a of the company's PAS submission

5.36 The company's base-case results for recurrent events/polyvascular disease are presented in Table 15. The company's base-case ICERs for the recurrent events/polyvascular disease population were £19,447 per QALY gained (incremental costs £31,953; incremental QALYs 1.64) for alirocumab with a statin compared with statin alone and £23,078 per QALY gained (incremental costs £28,781; incremental QALYs 1.25) for alirocumab with a statin compared with ezetimibe with a statin. For the recurrent events/polyvascular disease population for whom statins cannot be tolerated, the ICERs were £13,669 per QALY gained (incremental costs £32,798; incremental QALYs 2.40) for alirocumab with ezetimibe compared with ezetimibe alone and £13,469 per QALY gained (incremental costs £28,820; incremental QALYs 2.14) for alirocumab alone compared with ezetimibe alone.

Table 15 Company's base-case results for recurrent events/polyvascular disease

	Total costs	Total QALYs	Total LYG	Incremental costs	Incremental QALYs	ICER
Recurrent events/ Polyvascular Disease (baseline LDL-c ≥2.59 mmol/L)						
Alirocumab + statins	[redacted]	[redacted]	[redacted]	31,953	1.64	19,447
Statins	[redacted]	[redacted]	[redacted]	-	-	-
Recurrent events/ Polyvascular Disease (baseline LDL-c ≥2.59 mmol/L) – statin intolerant						
Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	32,798	2.40	13,669
Ezetimibe	[redacted]	[redacted]	[redacted]	-	-	-
Recurrent events/Polyvascular Disease (baseline LDL-c ≥2.59 mmol/L) – comparison with ezetimibe						
Alirocumab + statins	[redacted]	[redacted]	[redacted]	28,781	1.25	23,078
Ezetimibe + statins	[redacted]	[redacted]	[redacted]	-	-	-
Recurrent events/Polyvascular Disease (baseline LDL-c ≥2.59 mmol/L) – statin intolerant comparison with ezetimibe						
Alirocumab	[redacted]	[redacted]	[redacted]	28,820	2.14	13,469
Ezetimibe	[redacted]	[redacted]	[redacted]	-	-	-

Source: table 2a of the company's PAS submission

Sensitivity analyses

5.37 The company explored parameter uncertainty using probabilistic sensitivity analyses (see pages 239 to 245 of the company's submission). The company stated that the uncertainty in the results reflects the wide confidence intervals from preliminary PCSK9 inhibitor outcomes data.

- For the HeFH primary prevention population, the probability of cost-effectiveness was between 15% to 36% for a willingness to pay between £20,000 to £30,000 per QALY gained for alirocumab with statin and ezetimibe compared with statin with ezetimibe.
- For the HeFH secondary prevention population, the probability of cost-effectiveness was between 56% to 79% for a willingness to pay between £20,000 to £30,000 per QALY gained for alirocumab with statin and ezetimibe compared with statin and ezetimibe.

- For the high risk cardiovascular disease population, the probability of cost-effectiveness was between 46% to 78% for a willingness to pay between £20,000 to £30,000 per QALY gained for alirocumab with statin compared with statin alone.
- For the recurrent events / polyavascular disease population, the probability of cost-effectiveness was between 49% to 80% for a willingness to pay between £20,000 to £30,000 per QALY gained for alirocumab with statin compared with statin alone.

Cost-effectiveness acceptability curves and scatter plots are available in the company's PAS submission (Figures 1 to 4).

Table 16 Company's probability of cost-effectiveness

	HeFH primary prevention (baseline LDL-c ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	**HeFH secondary prevention (baseline LDL-c ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe**	**High-risk CVD (baseline LDL-c ≥3.36 mmol/L) – alirocumab + statins versus statins**	**Recurrent events/ polyvascular disease (baseline LDL-c ≥2.59 mmol/L) – alirocumab + statins versus statins**
Maximum acceptable ICER	Probability of cost-effectiveness			
20,000/QALY	15%	56%	46%	49%
30,000/QALY	36%	79%	78%	80%
40,000/QALY	51%	88%	86%	87%

Source: adapted from page 30 of the company's PAS submission

5.38 The company also explored parameter uncertainty using deterministic sensitivity analysis according to upper and lower bound of the confidence interval or by an arbitrary ± 20% for selected inputs in the company's model. The ICERs for all populations were most sensitive to changes in the relationship of LDL-c level to cardiovascular events and annual cardiovascular risk.

For further information on the deterministic sensitivity analyses (such as ICERs) see pages 22 to 25 of the PAS submission.

Company scenarios

5.39 The company conducted subgroup analyses by LDL-c levels, the ICER for each population decreased as the baseline LDL-c level increased from 2.59 mmol/L to 4.13 mmol/L for each population (Table 17).

Table 17 Company scenario by LDL-c level (cost per QALY)

Patient population	Baseline LDL-C (mmol/L)	Incremental costs (£)	Incremental QALY	ICER
HeFH primary prevention	2.59 (base-case)	52,256	1.42	36,793
	3.36	52,005	1.64	31,750
	4.13	51,804	1.79	28,923
HeFH secondary prevention	2.59 (base-case)	39,306	2.33	16,896
	3.36	39,224	2.48	15,838
	4.13	39,023	2.74	14,242
High Risk CVD	2.59	34,701	1.37	25,287
	3.36 (base-case)	34,684	1.76	19,751
	4.13	34,493	2.15	16,043
Recurrent events / Polyvascular disease	2.59 (base-case)	31,953	1.64	19,447
	3.36	32,085	2.09	15,332
	4.13	32,013	2.54	12,606

Source: adapted from table 2e. page 20 of the company's PAS submission

5.40 The company also undertook a range of scenario analyses:

- Increasing the discontinuation rate from 0% to 3% and 8% had a modest increase on ICERs in all populations
- Changing the cost and benefit discount rates from 3.5% to 0 or 5% substantially changes the ICERs in all populations
- Reducing the treatment duration from lifetime to 1 to 5 years substantially increased the ICERs in all populations
- Using a different source to link LDL-c reduction to cardiovascular relative risk instead of Navarese such as CTTC, LONG-TERM or pooled phase III trials all substantially increased the ICERs in all populations

- Using a different adjustment to baseline cardiovascular risk by using cardiovascular risks to a CTTC cox-model had a modest impact on ICERs in all populations
- Using alternative utility values from ODYSSEY instead of Ara 2010 significantly reduced ICERs in all populations.

For further information on all the company's scenarios, see tables 7 to 10 of the company's PAS submission.

Company's scenario analyses around the patient access scheme

5.41 The Department of Health's Patient Access Scheme (PAS) approval letter noted that "there may be a potential transition of patients from secondary to primary care after 2 to 3 years. This has potential implications for the proposed [redacted] patient access scheme. As [redacted] cannot be realised when drugs are prescribed through FP10 prescriptions, the actual [redacted] received by the NHS may be less than the [redacted] in the scheme." After receiving this letter, NICE invited the company to submit additional analyses on the time and proportion of people that would spend in secondary care before transitioning to primary care.

5.42 In response to NICE's request, the company stated that it believed that the vast majority of hypercholesterolaemia cases will be prescribed and manged in specialist settings in a hospital outpatient department. It also committed to providing the PAS [redacted] irrespective of care setting across England and Wales. It stated that:

- the most appropriate use of alirocumab was for people with familial hypercholesterolaemia and high risk cardiovascular disease who cannot achieve optimal LDL-c levels on current maximally tolerated routine lipid management therapies. The company stated that these groups require specialist support beyond the routine lipid management provided by primary care teams
- high risk patients in primary care should be referred to an expert lipid specialist as recommended in the NICE guideline on familial

hypercholesterolaemia. The company stated that this was expressed by clinical expert submissions in the technology appraisal of evolocumab. The company also provided a statement from a clinical expert stating that fewer than 10% of people on alirocumab would be followed-up in primary care after several years of specialist management (see Appendix 3 of the company's additional sensitivity analysis for FP10)

- alirocumab is listed on the proposed high cost drugs exclusion list for 2016/17 and expected to be funded outside the national tariff. Hospitals can recover alirocumab via the high cost drugs reimbursement system
- commissioners are seeking to limit the use of alirocumab in primary care
- the majority of general practitioners surveyed in July 2015 stated they were extremely unlikely to prescribe a self-injected sub-cutaneous treatment for hypercholesterolaemia
- The company has arrangements for the supply of alirocumab in the NHS via two routes, directly to hospital pharmacies and approved homecare companies.

5.43 The company explored the impact of the different proportions of patients transitioning from secondary to primary care over a period of 5 years (Table 18). In summary, the ICERs increased as the proportion of patients transitioning from secondary to primary care increases for alirocumab plus current maximal therapy compared with current maximal therapy.

For further information on each analysis (such as incremental costs and incremental QALYS) see Appendix 2 of the response to the request for additional sensitivity analyses (FP10).

Table 18 Company's deterministic ICERs for scenarios around the patient access scheme (cost per QALY)

Technology (and comparators)	Base case	Scenario 1[a] [redacted] by year 5 (start year 2)	Scenario 2[a] [redacted] by year 5 (start year 2)	Scenario 3[a] [redacted] by year 5 (start year 2)	Scenario 4[a] [redacted] by year 5 (start year 2)	Scenario 5[a] [redacted] by year 5 (start year 2)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)						
Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current maximal therapy (statins + ezetimibe)						
HeFH secondary prevention (LDL-C ≥2.59 mmol/L)						
Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current maximal therapy (statins + ezetimibe)						
High risk CVD (LDL-C ≥3.36 mmol/L)						
Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current maximal therapy (statins)						
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)						
Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current maximal therapy (statins)						
a proportion of patients transitioning from secondary to primary care increases linearly from year 2 reaching a peak at year 5						

Source: adapted from table 3 of the company's response to the request for additional sensitivity analyses (FP10)

5.44 The company explored parameter uncertainty using probabilistic sensitivity analyses. It stated that the ICERs were similar to the deterministic ICERs.

For more information, such as the probability of cost-effectiveness at

different maximum acceptable ICER, see table 4 in the company's response to the request for additional sensitivity analyses (FP10).

ERG exploratory analyses

5.45 The ERG did several additional exploratory analyses for all comparators and populations based on 7 changes made to the company's model. It presented ICERs for both Navarese and CTTC meta-analyses separately to show the uncertainty in the relationship between LDL-c reduction and cardiovascular events. In summary the ERG's exploratory analyses:

- applied annual post cardiovascular event costs (such as care for stroke) over the entire modelled time horizon (lifetime) instead of 3 years as in the company's base-case
- applied follow-up costs to the second half of first year of costs following a cardiovascular event
- applied an updated cost of £8,618 for stroke (inflated from a UK population study), and an annual care cost for stroke of £1,769 (inflated from Youman et al)
- used only trials informing the hazard ratios in Navarese instead of all trials. It applied a rate ratio of 0.67 per 1 mmol/L reduction for myocardial infarction and 0.58 per 1 mmol/L reduction in CV death
- applied a rate ratio of 0.79 per 1 mmol/L reduction in LDL-c for ischaemic stroke based on results from CTTC, instead of assuming the same rate ratio of 0.64 per 1 mmol/L reduction in LDL-c as in the company's model
- applied an annual discontinuation rate of 8% instead of 0% so that it is consistent with discontinuation observed in ODYSSEY and LONG-TERM
- Applying cardiovascular rates based on CTTC analysis for ezetimibe comparison.

Detailed information on these changes and rationale are outlined on page 159 and 160 of the ERG's report.

5.46 The ERG's exploratory analyses showed modest changes to ICERs for all comparisons in all populations using the Navarese to estimate the relationship between LDL-c and cardiovascular events compared with the company's base-case results. The ERG's exploratory analyses showed substantially increased ICERs for all comparisons in all populations using the CTTC to estimate the relationship between LDL-c and cardiovascular events compared with the company's base-case results. (Table 19)

Table 19 ERG exploratory analyses: deterministic base-case and additional comparison ICERs (cost per QALY)

Scenario	Company's base case with rate ratios from Navarese	Company's scenario analysis with ratios from CTTC	ERG base case with rate ratios from Navarese	ERG base case with rate ratios from CTTC
HeFH primary prevention				
Alirocumab + statins + ezetimibe vs statins + ezetimibe	36,793	60,736	41,243	67,215
Statin intolerant Alirocumab +ezetimibe vs ezetimibe	-	-	-	67,077
Comparison with ezetimibe Alirocumab + statins vs ezetimibe + statins	48,193	-	52,363	119,161
HeFH secondary prevention				
Alirocumab + statins + ezetimibe vs statins + ezetimibe	16,896	32,937	16,933	33,339
Statin intolerant Alirocumab +ezetimibe vs ezetimibe	-	-	-	33,185
Comparison with ezetimibe Alirocumab + statins vs ezetimibe + statins	20,352	-	19,437	56,968
High risk CVD				
Alirocumab + statins vs statins	19,751	41,431	19,432	42,131
Statin intolerant Alirocumab +ezetimibe vs ezetimibe	17,256	-	17,130	34,600
Comparison with ezetimibe Alirocumab + statins vs ezetimibe + statins	24,175	-	21,932	70,081
Statin intolerant comparison with ezetimibe Alirocumab vs ezetimibe	17,295	-	16,487	41,412
Recurrent events / polyvascular disease				
Alirocumab + statins vs statins	19,447	44,154	19,021	44,759
Statin intolerant Alirocumab + ezetimibe vs ezetimibe	13,669	-	15,791	33,519
Comparison with ezetimibe Alirocumab + statins vs ezetimibe + statins	23,078	-	20,891	73,941
Statin intolerant comparison with ezetimibe alirocumab vs ezetimibe	13,469	-	13,342	32,742

Source: adapted from tables 50 to 61 of the ERG's report and tables 1 to 2a of the company's PAS submission.

5.47 The ERG did subgroup analyses by LDL-c levels showing that ICERs for each population decreased as the baseline LDL-c level increased from 2.59 mmol/L to 4.13 mmol/L for each population. The ERG's subgroup analysis using Navarese showed modest changes in the ICERs compared with the company's base-case analysis. The ERG's subgroup analysis using CTTC showed significant increase in the ICERs compared with the company's base-case analysis (Table 20).

Table 20 ERG exploratory analyses: deterministic base-case ICERs per LDL-c level (cost per QALY)

Patient population	Baseline LDL-c (mmol/L)	Company's base-case ICER	ERG's base-case with rate ratios from Navarese	ERG's base-case with rate ratios from CTTC
HeFH primary prevention	2.59	36,793	41,243	67,215
	3.36	31,750	35,481	55,839
	4.13	28,923	32,256	49,678
HeFH secondary prevention	2.59	16,896	16,933	33,339
	3.36	15,838	15,938	30,603
	4.13	14,242	14,433	26,557
High Risk CVD	2.59	25,287	24,538	58,239
	3.36	19,751	19,432	42,131
	4.13	16,043	15,975	31,795
Recurrent events / Polyvascular disease	2.59	19,447	19,021	44,759
	3.36	15,332	15,286	32,622
	4.13	12,606	12,794	24,863

Source: adapted from tables 62 to 64 of the ERG's report

5.48 The ERG explored parameter uncertainty in its exploratory analyses using probabilistic sensitivity analyses (Table 21 and Table 22).
See pages 152 to 161 of the ERG's report for probabilistic incremental costs and incremental QALYs, probability of cost-effectiveness, cost-effectiveness plans and acceptability curves.

Table 21 ERG's exploratory analyses: probability of cost effectiveness (rate ratios from Navarese)

	HeFH primary prevention (baseline LDL-c ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	HeFH secondary prevention (baseline LDL-c ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	High-risk CVD (baseline LDL-c ≥3.36 mmol/L) – alirocumab + statins versus statins	Recurrent events/ polyvascular disease (baseline LDL-c ≥2.59 mmol/L) – alirocumab + statins versus statins
Maximum acceptable ICER	Probability of cost-effectiveness			
20,000/QALY	3.8%	57%	45%	46%
30,000/QALY	28.2%	84%	83%	80%
40,000/QALY	43.8%	90%	91%	90%

Source: adapted from table 56 in the ERG's report

Table 22 ERG's exploratory analyses: probability of cost effectiveness (rate ratios from CTTC)

	HeFH primary prevention (baseline LDL-c ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	HeFH secondary prevention (baseline LDL-c ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	High-risk CVD (baseline LDL-c ≥3.36 mmol/L) – alirocumab + statins versus statins	Recurrent events/ polyvascular disease (baseline LDL-c ≥2.59 mmol/L) – alirocumab + statins versus statins
Maximum acceptable ICER	Probability of cost-effectiveness			
20,000/QALY	0%	18%	0%	0%
30,000/QALY	10%	39%	7%	6%
40,000/QALY	24%	58%	43%	36%

Source: adapted from table 57 in the ERG's report

5.49 The ERG also explored parameter uncertainty in its exploratory analyses using deterministic sensitivity analysis according to upper and lower bound of the confidence interval or by an arbitrary ± 20% for selected inputs in the company's model. The ICERs for all populations were most

sensitive to changes in the baseline LDL-c, the relationship of LDL-c level to cardiovascular events and annual cardiovascular risk. The changes to the ICERs followed as similar pattern to the company's deterministic sensitivity analysis (see section 5.38)

For further information on the ERG's deterministic sensitivity analyses (such as ICERs) see pages 170 to 174 of the ERG's report.

Innovation

5.50 Justifications for considering alirocumab to be innovative:

- A clinical expert stated alirocumab is one of the first of a new class of lipid-lowering agents working by inhibition of PCSK-9 and that it is the first new class of lipid-lowering drugs licensed for 10 years
- The company stated that alirocumab was an innovation because it acts on a target that is not targeted by existing lipid modifying therapies (such as statins and cholesterol absorption inhibitors). It also stated that alirocumab would be a step forward in the management of patients who are not able to achieve therapeutic goals when treated with existing lipid modification therapies at maximal tolerated dose.
- The company stated that alirocumab may be an alternative for patients who are on LDL-apheresis and an option for people on an LDL-apheresis waiting list; or who have declined apheresis. A patient/carer organisation stated alirocumab is preferred over invasive and debilitating procedures such as apheresis.
- A patient/carer organisation stated that alirocumab is an innovation because it has the ability to further reduce cholesterol by 60% in addition to current standard of care.

5.51 Justification for not considering alirocumab to be innovative:

- A clinical expert stated that alirocumab is an injection and therefore more difficult to use than current tablet therapies.

6 Equality issues

6.1 The equalities issues raised during the scoping process relate to the inequality of access to LDL-apheresis due to high set up costs and appropriate expertise and that injection only treatment which might exclude people who will not accept injection based therapies, including many from ethnic minority groups. These issues could not be addressed through a Technology Appraisal and therefore do not need to be addressed by Committee.

6.2 No equality issues were raised in the submissions**.**

7 Authors

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Technical Lead

Joanne Holden
Technical Adviser

with input from the Lead Team (Stephen O'Brien, Paul Tappenden and Judith Wardle).

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

The European public assessment report (EPAR) is available here.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of alirocumab 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 disease 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.

The technology

Alirocumab (brand name unknown, although Sanofi and Regeneron are jointly developing alirocumab, Sanofi UK is the EMA marketing authorisation applicant) is a fully-human monoclonal antibody that targets proprotein convertase subtilisin/kextin type 9 (PCSK9). It prevents degradation of LDL receptors in the liver, thereby facilitating LDL clearance from circulation and lowering LDL-C levels in the blood. It is self-administered subcutaneously.

Alirocumab does not currently have a marketing authorisation in the UK for primary hypercholesterolaemia and mixed dyslipidaemia. It has been studied in clinical trials in adults with primary heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia or mixed dyslipidaemia compared with placebo, statins with or without ezetimibe, and ezetimibe alone.

Intervention(s)	Alirocumab 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	• Optimised statin therapy
	• When LDL-C is not adequately controlled with optimised statin therapy:
	  ○ Ezetimibe in combination with optimised statin therapy
	  ○ Evolocumab in combination with optimised statin therapy (subject to NICE guidance)
	• When LDL-C is not adequately controlled with optimised statin therapy in combination with ezetimibe:
	  ○ Evolocumab in combination with ezetimibe and a statin (subject to NICE guidance)
	• When statins are contraindicated or not tolerated:
	  ○ Ezetimibe
	  ○ Evolocumab (subject to NICE guidance)
	  ○ Evolocumab in combination with ezetimibe (subject to NICE guidance)

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'. Earliest anticipated date of publication May 2016. Proposed Technology Appraisal, 'Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia'. 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 tbc. 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

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolemia and mixed dyslipidaemia [ID779]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Companies • Sanofi Patient/carer groups • Black Health Agency • Blood Pressure UK • 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 • Pumping Marvellous Foundation • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • British Association for Nursing in Cardiovascular Care • British Cardiovascular Intervention Society • British Cardiovascular Society • British Dietetic Association • British Geriatrics Society • British Heart Foundation • British Hypertension Society • British Inherited Metabolic Disease Group • British Nuclear Cardiology Society • British Society of Cardiovascular Imaging • Nurses Hypertension Association	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British Cardiovascular Industry Association • 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 Possible comparator companies • Accord Healthcare (fluvastatin, pravastatin, simvastatin) • Actavis (atorvastatin, fluvastatin, pravastatin, simvastatin) • Amneal (pravastatin, simvastatin) • Aptil (fluvastatin, simvastatin) • Arrow Generics (simvastatin) • AstraZeneca (rosuvastatin) • Aurobindo Pharma (pravastatin, simvastatin) • Bristol-Myers Squibb (pravastatin) • Caduceus (fluvastatin) • Chelonia (simvastatin)

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • 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 Health Forum • Vascular Society of Great Britain & Ireland <u>Others</u> • Department of Health • NHS Birmingham South and Central CCG • NHS East Leicestershire and Rutland CCG • NHS England • Welsh Government	• Consilient (atorvastatin) • Crescent (pravastatin, simvastatin) • Dexcel-Pharma (atorvastatin, simvastatin) • Hexal (simvastatin) • Kent (simvastatin) • Kiron (simvastatin) • Lupin (simvastatin) • Medley (simvastatin) • Medreich (pravastatin) • Merck, Sharp & Dohme (ezetimibe, simvastatin, simvastatin with ezetimibe) • Metwest (simvastatin) • Mylan (fluvastatin, pravastatin, simvastatin) • Novartis Pharmaceuticals (fluvastatin) • Pfizer (atorvastatin) • Pharmathen (fluvastatin) • Pliva (pravastatin) • Ranbaxy (pravastatin, simvastatin) • Ratiopharm (fluvastatin) • Rosemont Pharma (simvastatin) • Sandoz (fluvastatin, pravastatin, simvastatin) • Teva UK (fluvastatin pravastatin, simvastatin) • Tillomed (pravastatin, simvastatin) • Winthrop (fluvastatin, pravastatin, simvastatin) • Wockhardt (atorvastatin) • Yiling (pravastatin) • Zanza (simvastatin) • Zentiva (atorvastatin, fluvastatin, simvastatin) <u>Relevant research groups</u> • Antithrombotic Trialists' (ATT) Collaboration • British Society for Cardiovascular Research • Central Cardiac Audit Database • Cochrane Heart Group • Cochrane Hypertension Group • Cochrane Peripheral Vascular Diseases

Consultees	**Commentators (no right to submit or appeal)**
	Group • Health Research Authority • MRC Clinical Trials Unit • National Centre for Cardiovascular Preventions and Outcomes • National Heart Research Fund • National Institute for Health Research • Wellcome Trust - Cardiovascular Research Initiative <u>Evidence Review Group</u> • Aberdeen HTA Group • 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 share it. 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 CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that manufactures 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 manufactures 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 statement[1], 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: manufacturers of 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.

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779]

Company evidence submission

September 2015

File name	Version	Contains confidential information	Date
	1.0 no PAS	**NO**	**08.11.15**

Contents

Tables and figures

Table of figures

Table of tables

Abbreviations

ACS	Acute Coronary Syndrome
ADA	Anti-Drug Antibodies
Admin	Administration
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
Apo A1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST	Aspartate Aminotransferase
ATOR	Atorvastatin
BMI	Body Mass Index
BNF	British National Formulary
CA$	Canadian dollar
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CE	Conformité Européenne
CG	Clinical Guideline
CHD	Coronary Heart Disease
CHF	Chronic Heart Failure
CHMP	Committee for Medicinal Products for Human use
CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed tomography
CTT	Cholesterol Treatment Trialists
CUA	Cost-utility analysis
CV	Cardiovascular
CVD	Cardiovascular Disease
dL	decilitre
DM	Diabetes Mellitus
DSU	Decision Support Unit
EAS	European Atherosclerosis Society
ECG	Electrocardiogram
e-CRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMDAC	Endocrinologic and Metabolic Drugs Advisory Committee

EQ-5D	EuroQol-5 dimensions
ESC	European Society of Cardiology
EZE	Ezetimibe
FDA	Food and Drug Administration
FH	Familial Hypercholesterolaemia
GDG	Guideline Development Group
HCP	Healthcare Professional
HDL-C	High-density Liproprotein cholesterol
HeFH	Heterozygous Familial Hypercholesterolaemia
HLT	Higher Level Term
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HS	Health state
HSE	Health Survey for England
HSUV	Health State Utility Values
HUI	Health Utility Index
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
IDL	Intermediate-density liproprotien
IgG	Immunoglobulin
IS	Ischaemic stroke
ITT	Intention to Treat
JBS	Joint British Societies
LDL-C	Low-density liproprotein Cholesterol
LDL-R	Low-density liproprotein Receptor
LLT	Lipid Lowering Therapies
LMT	Lipid Modifying Therapies
Lp(a)	Liproprotein (a)
LS	Least-Squares
LVEF	Left Ventricular Ejection Fraction
LVSD	Left ventricular systolic dysfunction
LYG	Life-years gained
MA	Marketing Authorisation
mAb	Monoclonal Antibody
MACE	Major Adverse Cardiac Events
MAR	Missing-at-Random
MD	Mean Difference
mg	Milligrams

MI	Myocardial Infarction
mITT	Modified Intention to Treat
mmol	Millimole
MMRM	Mixed Effect Model with Repeated Measures
Mon	Monitoring
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NCEP-ATP	National Cholesterol Education Program – Adult Treatment Panel
NEC	Not elsewhere classified
NF	Non-Fatal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMAR	Not-Missing-at-Random
NR	Not Recorded
NYHA	New York Heart Association
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PAS	Patient Access Scheme
PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein Convertase Subtilisinlike Kexin Type 9
PICOS	Population, Intervention, Comparison, Outcomes
P-IS	Post-ischaemic stroke
PO	Per Os (orally)
PMM	Pattern Mixture Model
PRA	Pravastatin
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PT	Preferred Term
PVD	Peripheral Vascular Disease
Q2W	Every Two Weeks
Q4W	Every Four Weeks
QALY	Quality-adjusted life years
QD	Every Day
QoL	Quality of Life
RCT	Randomised Controlled Trial
ROS	Rosuvastatin
RR	Rate ratio
SAE	Serious Adverse Event
SC	Subcutaneous

SCORE	Systematic Coronary Risk Estimation
SD	Standard Deviation
SE	Standard Errors
SF	Short form
SG	Standard Gamble
SI	Statin intolerance
SIGN	Scottish Intercollegiate Guidelines Network
SIM	Simvastatin
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA queries
STA	Single technology appraisal
STEMI	ST-Elevation Myocardial Infarction
TEAE	Treatment Emergent Adverse Events
TG	Triglyceride
TIA	Transient Ischemic Attack
Total-C	Total cholesterol
Treat	Treatment
TSD	Technical Support Document
TTO	Time Trade Off
UA	Unstable Angina
UK	United Kingdom
VAS	Visual Analogue Scale
VAT	Value-added tax
VLDL	Very low-density liproprotein
WHO	World Health Organisation

1. Executive summary

Key points

- **Alirocumab is an anti-PCSK9 monoclonal antibody (PSCK9 inhibitor) which acts upon a novel target to achieve substantial reductions in low-density lipoprotein-cholesterol (LDL-C) as an adjunct to existing therapy**
- **PCSK9 inhibitors are a significant step forward in the management of high cardiovascular risk patients who are unable to achieve cholesterol targets on existing therapy**
- **LDL-C is a major risk factor for cardiovascular events, including heart attacks, stroke and other manifestations of disease**
- **Statins are the current mainstay of therapy for cholesterol management. However there are some patients with high cardiovascular risk whose cholesterol is uncontrolled with current therapy either due to insufficient efficacy, inability to tolerate statins or contraindication to statins**
- **Patients at high cardiovascular risk include those with inherited high cholesterol (familial hypercholesterolaemia) as well as those who have previously suffered major adverse cardiovascular events**
- **There are limited alternative options for these patients whose cholesterol is uncontrolled. PCSK9 inhibitors will provide a valuable option in the care pathway as an adjunct to current maximal therapy**
- **Alirocumab has demonstrated substantial efficacy in LDL-C lowering in patients at high cardiovascular risk, with safety comparable to control, in an extensive trial programme including 36 UK NHS sites**
- **The anticipated use of alirocumab is in patients with high cardiovascular risk uncontrolled on current maximal therapy**

1.1 Clinical Background

1.1.1 The role of PCSK9 in cholesterol metabolism

Proprotein convertase subtilisin/ kexin type 9 (PCSK9) is a protein that binds to the LDL receptor (LDL-R) on the surface of hepatocytes to promote LDL-R degradation within the liver. LDL-Rs are responsible for clearance of LDL-C from the blood. The action of PCSK9 therefore results in higher blood levels of LDL-C. Alirocumab targets the PCSK9 protein, inhibiting its action and increasing the number of LDL-Rs available to clear LDL-C from the blood [1].

Genetic studies in humans provided the basis for identifying the role of PCSK9 in lipid metabolism. Loss-of-function mutations are associated with naturally low LDL-C levels and substantially reduced risk of coronary events (between 47% - 88% in the ARIC study)[2-4] Conversely, patients with gain-of-function mutations in PCSK9 have familial hypercholesterolaemia (FH) and increased risk of cardiovascular events. These discoveries formed the initial rationale for the clinical development programme for PCSK9 inhibitors.

1.1.2 Cholesterol and Cardiovascular disease

Atherosclerosis is the formation and hardening of fatty plaques on the inner surface of the arteries [5]. As plaques progress they are at risk of rupture, leading to thrombus formation and vessel occlusion and thus ischaemic events such as myocardial infarction and ischaemic stroke [6].

LDL-C is closely and strongly associated with atherosclerosis and major adverse cardiovascular (CV) event risk. Epidemiologic [7-9] and genetic studies [3, 10, 11] have demonstrated the link between elevated LDL-C, development of atherosclerosis, and increased risk for major adverse CV events. Clinical studies have shown that reducing LDL-C reduces the risk for major adverse CV events [12-21]. The majority of this evidence derives from the statin trials; meta-analyses including non-statin lipid-lowering therapies and the recent IMPROVE-IT trial of ezetimibe have also confirmed the link between LDL-C reduction and CV risk reduction [14, 21, 22].

1.1.3 Unmet need with current LDL-C lowering therapy

Statins are the mainstay of LDL-C lowering therapy and have contributed to significant reductions in cardiovascular morbidity and mortality in the UK. NICE clinical guideline 181 recommends high-dose, high-intensity statins for all high risk patients [23]. Ezetimibe is also approved by [24][TA132] for patients whose LDL-C is not controlled adequately with statins or who are unable to tolerate statins or for whom statins are contraindicated.

Not all patients are able to achieve adequate LDL-C control on existing therapies, either due to insufficient efficacy with current maximal dose of statin-based therapy (with or without ezetimibe) or contraindication/inability to tolerate statins.

Beyond statins and ezetimibe, there are limited alternative effective therapeutic options for patients to effectively lower LDL-C. In patients with severely elevated cholesterol (typically those with familial hypercholesterolaemia), apheresis (a dialysis-like process in which cholesterol is removed from the blood outside the body) may be used, however this poses significant burden on the NHS and the individual patient. Apheresis is limited to a very small number of UK centres and patients.

Patients at high risk of future cardiovascular events and who have inadequately controlled LDL-C with current therapy have a clear need for additional effective LDL-C lowering therapy.

1.1.4 Patient Groups

We focus in this submission on patients at high cardiovascular risk due to familial hypercholesterolaemia (inherited high cholesterol) and patients at high risk due to previous cardiovascular events. In these patient populations, PCSK9 inhibitors will provide a valuable new therapeutic option as an adjunct to current maximal tolerated therapy.

1.1.4.1 Familial hypercholesterolaemia

FH is an inherited condition caused by mutations in the genes encoding for the LDL-R, ApoB, or PCSK9 and resulting in elevated blood cholesterol. Most people with FH have inherited a defective gene for FH from only one parent and are therefore heterozygous. Rarely, a person will inherit a genetic defect from both parents and will have homozygous FH (HoFH) [25]. Heterozygous familial hypercholesterolaemia (HeFH) has an estimated prevalence of 1 in 500 whereas homozygous FH has an incidence of approximately one case per one million [25 26]. In HeFH patients, lifelong exposure to elevated LDL-C levels results in a high cumulative risk of developing coronary heart disease. Even with treatment, the risk of early-onset coronary heart

disease (CHD) and early mortality in patients with HeFH is still elevated above the general population [26-28]. In a Danish study the odds of developing CHD was ten times higher than in the general population in treated patients, and thirteen times higher in untreated patients [27].

It is particularly difficult for HeFH patients to reach recommended LDL-C treatment goals. The UK National FH audit found that only 44% of adult patients achieved the NICE guideline goal of 50% reduction in LDL-C from the untreated level. Overall, treated LDL-C was reduced from a median of 6.1 mmol to 3.5 mmol/L, still well above absolute target LDL-C levels of <1.8mmol/L recommended by European guidelines [29, 30].

1.1.4.2 Patients with existing cardiovascular disease (CVD)

Patients with a history of major cardiovascular events (e.g. myocardial infarction, unstable angina, coronary revascularisation, ischaemic stroke, peripheral arterial disease) are recognised as being at very high risk for further CV events [29,23]. Within this patient population, patients who have had recurrent/ multiple prior CV events are at even higher risk- the rate of further events or mortality is higher in patients who have experienced multiple myocardial infarctions (MIs) versus only one MI [31,32] or in patients with events in more than one vascular bed, i.e. polyvascular disease, compared to those with only one type of prior cardiovascular event [33-35].

A European study of over 7000 patients showed that significant numbers of high-risk and very high risk patients (60 – 80% respectively) were unable to adequately lower their LDL-C levels with statins or other lipid-lowering agents [36]. Poorly controlled cholesterol contributes to the burden of cardiovascular disease to the NHS. CVD as a whole is estimated to cause ~28% of all deaths and to cost in the region of £7 – 8 billion annually, with the majority of costs generated through hospital admissions/ urgent care [37,23].

1.2 Indication of alirocumab

Alirocumab was approved by the European Medicines Agency on September 25th 2015. Another PCSK9 inhibitor, evolocumab, was licensed in July 2015 and is

currently being appraised by NICE. The indication for Praluent (alirocumab) is detailed in Table 1.

Alirocumab is available in two different dosages (75 mg and 150 mg). In eight of the trials submitted in the regulatory dossier, an up-titration strategy was followed with initiation on 75 mg and up-titration to 150 mg at 12 weeks in order to meet therapeutic targets. Two trials used 150 mg throughout. The two different dosing options were developed to allow clinical flexibility in meeting individual patient treatment goals.

Table 1: Alirocumab indication details

UK approved name and brand name	Alirocumab (brand name Praluent)
Marketing authorisation/CE mark status	Approved by EMA
Indications and any restriction(s) as described in the SmPC	Alirocumab 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 LMTs in patients unable to reach LDL-C goals with the maximal tolerated dose of statin (when used as recommended by treatment guidelines) or, • alone or in combination with other LMTs in patients who are statin intolerant or for whom a statin is contraindicated The effect of this technology on CV morbidity and mortality has not yet been determined
Method of administration and dosage	Alirocumab is available at two doses, 75 mg and 150 mg, as a single-use, pre-filled auto-injector pen in either one pen or two pen packs

1.3 Clinical effectiveness of alirocumab

The evidence for the clinical effectiveness of alirocumab is supported by an extensive clinical development programme (ODYSSEY). Ten double-blind, multicentre randomised controlled trials, including over 5000 patients worldwide, were included in the regulatory dossier. Thirty-six UK centres participated in these trials. The significant investment in the evidence base for alirocumab continues with an ongoing Outcomes trial (CVOT), estimated to report in January 2018, including ~18,000 patients and thirty UK centres.

The ODYSSEY trial programme evaluated alirocumab as an add-on to maximal tolerated dose statins with or without other lipid-modifying therapies (LMT) including ezetimibe. The programme includes direct comparisons with ezetimibe on a statin background, and with ezetimibe as monotherapy or as add-on to existing non-statin LMT in patients with statin intolerance. Thus ODYSSEY provides direct data to assess clinical effectiveness against relevant comparators in the Scope.

The ODYSSEY programme included patient populations relevant to the scope and to the anticipated usage of alirocumab in the UK. 1377 (26%) of patients had HeFH, including patients in three specific FH trials, and 97% of patients were defined as being at high CV risk.

- The primary efficacy endpoint was percentage reduction in LDL-C at 24 weeks.
- Secondary endpoints included:
    - Total cholesterol
    - non-HDL-C (non-high-density-lipoprotein-C)
    - HDL-C (high-density-lipoprotein-C)
    - ApoB
    - Apo A-1
    - Triglycerides
    - Lp(a) (lipoprotein(a))
    - EQ-5D
    - Safety

Primary endpoint results from the pivotal trials are show in Table 2. A rapid onset (4 weeks) and sustained treatment effect was observed (with follow-up data up to 78

weeks). The treatment effect was consistent across a range of different patient subgroups and demographics and background therapies.

Table 2: ODYSSEY Clinical effectiveness data

Trial no. (acronym) Patient Numbers (N)	Intervention/ Comparator	Population	High/Very High CV risk patients (%)	Primary Outcome – Mean percentage change in LDL-C from baseline at Week 24	
				vs Placebo	vs Ezetimibe
EFC12492 (FH I) N = 486	Alirocumab vs Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs	100	-57.9% (p<0.0001)	
CL-1112 (FH II) N = 249	Alirocumab vs Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs	100	-51.5% (p<0.0001)	
EFC12732 (HIGH FH) N = 107	Alirocumab vs Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs and with LDL-C ≥160 mg/dL (4.14 mmol/L)	100	-39.1% (p<0.0001)	
EFC11568 (COMBO I) N = 316	Alirocumab vs Placebo	Patients at high CV risk with hypercholesterolaemia not adequately controlled with statin ± other LMTs	100	-45.9% (p<0.0001)	
EFC11569 (COMBO II) N = 720	Alirocumab vs Ezetimibe	Patients at high CV risk with hypercholesterolaemia not adequately controlled with statin therapy	100		-29.9% (p<0.0001)
LTS11717 (LONG TERM) N = 2341	Alirocumab vs Placebo	Patients with HeFH or non-FH at high CV risk not adequately controlled with a statin ± other LMTs	100	-61.8% (p<0.0001)	
CL-1119 (ALTERNATIVE) N = 314	Alirocumab vs Ezetimibe, Atorvastatin	Patients with primary hypercholesterolaemia and moderate, high, or very high CV risk who are intolerant to statins.	82.4		-30.4% (p<0.0001)
EFC11716 (MONO) N =103	Alirocumab vs Ezetimibe	Patients at moderate CV risk with LDL-C ≥100 mg/dL (2.59 mmol/L) and ≤190 mg/dL (4.91 mmol/L)	0		-31.6% (p<0.0001)
				vs Statin Up-titration	vs Ezetimibe
CL-1110 (OPTIONS I) N = 355	Alirocumab + Atorvastatin vs Atorvastatin+Ezetimibe; Atorvastatin (up-titrated); Rosuvastatin (switch)	Patients at high CV risk with non-FH or HeFH not adequately controlled with atorvastatin (20 mg or 40 mg) ± other LMT excluding ezetimibe	100	1. Atorva 20mg: 39.1% (p<0.0001) 2. Atorva 40mg: 49.2% (p<0.0001) 3. Rosuva Switch: 32.6% (p<0.0001)	1. 23.6% (p<0.0001) 2. 31.4% (p<0.0001)
CL-1118 (OPTIONS II) N = 305	Rosuvastatin+Alirocumab vs Rosuvastatin+Ezetimibe; Rosuvastatin (up-titrated)	Patients at high CV risk with non-FH or HeFH not adequately controlled with rosuvastatin (10 mg or 20 mg) ± other LMT excluding ezetimibe	100	1. Rosuva 10mg: 34.3% (p<0.0001) 2. Rosuva 20mg: 20.4 % (p=0.0453)	1. 36.2% (p<0.0001) 2. 25.3% (p=0.0136)

The CV outcomes benefit of alirocumab is being evaluated in CVOT. Although not powered or designed to demonstrate outcomes, a post-hoc analysis of the ODYSSEY LONG TERM safety study (data up to 78 weeks), showed a significantly lower rate of major adverse cardiovascular events (MACE) in the alirocumab arm (1.7% versus 3.3%, HR = 0.52 [CI:0.31 – 0.90])[38]. Consistent with this, an independent peer-reviewed meta-analysis of PCSK9 inhibitor outcomes data (alirocumab and evolocumab) to date reported significant reductions in MI and all-cause mortality, with a trend towards reduced CV mortality [39].

The safety database was based on 3451 years of patient exposure to alirocumab, with 638 patients exposed for at least 78 weeks. Since submission of the regulatory dossier, the number of patients exposed for at least 78 weeks has increased to 1717 patients (as of Dec 2014). Alirocumab demonstrated a similar safety profile to control, with good tolerability and a limited number of serious adverse events.

1.4 Place in Therapy

Alirocumab will align to the existing 'Cardiovascular Disease Prevention' and the 'Familial Hypercholesterolaemia' NICE pathways [40, 41].

It is anticipated that alirocumab will be initiated as an adjunctive therapy in patients who have not reached treatment targets on maximally tolerated dosage of statins with or without other LMTs. Based upon NICE approval of ezetimibe in [24](TA132), alirocumab will be used as an add-on to ezetimibe plus statins where relevant. This reflects usage in ODYSSEY where ~50% of patients in the FH trials were already receiving statins plus ezetimibe. Ezetimibe usage in the NHS is however limited and highly varied and therefore alirocumab may also be used as an add-on therapy to maximal tolerated dose statins (alone, not in combination with ezetimibe).

In patients who are statin intolerant or for whom statins are contraindicated, alirocumab may be used as an add-on to ezetimibe alone or as monotherapy in patients who have not reached treatment targets.

1.5 Cost-effectiveness analysis

A Markov model was developed to evaluate the cost-effectiveness of alirocumab as an adjunctive therapy to existing maximal tolerated LMT. The model includes major CV events (MI, unstable angina (UA), ischaemic stroke (IS), revascularisation) and CV and non-CV death. The model considers different patient populations separately due to differences in disease history and CV risk, although the relative treatment effect of alirocumab is consistent across different groups. The key patient populations included in the model are:

- HeFH (both primary and secondary prevention)
- Patients at high CV risk due to existing CV disease (secondary prevention – patients with MI, unstable angina, history of revascularisation or other evidence of CHD, ischaemic stroke, peripheral arterial disease (PAD))
- A subgroup of the above patients with existing CV disease at even higher risk, namely patients with recurrent CV events/ polyvascular disease

All of these patient groups were included in ODYSSEY (NB patients with recurrent events were not evaluated as a separate predefined subgroup).

In the base case alirocumab is modelled as an adjunctive therapy to existing maximally tolerated current therapy. For those patients able to tolerate statins, this can be either maximal tolerated dose of statins or maximal tolerated dose of statins plus ezetimibe. Based on UK current usage of ezetimibe, the latter is considered more common for FH patients and the former more common for high CV risk patients.

For patients who are completely intolerant to statins alirocumab is modelled as an adjunctive therapy to ezetimibe alone (no statins). In these patients a higher starting LDL-C level is also applied in the model.

The base case for HeFH and for the recurrent events/ polyvascular population models patients with an LDL-C of at least 2.59 mmol/L (100mg/dL), a level that is considered to require treatment in current guidelines [29]. For the high risk CVD

population we model an LDL-C of at least 3.36 mmol/L (130m g/dL), representing patients who are clearly far from target levels on existing therapy. For this broader population we consider that this higher cut-off, where LDL-C is clearly likely to be a driving factor of disease, is a realistic clinical and economic threshold for alirocumab initiation.

Real-world UK data were used to inform the baseline CV event risk of the patient groups included. The LDL-C lowering effect of alirocumab and comparator arms is taken directly from the ODYSSEY trials. The relationship between LDL-C lowering and CV event reduction is taken from a published meta-analysis of the PCSK9 inhibitors [39] and alternative sources were investigated in sensitivity analyses. Baseline utilities came from ODYSSEY and from UK Health Survey for England (HSE) data [42, 43]. Costs were taken from the NICE lipid modification guideline [23][CG181].

Cost-effectiveness results are shown in Table 3 below.

Table 3: Incremental cost-effectiveness results

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	[redacted]	1.62	1.42	[redacted]
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	[redacted]	3.04	2.33	[redacted]
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins	[redacted]	[redacted]	[redacted]	[redacted]	2.38	1.76	[redacted]
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins	[redacted]	[redacted]	[redacted]	[redacted]	2.42	1.64	[redacted]
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				

Statement of decision problem

Table 4 describes how the decision problem is addressed in the submission.

Table 4: 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 LMTs, in line with current NICE guidance, would be considered	As per the final scope	N/A
Intervention	Alirocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe	Alirocumab in combination with maximal tolerated dose of statins, with or without ezetimibe, or alirocumab on a background of no statins, with or without ezetimibe.	In line with the scope but adjusted to reflect current NHS usage of ezetimibe
Comparator(s)	When LDL-C is not adequately controlled with optimised statin therapy: • Ezetimibe in combination with optimised statin therapy • Evolocumab in combination with optimised statin therapy (subject to NICE guidance) When LDL-C is not adequately controlled with optimised statin therapy in combination with ezetimibe: • Evolocumab in combination with ezetimibe and a statin (subject to NICE guidance) When statins are contraindicated or not tolerated: • Ezetimibe • Evolocumab (subject to NICE guidance)	When LDL-C is not adequately controlled with optimised (maximal tolerated dose) statin therapy: • Optimised statin therapy alone (i.e. no additional comparator) • Optimised statin therapy plus ezetimibe When LDL-C is not adequately controlled with optimised statin therapy in combination with ezetimibe: • Optimised statin therapy plus ezetimibe (i.e. no additional comparator) When statins are contraindicated or not tolerated: • No additional therapy (on background of ezetimibe) As a base case, we consider alirocumab as an adjunctive agent to current maximal therapy (maximal tolerated dose statins with or without ezetimibe, or a background of no statins with or	We anticipate that alirocumab will be used in patients who are not adequately controlled on all maximally used existing therapy. This is discussed in further detail in the submission

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Evolocumab in combination with ezetimibe	without ezetimibe). The comparison is therefore versus no active comparator. We present scenario comparisons versus ezetimibe We have not conducted a formal economic comparison versus evolocumab as NICE have not yet issued guidance and it is not NHS standard of care	
Outcomes	• Plasma lipid and lipoprotein levels, including LDL-C, non-HDL-C, Apo B and lipoprotein a • Requirement of procedures including LDL-apheresis and revascularisation • Fatal and non-fatal CV events • Mortality • Adverse effects of treatment • HRQoL	As per the final scope	
Economic analysis	Reference case	As per the final scope	N/A
Subgroups to be considered	• Presence or risk of CVD • People with HeFH • People with statin intolerance • Severity of hypercholesterolaemia	The economic analysis evaluates: • Patients with HeFH (with and without existing CVD) • Patients with existing CVD • A higher risk subgroup of patients with CVD, namely patients with recurrent events/polyvascular disease • Statin intolerant patients are not considered as one separate group but are modelled as subsets of the above high risk groups, differing in terms of the background therapy and in terms of their baseline LDL-C levels. • Analysis is also conducted by severity of hypercholesterolaemia by variation of LDL-C levels	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	None	None considered relevant	N/A

Apo, apolipoprotein; CV, cardiovascular; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; HRQoL, Health-related quality of life; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; N/A, not available; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence

2. The technology

2.1 Description of the technology

Brand Name: **Praluent®**

Approved Name: **Alirocumab**

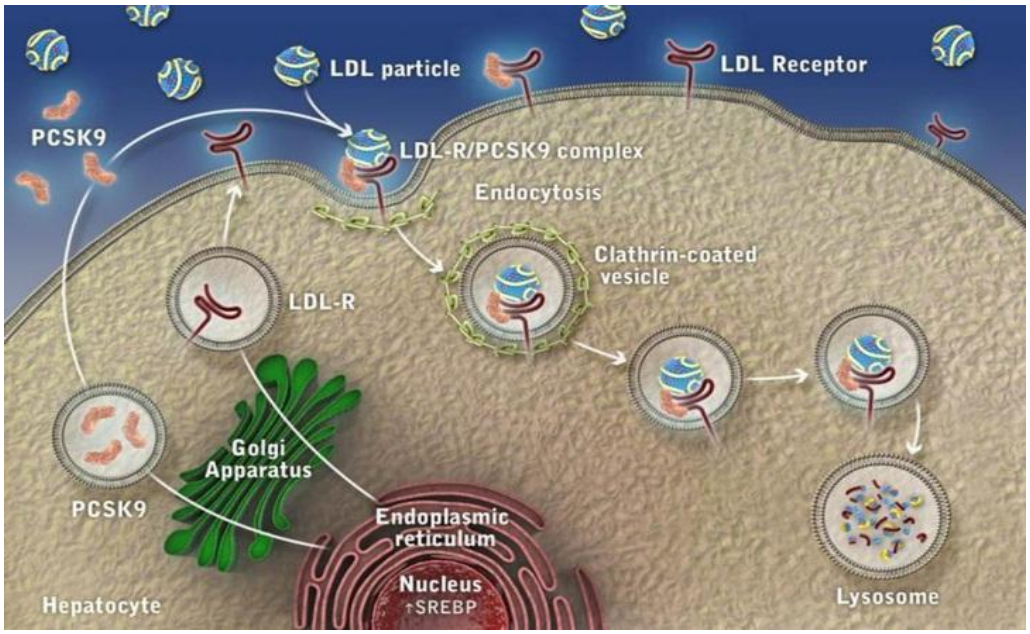
Therapeutic Class: **PCSK9 Inhibitor**

Alirocumab is a fully human monoclonal antibody (mAb) (immunoglobulin [IgG]1 isotype) that binds with high affinity and specificity to circulating proprotein convertase subtilisin/kexin type 9 (PCSK9).

Elevated serum LDL-C is a major risk factor for atherosclerosis and the development of cardiovascular disease (see Section 3). The principal means by which LDL-C is removed from the circulation is by LDL-receptors (LDL-R) on the surface of hepatocytes (in the liver)[4]. Statins, the current mainstay of LDL-C-lowering therapy, inhibit intracellular synthesis of cholesterol, leading to increased synthesis of LDL-Rs and thus increased clearance of LDL-C.

Identification of the PCSK9 gene/ protein in 2003 led to the discovery of a new pathway and mechanism by which to lower LDL-C [2]. PCSK9 binds to the LDL-R on the surface of hepatocytes to promote LDL-R internalisation and degradation. The resultant decrease in LDL-Rs leads to higher blood levels of LDL-C. By inhibiting the binding of PCSK9 to the LDL-R, alirocumab increases the number of receptors available to clear LDL, thereby lowering LDL-C levels (Figure 1) [1].

Figure 1: The role of PCSK9 in cholesterol metabolism



LDL=low-density lipoprotein; LDL-R=low-density lipoprotein receptor; PCSK9=proprotein convertase subtilisin/kexin type 9

The PCSK9 pathway was discovered through genetic studies in humans [44]. Gain-of-function mutations in the PCSK9 gene are associated with diagnoses of familial hypercholesterolaemia, increased LDL-C levels, and increased risk of CHD [44, 45]. Untreated LDL-C levels in patients with such gain-of-function mutations are in a similar range to those in patients with the more traditional mutations (in the LDL-R gene) that cause HeFH [46].

Conversely, individuals with PCSK9 loss-of-function mutations have lower levels of LDL-C, and a significantly lower incidence of CHD (MI, fatal CHD, or coronary revasularisation) compared to matched controls [3]. The impact on LDL-C and CHD is dependent on the individual mutation – in the ARIC study, mutations that lowered LDL-C by ~0.5 mmol/L were associated with a 47% reduction in the incidence of CHD, while mutations that lowered LDL-C by ~1mmol/L were associated with an 88% reduction in the incidence of CHD [3].

In addition, the LDL-R binds TG-rich VLDL remnant lipoproteins and IDL. Therefore, alirocumab treatment can produce reductions in these remnant lipoproteins, as evidenced by its reductions in ApoB, non-HDL-C, and TGs. Alirocumab also results

in a reduction in Lp(a), however, the exact mechanism by which alirocumab lowers Lp(a) is not fully understood [47]

2.2 Marketing authorisation/CE marking and health technology assessment

.Alirocumab was approved by the EMA on September 25th 2015.

The approved indication is:

Alirocumab 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 statin (when used as recommended by treatment guidelines) or,*
- *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 this technology on cardiovascular morbidity and mortality has not yet been determined.

There are no anticipated restrictions or contraindications that are likely to be included in the Summary of Product Characteristics. No data are available in patients with severe hepatic impairment and limited data are available in patients with severe renal impairment. The only contraindication is hypersensitivity to the active substance or to any of the excipients. Alirocumab, however, must not be co-administered with other injectable medicinal products at the same injection site.

The draft SmPC and EPAR are provided in Appendix 1.

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the U.S. Food and Drug Administration (FDA) recommended the approval of alirocumab (Praluent®) injection for patients with hypercholesterolaemia on the 9th June 2015 and it was subsequently approved by the FDA on the 24th July 2015 as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with

heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-Cholesterol (LDL-C) [48].

A submission to the Scottish Medicines Consortium (SMC) is planned for December 2015.

2.3 Administration and costs of the technology

2.3.1 Costs of Technology being appraised

Table 5: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Solution for injection	Draft SmPC
Acquisition cost (excluding VAT)*	The list price acquisition cost (submitted to Department of Health) is: • £168 per one-pen pack • £336 per two-pen pack The price is the same for both the 75 mg and 150 mg doses A patient access scheme is proposed for alirocumab but has not yet been agreed.	
Method of administration	Sub-cutaneous (SC) injection	Draft SmPC
Doses	75 mg and 150 mg as a single use, pre-filled auto-injector pen	Draft SmPC
Dosing frequency	Q2W	Draft SmPC
Average length of a course of treatment	It is anticipated that alirocumab will be used continuously once initiated	Primary hypercholesterolaemia is a chronic condition that requires continuous management (c.f. NICE Clinical Guideline CG71; recommendation 1.3.1.1)
Average cost of a course of treatment	Not applicable; see above for acquisition cost	
Anticipated average interval between courses of treatments	Not applicable	
Anticipated number of repeat courses of treatments	Not applicable	
Dose adjustments	The usual starting dose is 75 mg administered SC Q2W Patients requiring larger LDL-C reductions (>60%) may be started on 150 mg administered SC Q2W The dose can be individualised based on patient characteristics such as goal of therapy and response. Lipid levels can be assessed as early as 4 weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved,	Draft SmPC

	Cost	Source
	and dosage adjusted accordingly. No dose adjustment is needed for alirocumab for elderly patients No dose adjustment based on weight is needed for alirocumab No dose adjustment is needed for alirocumab for patients with mild or moderate hepatic impairment (note: no data are available for alirocumab in patients with severe hepatic impairment) No dose adjustment is needed for alirocumab for patients with mild or moderate renal impairment (note: limited data are available for alirocumab in patients with severe renal impairment). Note: The safety and efficacy of alirocumab has not been established in paediatric patients	
Anticipated care setting	Secondary care After secondary care initiation, subsequent injections can be safely managed in the community – in a patient's home, local pharmacy or in a general practice setting It is anticipated, however, that alirocumab will be initiated and continued in secondary care via a sponsored homecare service	

LDL-C, low-density lipoprotein cholesterol; NICE, The National Institute for Health and Care Excellence; Q2W, every 2 weeks; SC, subcutaneous; SmPC, summary of product characteristics; VAT, value-added tax

2.3.2 Patient Access Scheme (PAS)

A simple patient access scheme has been submitted but not yet agreed. Therefore modelling results are presented based on the list price.

2.4 Changes in service provision and management

Alirocumab is anticipated to be initiated in secondary care. The type of patients who will be eligible for alirocumab are high risk patients who are not able to achieve treatment targets on current therapies; these patients are likely to be already be managed in specialist lipid clinics, with regular monitoring of lipid levels. There are no additional tests or investigations expected for initiation above and beyond what is routine clinical practice in this patient population.

After initiation it is anticipated that alirocumab will be continued in secondary care via a sponsored homecare service, with a follow up consultation in line with current practice for follow‑up of people started on statin treatment[23] [CG181] to assess impact on lipid levels and discuss dose modification. The dose of alirocumab can be individualised based on patient characteristics such as goal of therapy and LDL-C response and any potential dose modification will be undertaken via this follow-up consultation. Monitoring would then be undertaken on an annual basis (in line with the current recommendation to provide annual medication reviews for people taking statins). There are unlikely to be any additional NHS infrastructure requirements associated with the introduction of alirocumab.

Alirocumab should be stored in a refrigerator (2°C to 8°C) and time out of refrigeration should not exceed a maximum of 24 hours. The patient may either self-inject alirocumab, or a caregiver may administer, after initial guidance has been provided by a healthcare professional on proper subcutaneous injection technique. Support will be provided to patients and HCPs on establishing the correct injection technique in patients started on alirocumab as part of the Praluent Patient Support Programme.

Alirocumab is indicated to be used in combination with statin and/or with other LMT in patients unable to reach LDL-C goals with maximally tolerated dose. Within the ODYSSEY Phase III clinical trial programme patients' current LMT was permitted as concomitant therapy. Permitted background therapy medications included statins (rosuvastatin, atorvastatin, simvastatin); cholesterol absorption inhibitors (ezetimibe – except in trials with ezetimibe as an active control); bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam); nicotinic acid; fenofibrate and

omega-3 fatty acids (≥1000 mg daily). Other than statins and ezetimibe none of the other LMTs are approved by NICE [23][CG181].

2.5 Innovation

Genetic studies in humans led to the discovery of PCSK9. PCSK9 gain-of-function mutations are associated with FH and increased incidence of CVD[45,44]. Loss-of-function mutations are associated with decreased LDL-C and a significantly lower incidence of CHD (by 47% - 88% in the ARIC study)[3, 10]. These data suggested a strong association between PCSK9, LDL-C, and cardiac risk and formed the rationale for the alirocumab development programme.

Alirocumab is a fully human monoclonal antibody that binds with high affinity and specificity to circulating PCSK9. Alirocumab acts on a target that is not targeted by existing lipid modifying therapies (e.g statins and cholesterol absorption inhibitors). Alirocumab has been shown in clinical trials to have a substantial cholesterol-lowering effect when used alone or on top of existing therapy (Section 4.2).

Alirocumab will therefore be a step forward in the management of patients who are not able to achieve therapeutic goals when treated with existing LMT at maximal tolerated dose. In particular:

- Patients with HeFH, whose genetic condition results in significantly raised cholesterol levels over a lifetime. HeFH patients have an increased risk of early mortality and CHD, experiencing CV events at a younger age compared to the general population, and few achieve target LDL-C levels with existing treatment

- Patients who remain at high, or very high CV risk with persistently and significantly raised cholesterol levels despite current maximum indicated or tolerated dose of LMT

- Those high or very high risk patients with persistently and significantly raised cholesterol levels who have been clinically defined as being unable to tolerate statins and who therefore have limited treatment options.

LDL-apheresis is a type of ‘extracorporeal’ procedure to remove LDL-C from the blood [49]. LDL-apheresis is only provided in a small minority of severe FH patients given the significant burden on the patient and the NHS and is only available in a small number of centres nationally. Given alirocumab’s efficacy as an adjunct to other lipid lowering therapies, it may be a possible treatment alternative for patients who are on LDL-apheresis and an option for those who are on an apheresis waiting list; or who have declined apheresis.

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

3.1 Relationship between cholesterol and CV risk

Lipoproteins are complex aggregates of lipids and proteins that circulate in the bloodstream. The predominant function of lipoproteins is to transport lipids, mainly cholesterol and triglycerides (TGs), through the bloodstream. Lipoproteins are categorised according to density as very-low-density lipoproteins (VLDL), low-density lipoproteins, intermediate-density lipoproteins (IDL), and high-density lipoproteins. Apolipoproteins (Apo A, B, C, D, and E) attached to lipoproteins assist in uptake and metabolism. An LDL has one ApoB per particle [6, 50].

LDL-C is closely and positively associated with atherosclerosis and major adverse CV event risk:

- Atherosclerosis of the coronary arteries is an important causative factor associated with myocardial infarction (MI) and angina pectoris
- Atherosclerosis of the arteries supplying the brain has been associated with thrombo-embolic strokes
- In the peripheral circulation, atherosclerosis can result in peripheral arterial disease (PAD).

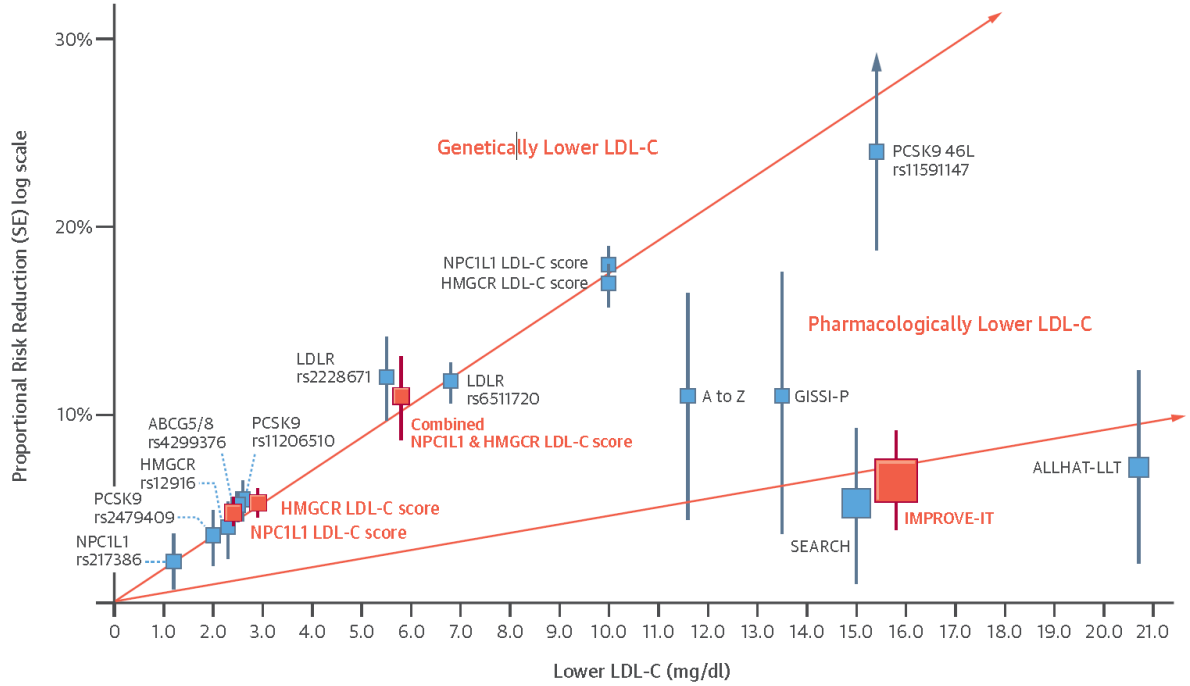
Atherosclerosis refers to the formation and hardening of fatty plaques (atheroma) on the inner surface of the arteries [5]. Once atherosclerotic disease is present, acute major adverse cardiovascular events can occur. Plaque build-up causes narrowing of the arteries (stenosis). Soft and stable plaques can progress to brittle and unstable lesions prone to rupture. Plaque rupture exposes thrombogenic components of the plaque to the circulatory system, activating the clotting cascade and promoting thrombus formation. Vessel occlusion from thrombus formation can cause ischaemic events [5,6].

Clinical [12-21], genetic [3, 10, 11], and epidemiologic studies [7-9] have demonstrated the link between elevated LDL-C, development of atherosclerosis, and increased risk for

major adverse CV events, and also between lower LDL-C and reduced risk for major adverse CV events. In addition to the extensive work in this area by the Cholesterol Treatment Trialists' (CTT) Collaboration, other large meta-analyses have been undertaken that demonstrate pharmacological lowering of LDL-C is associated with reduction in CV events [22,20,21,12]. The main body of evidence for this comes from statin trials, but some meta-analyses included non-statin therapies [22,21], and the recently published IMPROVE-IT trial of ezetimibe confirmed a link between LDL-C lowering and cardiovascular benefit [14,51].

Evidence that pharmacological lowering of LDL-C is associated with a reduction of CV events is consistent with evidence from genetic studies. Mutations (such as those described above in the PCSK9 gene) that result naturally in lower LDL-C are associated with reduced cardiovascular risk. Genetically lower LDL-C is however associated with a more substantial reduction in CV risk than pharmacologically lowered LDL-C. When statins lower LDL-C by 15%, they lower coronary events by 15%, compared to the ~47% reduction observed when LDL-C is reduced to a similar extent by a PCSK9 mutation, and when statins lower LDL by 30%, they lower coronary events by 30%, compared to the nearly 90% event reduction observed when LDL-C is lowered by 30% as a result of a PCSK9 mutation [4,3,52]. This is illustrated in Figure 2, which shows the relationship between a 1 mmol/L reduction in LDL-C and the corresponding decrease in CV event risk associated with pharmacologically lower LDL-C, and genetically lower LDL-C. This difference may be due to the fact that earlier LDL-C lowering is more effective in long-term prevention of atherosclerotic plaques, and that genetic changes impact over a lifetime [52].

Figure 2: Log-linear association between genetically and pharmacologically mediated lower LDL-C and risk of coronary heart disease (Figure from Ference et al 2015 [53])



Boxes represent proportional risk reduction (1–OR) of CHD for each exposure allele, genetic score, or randomised trial plotted against the absolute magnitude of lower LDL-C associated with that allele or genetic score; or the absolute difference in LDL-C between treatment groups for each trial. Vertical lines represent 1 SE above and below point estimate of proportional risk reduction. SNPs, genetic scores, and trials are plotted in order of increasing absolute magnitude of effect on lower LDL-C. The lines(which are forced to pass through the origin) represent the increase in proportional risk reduction of CHD per unit lower LDL-C. In the top line, the red boxes represent results of the 2x2 factorial mendelian randomisation study and the blue boxes represent results derived from CARDIoGRAMplusC4D consortia data. In the lower line, the red box represents the results of the IMPROVE-IT trial and the blue boxes represent the results of prior statin trials.

CHD, coronary heart disease; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SE, standard error; SNP, single-nucleotide polymorphism

Other lipid parameters measured in ODYSSEY are associated with CV disease risk [54]. Non-HDL-C comprises cholesterol carried by all potentially atherogenic lipoproteins. Analyses from intervention studies have shown that non-HDL-C changes and levels during treatment are strongly associated with risk for CHD and this parameter is now recommended by NICE as a key target to measure [55,56,57,58]. ApoB and Lp(a) are also associated with CV risk [59].

In conclusion, cholesterol levels are a key modifiable risk factor for CVD. Cardiovascular conditions such as heart disease and stroke are associated with serious acute symptoms, long-term disability, and substantial costs for patients and healthcare systems [60, 60, 61]. Office of National Statistics (ONS) estimates indicate

approximately 28% of all UK deaths are due to CVD [37]. In 2010, 180,000 people died from CVD – around 80,000 of these deaths were caused by coronary heart disease and 49,000 were caused by strokes [23] [CG181]. CVD has significant cost implications and was estimated to cost the NHS in England £6.8 billion, £4.3 billion of which was in secondary care. CVD accounted for ~10% of inpatient episodes in men and ~6% in women, with emergency admissions constituting 5.9% of the total spend [37].

3.2 Patient populations at elevated CV risk linked to LDL-C

3.2.1 HeFH

FH is an inherited autosomal dominant condition resulting in elevated serum LDL-C levels. It is caused by mutations in the genes encoding for the LDL-R, ApoB, or PCSK9. HoFH (where both copies of the allele are defective) is a rare and very severe condition, but HeFH is a relatively common genetic disorder with an estimated prevalence of 1 in 500 [26]. FH leads to elevated LDL-C levels from a young age. This results in the incidence of CV events in a younger patient population (compared to typical CVD populations). In patients with HeFH, lifelong exposure to elevated LDL-C levels results in a high cumulative risk of developing coronary heart disease and associated complications, with a greater than 50% risk of coronary heart disease in men by the age of 50 years and at least 30% in women by the age of 60 years if the disease is left untreated [62]. Notwithstanding the introduction of statins, HeFH patients still experience elevated cholesterol levels, and an increased risk of early mortality and CHD [26-28, 63]. In the study by Benn et al, the odds of coronary artery disease was ten times higher in HeFH patients compared to non-FH patients, even after treatment, and thirteen times higher in untreated patients [27].

3.2.2 Patients with high risk CVD

Another key patient group are patients who are recognised as being at very high cardiovascular risk due to the presence of existing CVD (e.g. previous MI, UA, coronary revascularisation, other forms of coronary heart disease, IS and PAD) [29]. Patients with established CVD are recognised as being at high risk of further events. An intensive approach to risk factor modification is recommended for all patients with established CVD [64]. The NICE lipid modification guideline CG181 recommends high

dose (80 mg) atorvastatin for all patients with existing CVD (secondary prevention patients).

Patients with recurrent (multiple) events or multiple types of event are an even higher risk group within the CVD population. A study of over 380,000 UK patients showed the risk of death was 1.5 times higher in patients with recurrent, versus first, MI [32]. In the PEGASUS-TIMI trial the event rate was approximately double (CV death, MI, stroke) in patients who had experienced two MIs as opposed to one MI [31]. Patients with multiple types of event i.e. polyvascular disease (vascular disease in more than one vascular bed, for example a cardiac event and a cerebrovascular event or with peripheral arterial disease) also have a higher event rate than patients with disease in only one vascular bed, as shown in extensive data from the REACH registry [33,34].

Patients in these high risk groups who have elevated cholesterol, despite existing treatment, are at continued high risk of further events.

3.3 Achievements with current LDL-C lowering therapy

The introduction of statins changed the landscape of LDL-C management and has contributed to substantial reductions in LDL-C and in cardiovascular risk [17,26]. Recently, the benefit of early, aggressive LDL-C lowering has been emphasised [52,65] as treatment of early-stage plaques may have a greater impact on long-term disease trajectories. This is supported by evidence such as long-term follow-up of the WOSCOPs trial (which was conducted in relatively young patients) showed a continued divergence of the curves beyond trial follow-up [66] and evidence from genetic studies which show a much steeper relationship between LDL-C and CV risk than that observed in intervention trials [4, 52].

3.4 Unmet need in LDL-C lowering with existing treatment

Statins and ezetimibe are currently the most common drugs used for achieving target LDL-c reductions in patients with hypercholesterolaemia [67,13, 68]. However, not all patients are able to achieve LDL-C goals on existing therapies for three key reasons: insufficient efficacy with current maximal dose therapy, insufficient titration or failure to adequately comply with therapy, and intolerance to one or more treatments. As a monoclonal antibody it is anticipated alirocumab will be initiated in specialised lipid clinics in secondary care. In this setting, the majority of patients will

be those who are unable to achieve goals on maximal dose current therapy or those who are truly statin intolerant.

Due to genetically high baseline levels of LDL-C, it is particularly difficult for HeFH patients to reach recommended goals. The UK National FH audit found that only 44% of adult patients achieved the NICE guideline goal of 50% reduction in LDL-C from the untreated level. Overall, treated LDL-C was reduced from a median of 6.1 mmol/L to 3.5 mmol/L (mean reduction 37%, median 33%, IQR 23% - 47%), which is still well above absolute target LDL-C levels recommended by guidelines [30]. The clinical consequences of not achieving targets are that even after treatment, the risk of CHD and early mortality in patients with HeFH is still elevated above the general population [26-28, 63].

In the European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice (EURIKA) study of more than 7600 European patients, more than 60% of high-risk patients were unable to adequately lower their LDL-C levels with statins or other currently approved lipid-lowering agents, and among very high-risk patients, the percentage increased to more than 80% [36] . Even within trials, a meta-analysis of several statin trials noted that more than 40% of patients did not reach treatment goals on statins [12]. Analysis of the UK THIN database shows significant proportions of patients with LDL-C levels greater than recommended goals despite existing therapy (Table 100).

Patients at high cardiovascular risk who are completely intolerant to statins are of particular concern because they have very limited treatment options. Although statins have proved relatively free of side effects in randomised clinical trials, in clinical practice for a minority, intolerance to statins due to myotoxicity has been raised as a concern [69,70]. The clinical spectrum of statin-induced myotoxicity varies from asymptomatic elevations of creatine kinase (CK) without muscle pain, to muscle pain or weakness with raised CK levels, myositis with biopsy-proven muscle inflammation, and, finally, rhabdomyolysis with muscle symptoms, high CK, and potential for acute kidney injury[70].

The real-world incidence of true statin intolerance due to non-severe side effects is estimated to be only 5–10% [71, 72]; the incidence of more severe side effects such as

rhabdomyolysis, is much rarer. In the individual case, statin intolerance is defined as adverse symptoms, signs, or laboratory abnormalities, and attributed by the patient (or provider) to the statin. In most cases, these abnormalities are perceived by the patient to interfere unacceptably with activities of daily living (such as sleep, work/ housework, or leisure-time activity), may lead to a decision to discontinue or reduce statin therapy [73] .

The 2014 NICE lipid modification guideline recommends that patients with intolerance to high intensity statins should be treated with the maximum tolerated dose in the same intensity group or switched to a lower intensity group.[23] High intensity statins are classified as those that result in an at least 40% reduction in LDL-C, including atorvastatin 20 – 80 mg, rosuvastatin 10 – 40 mg, and simvastatin 80 mg.The guideline recommends that specialist advice be sought for patients who are intolerant to 3 different statins [23,64].

Guidelines indicate that for those with complete intolerance to statins, alternative agents including ezetimibe should be considered. However, they also recognise that newer, non-statin, approaches to lower LDL-C, for example, PCSK9 inhibitors, are in development [64].

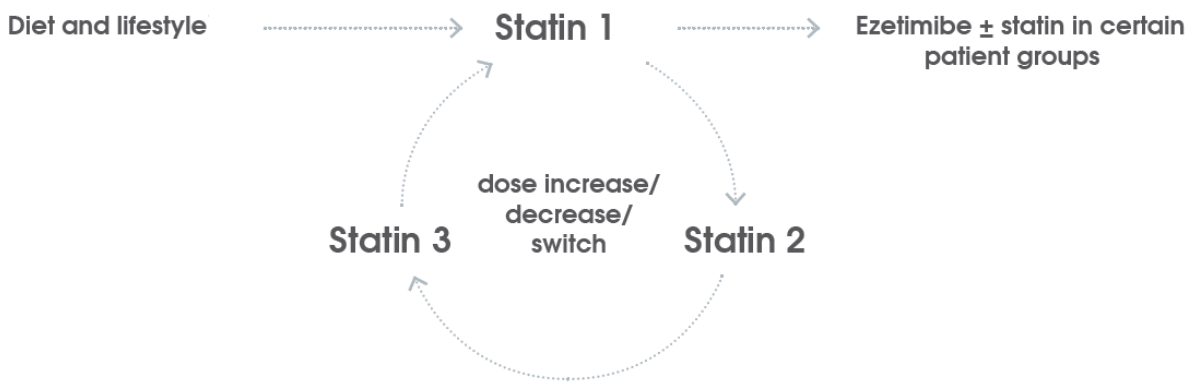
3.5 Current Guidelines:

3.5.1 NICE Guidelines

CG71 Identification and management of familial hypercholesterolaemia (published August 2008; review decision date November 2014 – not updated) [25].

CG181 Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (published July 2014) [23] (c.f. Figure 3).

Figure 3 Schematic of current NICE recommended treatment options to lower LDL-C



3.5.2 NICE Technology Appraisals

TA132 Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (published November 2007) [24] (c.f. Figure 3).

- After first line treatment with statin therapy, ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who are intolerant to statin therapy (see also NICE Familial Hypercholesterolaemia Pathway, NICE Cardiovascular Disease Prevention Pathway)[40, 41].

- Ezetimibe, coadministered with initial statin therapy, is also recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who have been initiated on statin therapy when serum total or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (see also NICE Familial Hypercholesterolaemia Pathway)[41].

3.5.3 Other Guidance

NICE Key Therapeutic Topics: Lipid Modifying Drugs [74]

Joint British Societies' consensus recommendations for the prevention of cardiovascular disease [64]

3.5.4 European Guidelines

ESC/EAS Guidelines for the management of dyslipidaemias (published 2011) [29]

3.5.5 Summary Recommendations of Guidelines on Treatment Goals

Current NICE guidelines [23] recommend measurement of total cholesterol, HDL cholesterol and non‑HDL-C at 3 months in all patients who have been started on high‑intensity statin treatment. CG181 recommends an aim of a 40% or greater reduction in non‑HDL-C. For HeFH patients NICE Clinical Guideline CG71 recommends a goal of a 50% or greater reduction in LDL-C from baseline. CG181 recommends percentage reductions to aim for but not absolute treatment goals, stating that “the GDG did not therefore set a target for treatment as people taking atorvastatin 80 mg are on the highest available dose” (high dose atorvastatin was recommended for all high risk patients).

Guidance from the ESC/EAS and JBS recommend percentage reductions in LDL, however, they have also considered absolute treatment values [29 75]. The recent JBS3 guidelines recommend statins should be prescribed with a ‘lower is better’ approach for secondary prevention patients at high cardiovascular risk (e.g. to achieve values of <1.8 mmol/L for LDL-C for patients with established CVD or post-MI) [64]. In clinical practice, while guidelines on percentage reductions to aim for are taken into account, absolute LDL-C levels are also considered, because if patients have elevated LDL-C despite large percentage reductions, clinically they will still be considered as being at risk due to elevated LDL-C.

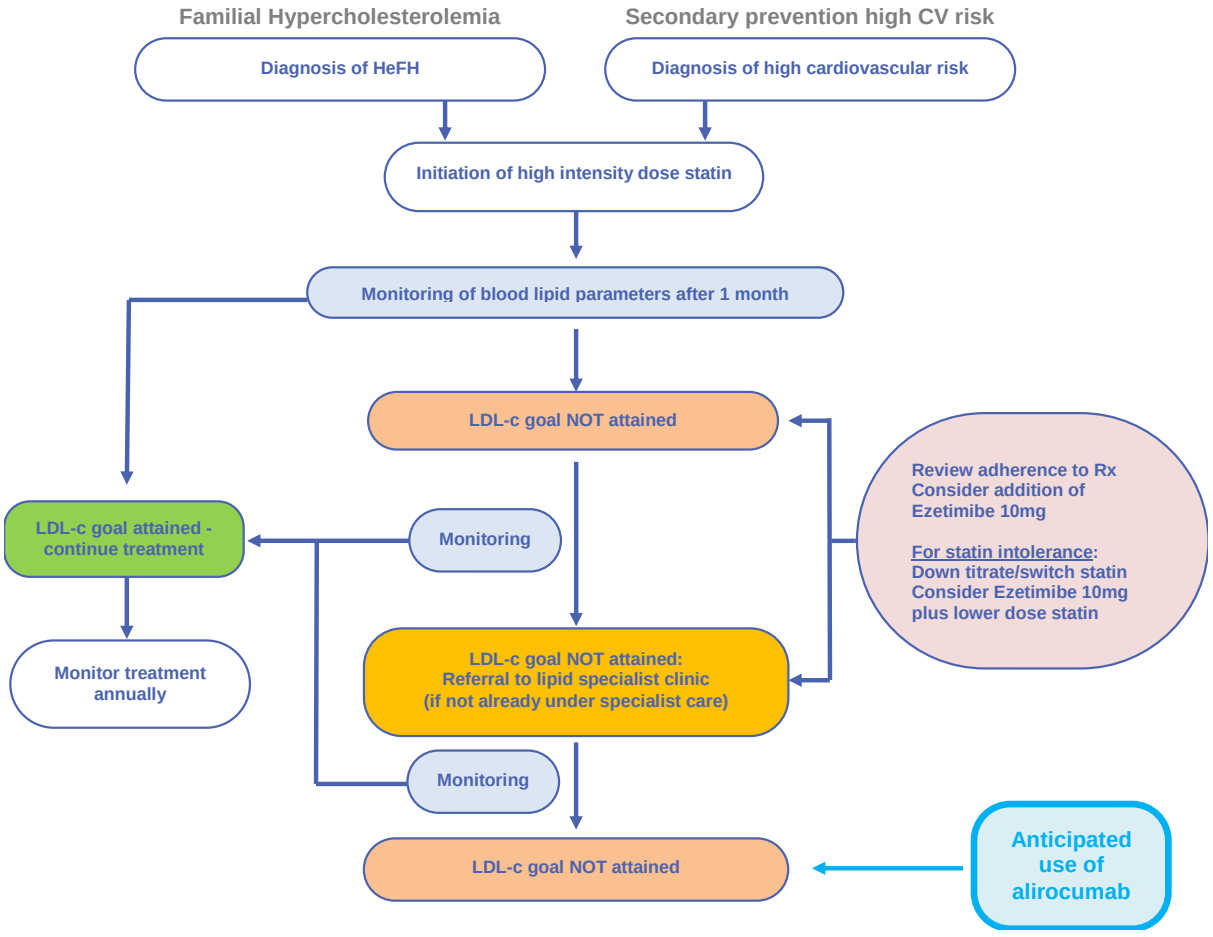
A recent UK publication emphasised the benefit of taking into account absolute LDL-C levels as well as cardiovascular risk in treatment decisions [76]. This approach, taking into account both absolute LDL-C and CV risk, is likely to be increasingly important with the advent of new lipid-lowering therapies such as the PCSK9 monoclonal antibodies which can effect a substantial lowering in LDL-C on top of currently used therapies.

3.6 Anticipated place of therapy of alirocumab in UK practice

It is anticipated that alirocumab will align to the existing 'Cardiovascular Disease Prevention' and the 'Familial Hypercholesterolaemia' NICE pathways[40, 41].

Figure 4 summarises current clinical practice in England and Wales and the anticipated place of alirocumab within this pathway. This was developed based on current clinical pathways, with input from a UK lipidologist.

Figure 4 Anticipated place of therapy of alirocumab in clinical practice in England and Wales



It is anticipated that alirocumab will be initiated as an adjunctive therapy in patients who have reached their maximal tolerated dosage of statins and/ or with other LMTs and are still far from treatment goals.

TA132 [24] recommends the use of ezetimibe in addition to statins in patients who are not adequately controlled on a statin or are intolerant to statins. It is anticipated that

alirocumab will be used as an add-on to this combination in patients who are unable to reach treatment goals on existing management with statins plus ezetimibe. This reflects usage in ODYSSEY where ~50% of patients in the FH trials were already receiving statins plus ezetimibe.

However, ezetimibe usage is not universal, with wide variation in regional formulary access and in uptake. IMS Sales data indicates a reduction in units of ezetimibe prescribed in the UK from approximately 3.5M in 2011 to approximately 2.5M in 2014 [77]. The Health and Social Care Information Centre prescribing comparator indicated that for the quarter April to June 2014 there was a 5.9 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.91% to 5.38% [74]. Because ezetimibe usage in the NHS is highly varied we consider that alirocumab may also be used as an add-on therapy to maximal tolerated dose statins (alone, not in combination with ezetimibe).

In addition, it is anticipated that patients with very high LDL-C levels would require an LDL-C reduction in excess of what is achievable with ezetimibe. NHS choices recommends an absolute LDL level of 2 mmol/L or less for those at high risk [78], similar to the 1.81 mmol/L target in ESC guidelines . For high risk patients with a high LDL-C level despite statin therapy – eg ≥2.5 mmol/L, addition of ezetimibe treatment will not achieve these desired LDL-C levels (assuming approximate 20% reductions in LDL-C from baseline with ezetimibe treatment, in line with what was observed in ezetimibe clinical trials). This may explain limited NHS usage of ezetimibe despite a NICE recommendation. Treatment for patients such as these with alirocumab, would, however, allow recommended levels to be achieved in combination with statins alone.

Patients who are completely unable to tolerate statins may be managed with ezetimibe alone or with other LMTs without ezetimibe. They therefore have limited treatment options to substantively lower LDL-C.

It is not anticipated that the use of this technology is likely to raise any equality issues.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Search Strategy

A systematic literature review (SLR) identified randomised-controlled trials (RCTs) reporting efficacy and/or safety outcomes for pharmacotherapies for the treatment of hypercholesterolaemia in adults (>18 years of age) at high CVD risk:

- who are unable to achieve desired LDL-C levels, on a statin, or a statin in combination with non-statin LMT (i.e. niacin, fibrate, bile-acid sequestrant); or
- for whom statins are not appropriate or are not tolerated, and who are unable to achieve LDL-C levels on non-statin LMT (i.e. niacin, fibrate, bile-acid sequestrant).

The search was designed to identify RCTs published from 1980 to current, including alirocumab, evolocumab, other PCSK9 inhibitors and ezetimibe. The search strategy was initially implemented on January 14th 2015 with an update run on May 15th 2015. The SLR was conducted consistent with the population, intervention, comparison, outcomes (PICOS) framework, as defined in The Cochrane Collaboration Handbook [79].

4.1.2 Data Sources

4.1.2.1 Medical Literature Databases

To identify trials from the peer-reviewed literature, the following databases were searched: MEDLINE®; EMBASE®; CENTRAL®

Search strategies for MEDLINE® and EMBASE® were implemented using the OVID portal. CENTRAL® was searched directly.

Publications presenting primary data were retained, and reference lists of publications reporting secondary data were reviewed to identify additional studies.

4.1.2.2 Conference Abstracts/Posters

Proceedings from the following five conferences (for 2013 and 2014) were searched: American College of Cardiology; European Society of Cardiology; American Heart Association; European Atherosclerosis society; National Lipid Association.

Details of the search strategies are provided in Appendix 2.1

4.1.3 Study Selection

Articles suitable for inclusion in the review were selected using strict predefined criteria, based on the PICOS approach (Table 6) [79].

Two reviewers independently determined whether studies met the inclusion criteria. Reasons for rejections and exclusions of studies were recorded. Discrepancies between reviewers were resolved by consensus and a third reviewer would adjudicate unresolved disputes; the judgment of the third reviewer was considered final.

To gain insight into the external and internal validity of study design that may affect interpretation of results, the quality of studies identified in the literature searches was considered using the Cochrane Collaboration's tool for assessing risk of bias (Appendix 2.2) as recommended by NICE.[79]

The study selection process was documented in a flow diagram, as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 5) [80].

Table 6: Inclusion criteria - PICOS framework

Criteria	Efficacy/safety evidence	
	Population 1	Population 2
Population	Adults (>18 years of age) at high CVD* risk who are unable to achieve desired LDL-C levels, on a statin, or a statin in combination with a non-statin LMT (i.e. niacin, fibrate, bile acid sequestrant)	Adults (>18 years of age) at high CVD* risk, for whom statins are not appropriate or are not tolerated and who are unable to achieve LDL-C levels on non-statin LMT (i.e. niacin, fibrate, bile acid sequestrant)
Interventions	<u>Add-on therapy:</u> • Alirocumab • Evolocumab • Other PCSK9 inhibitors • Ezetimibe	• Ezetimibe <u>PCSK9 inhibitors</u> • Alirocumab • Evolocumab • Other PCSK9 inhibitors
Comparators	• Any active agent	• Any active agent

Criteria	Efficacy/safety evidence	
	Population 1	Population 2
	• Placebo (with background therapy)	• Placebo (with background therapy)
Outcomes	<u>Efficacy outcomes</u> • Definition of target LDL-C level • Number and proportion (%) of patients reaching target LDL-C • Mean change (SE) from baseline – absolute and % for the following: – LDL-C – HDL-C – Non-HDL-C – Lipoprotein(a) – Triglycerides – Apo A1 – Apo B • Non-fatal CV events: – MI – Unstable angina with hospitalisation – Coronary revascularisation – Ischaemic stroke • All-cause mortality • CV-related mortality <u>Safety outcomes – number and proportion</u> • Death related to the intervention • Discontinuation due to an AE • Any SAE • TEAEs – Myalgias (without CK elevation) – CK elevation – Myositis – Rhabdomyolysis – Transaminase elevation (ALT or AST) – New onset of diabetes – Cancer incidence – Neurocognitive disorder – Haemorrhagic stroke – Injection site reaction	
Study design	• Randomised active-controlled trials (defined as trials in which an active intervention is included in the control arm of the trial, e.g. control arm is statin plus placebo) • Outcome measurements at ≥10 weeks	
Time horizon	• 1980 to date of executing search strategy (Jan 14th, 2015 and updated May 15th, 2015)	

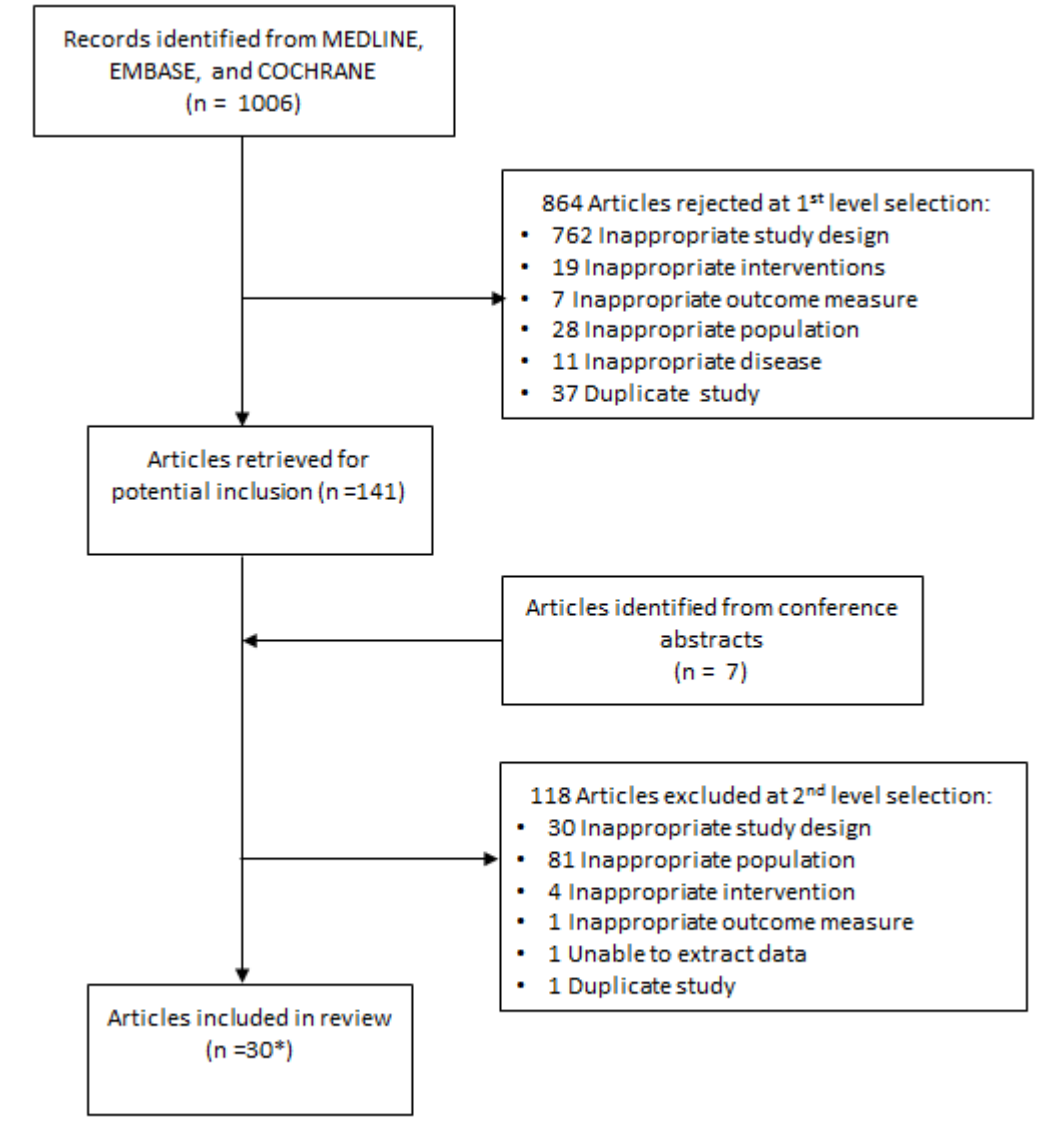
AE=adverse event; ACS=Acute coronary syndrome; ALT=alanine aminotransferase; Apo = apolipoprotein; AST=aspartate transaminase; CHD=Coronary heart disease; CK=creatinine kinase; CVD= Cardiovascular disease; FH=Familial hypercholesterolaemia; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low density lipoprotein cholesterol; LMTs=Lipid-lowering therapies; MI=Myocardial infarction; PICOS= population, intervention, comparison, outcomes, and study design; SAE = serious adverse event; TEAEs=Treatment emergent adverse events

*Where high CVD risk is defined as patients with:

- FH
- Recent ACS (i.e. MI or unstable angina with inpatient hospitalisation during past 0-12 months)
- CHD (i.e. patients with a history of ACS, coronary revascularisation or non-invasive diagnosis of CHD)
- History of ischaemic stroke, PAD, diabetes; or
- As defined by study authors

The combined literature search of the electronic databases identified 1006 articles for potential inclusion in the review. Among those, 864 articles were excluded during the first-level selection and an additional 118 were excluded during the second-level study selection after 7 articles were added from a review of conference abstracts. Thus, a total of 30 articles were included in the review (Figure 5).

Figure 5 Flow diagram of SLR study selection



*Includes two articles which each describes two studies, for a total of 32studies.

In summary, across the original and updated SLR:

- Ten of the included trials were conducted among patients with familial hypercholesterolaemia (FH). Among these there were:

    - Five alirocumab studies (ODYSSEY HIGH FH, FH I and II, LONG TERM,[81]
    - Three evolocumab studies (RUTHERFORD, RUTHERFORD-2, TESLA Part B)
    - Two ezetimibe studies
- Among the 22 studies in the non-FH populations:
    - Five were alirocumab studies (ODYSSEY COMBO I and II, OPTIONS I and II, [82]
    - Three were evolocumab studies (YUKAWA, YUKAWA-II, LAPLACE-TIMI-57 High Risk Subgroup)
    - 14 were ezetimibe studies - of which two were compared to a statin up-titration arm.

A list of included and excluded studies can be found in Appendix 2.3

None of the included studies were conducted in patients who were intolerant to statins or for whom statins are not appropriate (defined as population 2 in the PICOS framework). Several alirocumab and evolocumab studies were identified in this population, but included patients with moderate CV risk as well as high CV risk patients (ODYSSEY ALTERNATIVE, GAUSS, GAUSS-2) and hence were not included in the review[83, 84].

All studies included in this review included only patients at high CV risk, which was specified in the PICOS, in line with the decision problem. As noted above however, some PCSK9 trials were conducted in patient populations that also included individuals at moderate CVD risk, and thesewere excluded from the review. In order to resolve this and to ensure all relevant PCSK9 inhibitor data was captured, a separate review was undertaken of PCSK9 inhibitor trials, in which the population of interest included individuals at moderate or high CVD risk.

To identify relevant randomised controlled trials (RCTs), a search strategy including key words and terms for the interventions and population of interest was developed.

The search strategy was implemented in MEDLINE®, EMBASE®, and Cochrane CENTRAL, searching from database inception to May 2015. Abstracts from five conference proceedings were also searched. All searches were limited to English-publications, humans and RCTs. Articles suitable for inclusion in the review were selected using strict predefined inclusion/exclusion criteria, based on the population, intervention, comparators, outcomes and study design (PICOS) (Table 7). Data extraction was conducted by two independent reviewers. Study quality was also assessed using Cochrane risk of bias tool (Appendix 2.2). Details of the search strategies are provided in Appendix 2.4

Table 7 Modified SLR Update Inclusion criteria - PICOS framework

Criteria	Eligibility	
	Population 1	Population 2
Population	Adults (>18 years of age) at moderate or high CVD* risk who are unable to achieve desired LDL-C levels, on a statin, or a statin in combination with non-statin LMT (i.e. niacin fibrate, bile acid sequestrant)	Adults (>18 years of age) at moderate or high CVD* risk, for whom statins are not appropriate or are not tolerated (complete intolerance), and who are unable to achieve LDL-C levels on non-statin LMT (i.e. niacin, fibrate, bile acid sequestrant)
	Where high risk is defined as patients with: • FH • Recent ACS (i.e. MI or unstable angina with inpatient hospitalisation during the past 0–12 months) • CHD (i.e. patients with a history of ACS or non-invasive diagnosis of CHD) • History of ischaemic stroke, PAD, diabetes or as defined by study authors And moderate risk is defined as patients with: • LDL-C ≥75 mg/dL	
Interventions/ comparators	• Evolocumab • Alirocumab	
Outcomes	**Efficacy** • Proportion (%) of patients reaching target LDL-C • Mean % change in LDL-C from baseline • Mean % change in HDL-C from baseline • Mean % change in non-HDL-C from baseline • Mean % change in total cholesterol from baseline • Mean % change in lipoprotein(a) from baseline • Mean % change in triglycerides from baseline • Mean % change in Apo A1 from baseline • Mean % change in Apo B from baseline • Non-fatal CV events: – MI – Unstable angina with hospitalisation – Coronary revascularisation – Ischaemic stroke • All-cause mortality	

Criteria	Eligibility	
	Population 1	Population 2
	• CV-related mortality **Safety** • Death related to the intervention • Discontinuation due to an AE • Any SAE • TEAEs – Myalgias (without CK elevation) – CK elevation – Myositis – Rhabdomyolysis – Transaminase elevation (ALT or AST) – New onset of diabetes – Cancer incidence – Neurocognitive disorder – Haemorrhagic stroke – Injection site reaction	
Study design	RCTs published between 1980 and date of executing search strategy, (May 15th 2015)	

AE=adverse event; ACS=Acute coronary syndrome; ALT=alanine aminotransferase; Apo = apolipoprotein; AST=aspartate transaminase; CHD=Coronary heart disease; CK=creatinine kinase; CVD= Cardiovascular disease; FH=Familial hypercholesterolaemia; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low density lipoprotein cholesterol; LMTs=Lipid-lowering therapies; MI=Myocardial infarction; PICOS= population, intervention, comparison, outcomes, and study design; SAE = serious adverse event; TEAEs=Treatment emergent adverse events

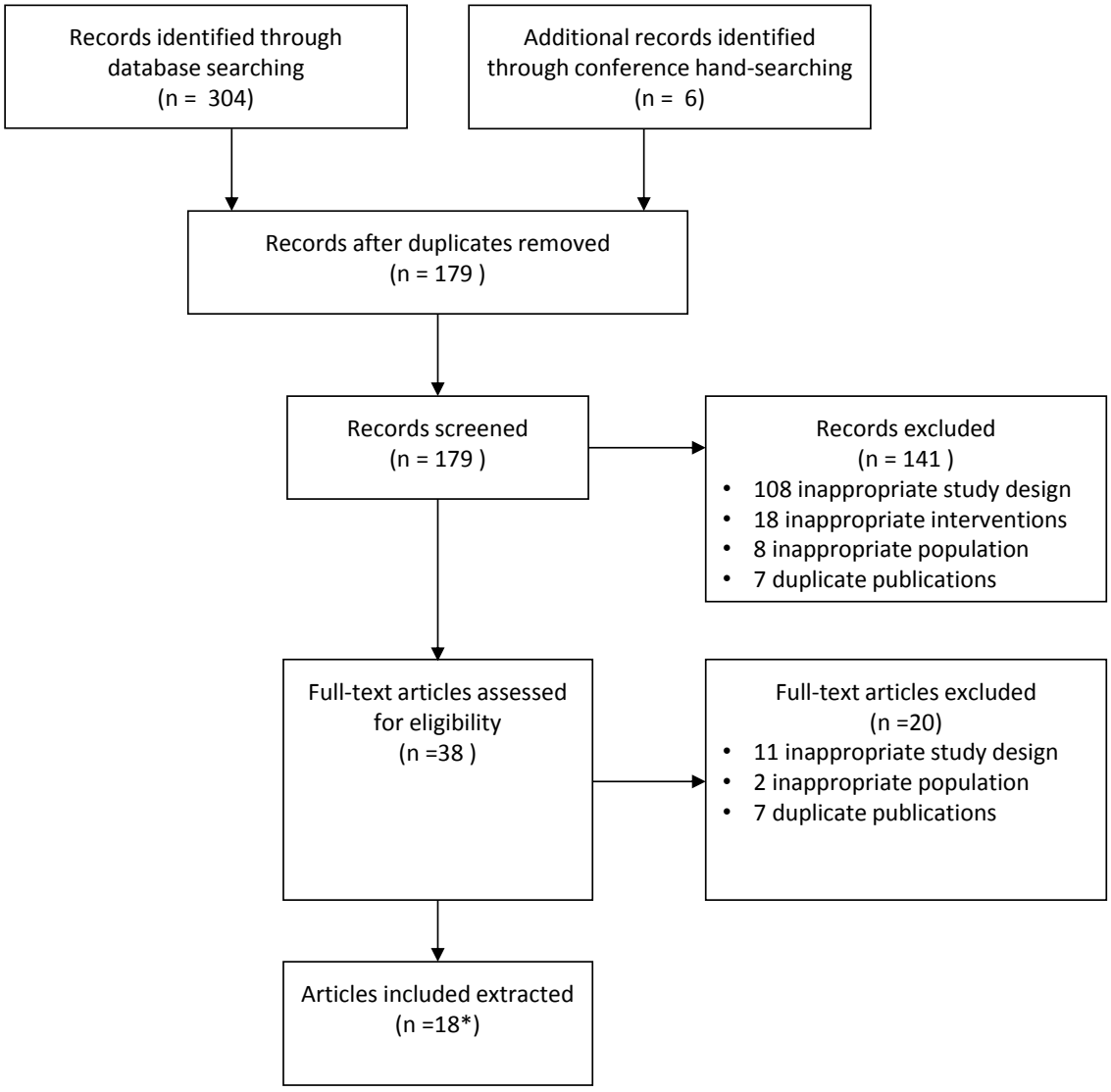
*Where high CVD risk is defined as patients with:

- FH
- Recent ACS (i.e. MI or unstable angina with inpatient hospitalisation during past 0-12 months)
- CHD (i.e. patients with a history of ACS, coronary revascularisation or non-invasive diagnosis of CHD)
- History of ischaemic stroke, PAD, diabetes; or
- As defined by study authors

The literature search of the electronic databases identified 304 articles for potential inclusion in the review. After de-duplication across databases, 173 articles remained, and an additional 6 abstracts were added based on hand searching of conference proceedings. Among those 179 publications, 141 were excluded during the first-level selection and an additional 20 were excluded during the second-level study selection. Thus, a total of 18 publications describing 20 studies were included in the review (

Figure **6**).

Figure 6 Flow diagram of Modified SLR study selection



*Includes two articles which each respectively describe two studies, for a total of 20 studies.

Overall, eleven alirocumab trials (ODYSSEY HIGH FH, FH I and II, LONG TERM, COMBO I and II, OPTIONS I and II, MONO and ALTERNATIVE, Teramoto et al. 2014) and nine evolocumab trials (YUKAWA II, RUTHERFORD-2, TESLA Part B, DESCARTES, LAPLACE-TIMI-57, LAPLACE-2, GAUSS, GAUSS-2, OSLER) were identified. Some systematic differences were observed across alirocumab and evolocumab trials, respectively: with the exception of two 52-week studies, the majority of evolocumab studies reported results at 12 weeks, while 10 of the 11 alirocumab trials (including all Phase III alirocumab trials) reported results at 24

weeks. The majority of alirocumab trials included a trial population of individuals at high CVD risk on a maximum tolerated dose of statins, while evolocumab trials tended to include moderate CVD risk patients and/or individuals with the potential for statin up-titration. No studies included a direct comparison of alirocumab vs. evolocumab.

A list of included and excluded studies can be found in Appendix 2.5.

4.2 List of relevant randomised controlled trials

The ODYSSEY programme includes comparisons against all relevant comparators and in patient populations/ lines of therapy in the decision problem (Table 4). Table 8 lists the RCTs in the ODYSSEY programme. A list of RCTs identified in the SLR which did not evaluate the use of alirocumab and therefore do not provide data relevant to the decision problem is included in Appendix 2.3 and 2.5.

Table 8 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref. and Notes
Phase II studies				
DFI11565	Alirocumab	Placebo	Patients with hypercholesterolaemia and LDL-C ≥2.59 mmol/L treated with a stable dose of atorvastatin (10, 20, or 40 mg)	McKenney et al. [82]
CL-1003	Alirocumab	Placebo	Patients with HeFH on a stable daily statin dose (with or without ezetimibe) and with LDL-C levels ≥2.59 mmol/L	Stein et al. [81]
DFI11566	Alirocumab + Atorvastatin	Placebo	Patients with hypercholesterolaemia and LDL-C ≥ 2.59 mmol/L treated with a stable dose of atorvastatin (10 mg)	Roth et al [85]
CL-1018	Alirocumab	Placebo	Patients with ADH: GOFm in 1 or both alleles of PCSK9 gene or LOFm in 1 or more alleles of the ApoB gene	
DFI12361	Alirocumab	Placebo	Patients with hypercholesterolaemia (non-FH) and LDL-C ≥2.59 mmol/L treated with a stable dose of atorvastatin (5 to 20 mg) for at least 6 weeks	
Phase III studies				
EFC12492 (FH I)	Alirocumab	Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs	Kastelein et al [86]
CL-1112 (FH II)	Alirocumab	Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs	Kastelein et al [86]
EFC12732 (HIGH FH)	Alirocumab	Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs and with LDL-C ≥4.14 mmol/L	
EFC11568 (COMBO I)	Alirocumab	Placebo	Patients at high CV risk with hypercholesterolaemia not adequately controlled with statin ± other LMTs	Kereiakes et al [87]
EFC11569 (COMBO II)	Alirocumab	Ezetimibe	Patients at high CV risk with hypercholesterolaemia not adequately controlled with statin therapy	Cannon et al. [88]
LTS11717 (LONG TERM)	Alirocumab	Placebo	Patients with HeFH or non-FH at high CV risk not adequately controlled with a statin ± other LMTs	Robinson et al [38]

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref. and Notes
CL-1110 (OPTIONS I)	Alirocumab + atorvastatin	Atorvastatin+Ezetimibe; Atorvastatin (up-titrated); Rosuvastatin (switch)	Patients at high CV risk with non-FH or HeFH not adequately controlled with atorvastatin (20 mg or 40 mg) ± other LMT excluding ezetimibe	Bays et al [89]
CL-1118 (OPTIONS II)	Rosuvastatin+ alirocumab	Rosuvastatin+ Ezetimibe; Rosuvastatin (up-titrated)	Patients at high CV risk with non-FH or HeFH not adequately controlled with rosuvastatin (10 mg or 20 mg) ± other LMT excluding ezetimibe	
CL-1119 (ALTERNATIVE)	Alirocumab	Ezetimibe, Atorvastatin	Patients with primary hypercholesterolaemia and moderate, high, or very high CV risk who are intolerant to statins	Moriarty et al [90]
EFC11716 (MONO)	Alirocumab	Ezetimibe	Patients at moderate CV risk with LDL-C ≥ 2.59 mmol/L and ≤4.91 mmol/L	Roth et al [91]
Phase III studies not submitted to support marketing authorisation				
CL-1308 (CHOICE I)	Alirocumab	Placebo	Patients with hypercholesterolaemia inadequately controlled and at moderate, high, or very high CVD risk	Not submitted to support marketing authorisation
EFC13786 (CHOICE II)	Alirocumab	Placebo	Patients with primary hypercholesterolaemia not treated with a statin and who are at moderate, high, or very high CVD risk	Not submitted to support marketing authorisation
EFC13672	Alirocumab	Placebo	Japanese patients with heterozygous familial hypercholesterolaemia or non-familial hypercholesterolaemia who are not adequately controlled with statin ± other LMTs	Not submitted to support marketing authorisation for the European Centralised procedure

Apo, apolipoprotein; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomised controlled trial

The primary objective of the CHOICE I (CL-1308) and CHOICE II (EFC13786) trials was to demonstrate the efficacy and safety of different dosing regimens of alirocumab. They have been excluded from further discussion as they involve investigation of an alternative dosing regimen that was not submitted to support the marketing authorisation and therefore will not be reflected in the SmPC.

Note: Details of Phase II trials have been included in order to provide a comprehensive review and due to their inclusion in pooled safety data presented in Section 4.12. However, they are not described in any detail.

4.3 Summary of methodology of the relevant randomised controlled trials

Key Points

- **The ODYSSEY programme is an extensive series of Phase III clinical trials including more than 5000 patients in the regulatory dossier and 23,500 patients overall and:**
    - Contains the largest double-blind study of a PCSK9 inhibitor (LONG-TERM) with current analysis providing 2,330 patient-years of double-blind patient exposure to alirocumab 150 mg Q2W
    - Contains the largest HeFH programme for a PCSK9 inhibitor with 3 dedicated studies (FHI, FHII, HIGH FH) and >1300 patients with HeFH across the programme
- **The primary endpoint of most studies was the reduction of LDL-C at Week 24 (the overall primary objective of LONG-TERM was the evaluation of long-term safety and tolerability of alirocumab)**
- **The aim of the programme was to demonstrate the superiority of alirocumab versus placebo or active control**
- **The programme was designed to address the needs of HeFH and high/very high CV risk patients (with and without statin intolerance) who are unable to achieve sufficient reductions in their LDL–C levels with existing therapies**
- **Eight of the Phase III studies evaluated up-titration of alirocumab dose**
- **HRQoL was assessed in 7 trials using EQ-5D**

4.3.1 ODYSSEY Phase III Clinical Trial Programme

4.3.1.1 Background and Rationale

The alirocumab Phase III clinical programme (ODYSSEY) is a series of randomised, double-blind, parallel-group, multicentre, multinational trials designed to demonstrate

the efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolaemia (HeFH) and non-familial hypercholesterolaemia, including patients with mixed dyslipidaemia (See Section 4.2, Table 8). The clinical programme was rigorously designed in accordance with GCP and appropriate international recommendations for standard of medical care in hypercholesterolaemia, as well as with the CHMP Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders (CPMP/EWP/3020/03). It is also in line with the updated Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013).

4.3.1.2 Clinical Objectives

The primary endpoint of most studies was the reduction of LDL-C at Week 24, regardless of their overall duration.The overall primary objective of LONG TERM was the evaluation of long-term safety and tolerability of alirocumab, with reduction in LDL-C at week 24 the primary efficacy endpoint.

The proportion of patients reaching certain predefined LDL-C targets was evaluated as a secondary objective. The effect of alirocumab on LDL-C at other time-points (e.g., Weeks 12 and 52) and on other lipid parameters, such as ApoB, non-HDL-C, TC, Lp(a), HDL-C, TGs, and ApoA1, were also evaluated as secondary endpoints.

In all Phase III studies except OPTIONS I, OPTIONS II and ALTERNATIVE, quality of life was assessed using the EQ-5D-3L [92].

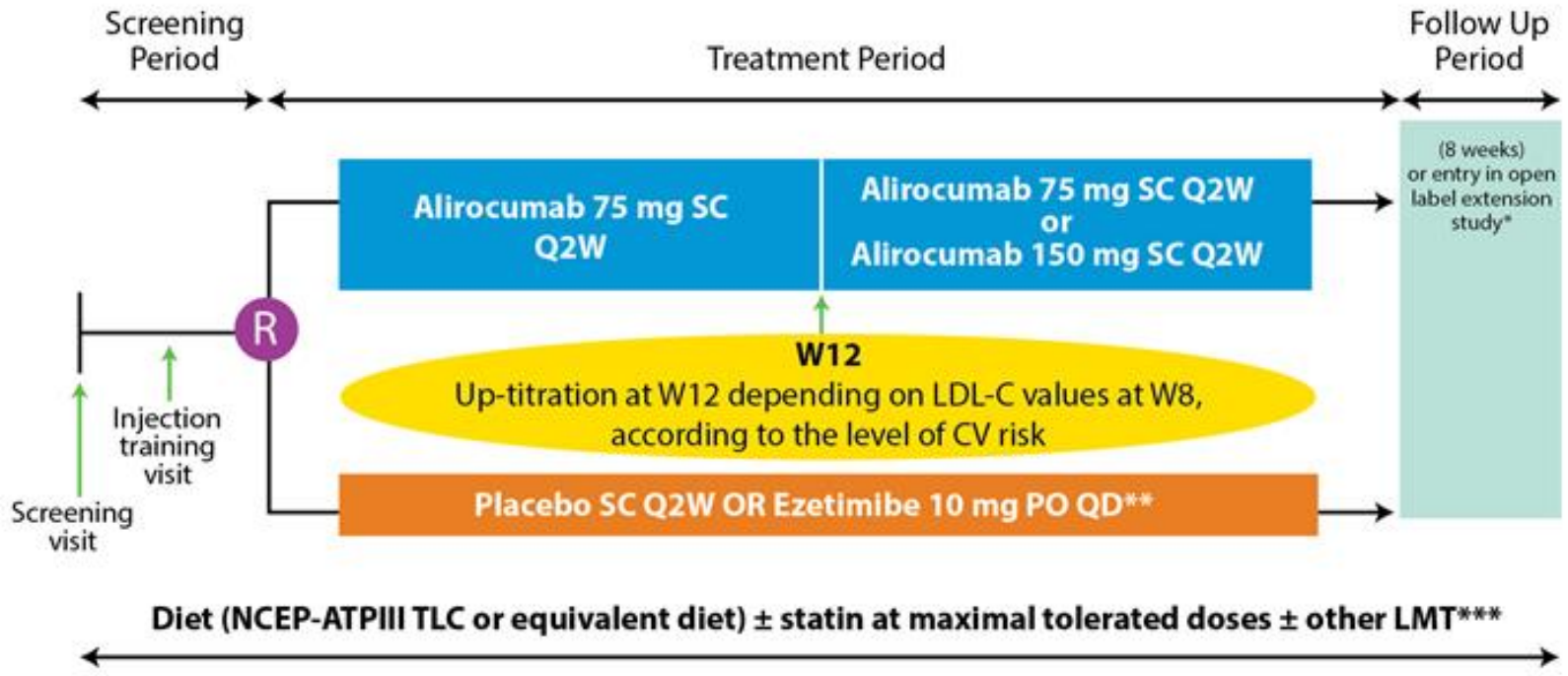
All Phase III studies were double-blind, parallel-group, controlled, randomised studies. A double-dummy design was used in studies evaluating alirocumab versus an active comparator. Studies usually included a screening period, a double-blind treatment period, and a follow-up period. Patients were asked to follow a stable diet (National Cholesterol Education Programme – Adult Treatment Panel III [93 NCEP-ATP III] Therapeutic Lifestyle Changes [TLC] diet or equivalent diet) throughout the entire duration of the studies.

Alirocumab was evaluated as monotherapy (or add-on to non-statin LMT) in ALTERNATIVE and MONO. In the other studies alirocumab was evaluated as an add-on to statins with or without other LMT. The aim of the programme was to

demonstrate the superiority of alirocumab versus placebo and versus ezetimibe. Placebo was the comparator in five studies (FH I, FH II, HIGH FH, COMBO I, and LONG TERM). The choice of placebo as control was considered appropriate in these studies as patients were already receiving high-intensity, LMT, including a statin. It provides a direct assessment of the add-on efficacy and safety of alirocumab. Ezetimibe 10 mg once per day by mouth was the main active comparator in the other five studies (COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO). Ezetimibe was selected because it is most often combined with statins, when LDL-C targets are not reached on statin alone, and as an alternative to statins in statin intolerant patients. In the OPTIONS studies, an additional comparison with statin intensification was also included.

Eight of the Phase III studies evaluated a dose of 75 mg of alirocumab every two weeks with up-titration to 150 mg at Week 12, if the pre-defined LDL-C target was not achieved at Week 8, for a total duration of either 6, 12, 18, or 24 months (Figure 7).

Figure 7 Phase III study design – with up-titration (FH I, FH II, COMBO I, COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO)



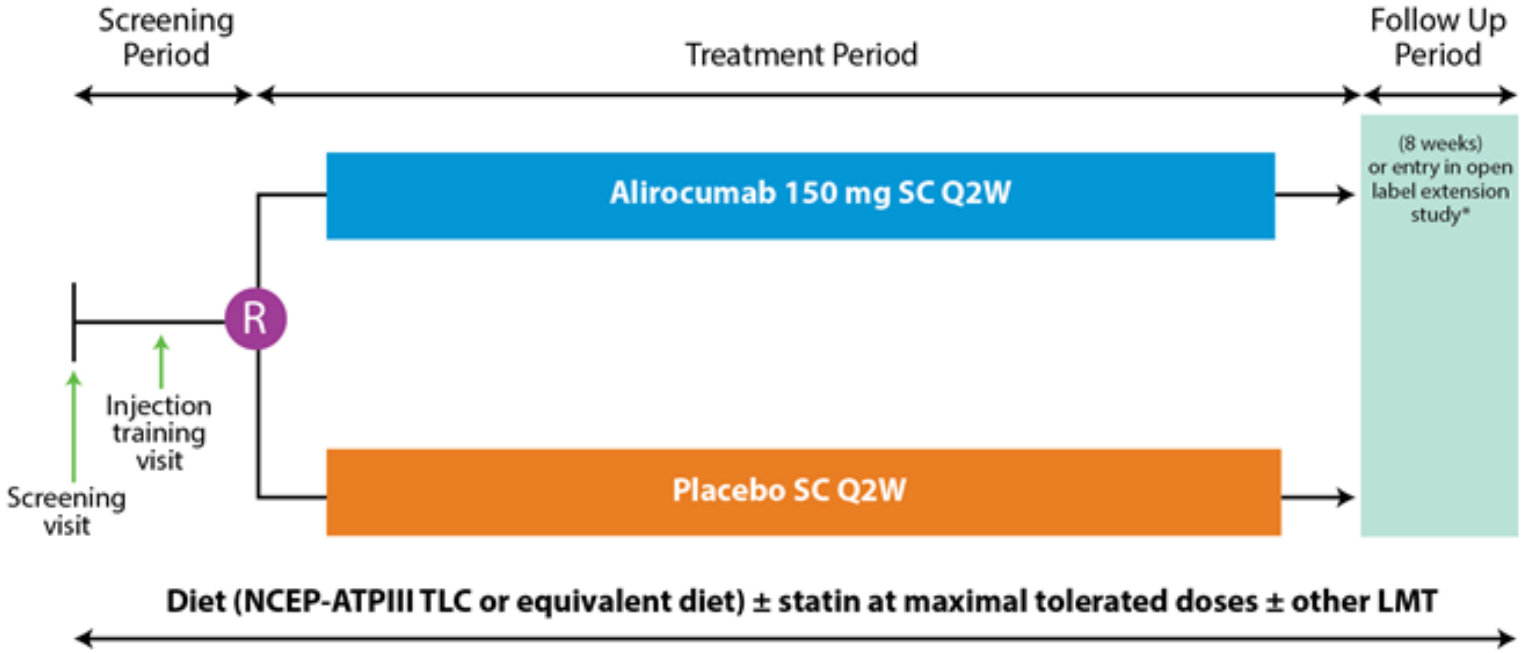
CV=cardiovascular; FU=follow-up; LDL-C=low-density lipoprotein-cholesterol; LMT=lipid-modifying therapy; NCEP-ATP III TLC=National Cholesterol Education Program - Adult Treatment Panel III Therapeutic Lifestyle Changes; PO=orally; QD=once daily; Q2W=every 2 weeks; R=randomization; SC=subcutaneous; W=week

* No follow-up period for patients entering in open-label extension study.

** For OPTIONS I, OPTIONS II, and ALTERNATIVE studies, an additional comparison was performed using statins.

*** Depending on studies.

Figure 8 Phase III study design – without up-titration (HIGH FH and LONG TERM)



FU=follow-up; LMT=lipid-modifying therapy; NCEP-ATPIII=National Cholesterol Education Program - Adult Treatment Panel III Therapeutic Lifestyle Changes; Q2W=every 2 weeks; R=randomization; SC=subcutaneous

* No follow-up period for patients entering in the open-label extension in HIGH FH.

In two of the Phase III studies, alirocumab was initiated at the dose of 150 mg SC Q2W and administered at this dose throughout the study treatment period. These studies were HIGH FH, where it was considered that patients with LDL-C ≥160 mg/dL (4.14 mmol/L) on their current, maximally-tolerated therapy required a higher magnitude of efficacy to reach their LDL-C goal, and LONG TERM, where it was considered relevant to provide the highest exposure to alirocumab to support safety as well as efficacy information on 150 mg Q2W as initiation dose (Figure 8).

The clinical development programme for alirocumab was designed to address key unmet medical needs in relation to the treatment of hypercholesterolaemia, mainly focusing on patients requiring substantial reductions in their LDL–C levels and unlikely to achieve those reductions with existing therapies. This includes patients with familial hypercholesterolaemia, individuals at highest risk of atherosclerotic CVD with an insufficient response to maximally tolerated doses of statins (in addition to other LMT in several studies), and statin intolerant patients.

4.3.1.3 Patient Populations

The definitions used for these 3 populations within the ODYSSEY clinical programme are:

HeFH

In Phase III studies conducted in patients with HeFH, in order to accommodate medical practices in different parts of the world, the definition of HeFH was based on either genotyping, or two widely accepted definitions based on patient clinical characteristics and phenotype for patients not genotyped: The Simon Broome criteria or the World Health Organisation (WHO)/Dutch Lipid Network criteria for clinical diagnosis of HeFH [94, 95]

High Risk CVD

For Phase III studies conducted in patients at high risk of atherosclerotic CVD, CV risk categories were defined in order to implement inclusion criteria and titration criteria appropriate for a worldwide clinical program. Risk categorisation was based on existing guidelines at the time of programme initiation [29, 93 96]. European

guidelines were used as a basis to delineate very high from high CV risk; of note, the 2012 update restricted the definition of very high risk patients with no history of CVD to diabetes mellitus (DM) with target organ damage and severe chronic kidney disease (CKD). Thus, inclusion criteria were adjusted in the subsequent protocols:

- Very high CV risk was defined in FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM, a history of CHD, ischaemic stroke, symptomatic peripheral artery disease (PAD) with severity criteria, moderate CKD (estimated glomerular filtration rate [eGFR]: 30 ≤eGFR <60 mL/min/1.73 m² for 3 months or more) or DM with at least 2 additional risk factors other than hypercholesterolaemia. The definition of prior CVD was more restricted than that in guidelines, to focus on easily substantiated CV events. In studies enrolling HeFH patients, those without history of CHD or CHD risk equivalent were classified as “high CV risk”; those with such a history were classified as “very high risk”. In COMBO I, COMBO II, and the non-FH stratum of LONG TERM, the patients were classified as “high CV risk” in the protocols, but they all meet the above definition, so were considered at “very high CV risk”

- OPTIONS I and OPTIONS II included non-FH and HeFH patients at high and very high CV risk with the following definitions:

    - Very high risk: Patients (non-FH and HeFH) with history of CHD, ischaemic stroke, transient ischaemic attack (TIA), symptomatic PAD, other peripheral arterial diseases (carotid or renal, or abdominal aortic aneurysm), DM with target organ damage

    - High risk: Distinction was made between HeFH and non-FH patients. As, HeFH patients without a history of CHD or CHD risk equivalent were classified as “high CV risk”. Non-FH patients were required to have either a calculated 10-year fatal CVD risk Systematic Coronary Risk Estimation (SCORE) ≥5%, or a moderate CKD, or DM with no target organ damage.

Patients with Statin Intolerance

Statin intolerant patients included in ALTERNATIVE were at high or very high CV risk (similar definition to OPTIONS studies) or at moderate CV risk, defined as a calculated 10-year fatal CVD risk SCORE ≥1 and <5%. This lower risk population was also included as currently available alternatives to statins may not provide sufficient LDL-C lowering for these patients to reach their LDL-C target. Different design features were used to ensure the enrollment of a population very likely to be statin intolerant:

- The inability to tolerate at least 2 statins: one statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued. Patients not receiving a daily regimen of a statin (e.g., 1 to 3 times weekly) were also considered as not able to tolerate a daily dose if they could not tolerate a cumulative weekly statin dose of 7 times the lowest approved tablet size and the criteria outlined above were also met

- Patients experiencing muscle-related symptoms on the atorvastatin placebo during the run-in period were excluded

- An atorvastatin re-challenge arm was included in the study design to validate that the patient population selected for inclusion was indeed indicative of having statin intolerance

As mentioned, alirocumab was initiated at the dose of 75 mg SC Q2W in 8 studies, with a possible up-with a possible up-titration to 150 mg Q2W at Week 12 depending on LDL-C values at Week 8, based on at Week 8, based on the CV risk of the patient at baseline.

Table 9 summarises for these 8 studies the LDL-C threshold considered at baseline for inclusion, depending on the level of CV risk of each patient population, and the threshold applied in the blinded automated process for up-titration.

Table 9 LDL-C threshold for baseline inclusion and for up-titration in Phase III studies

Studies	Baseline CV risk	LDL-C threshold in inclusion criteria	LDL-C threshold for up-titration
FH I/FH II	Prior CVD	≥1.81 mmol/L	≥1.81 mmol/L
	No prior CVD	≥2.59 mmol/L	
COMBO I/COMBO II	Prior CVD	≥1.81 mmol/L	≥1.81 mmol/L
	No prior CVD	≥2.59 mmol/L	
OPTIONS I/OPTIONS II	Very high	≥1.81 mmol/L	≥1.81 mmol/L
	High	≥2.59 mmol/L	≥2.59 mmol/L
ALTERNATIVE	Very high	≥1.81 mmol/L	≥1.81 mmol/L
	High and moderate	≥2.59 mmol/L	≥2.59 mmol/L
MONO	Moderate	≥2.59 mmol/L	≥1.81 mmol/L

CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol

Alirocumab was initiated at the dose of 150 mg SC Q2W in HIGH FH and in LONG TERM. For these 2 Phase III studies using 150 mg Q2W as the initiation dose, patients were included if, with the required background therapy, their LDL-C level was above the following thresholds:

- LDL-C ≥70 mg/dL (1.81 mmol/L) for LONG TERM: This study had safety as primary objective, with specific assessments for patients reaching LDL-C values below 25 mg/dL (0.65 mmol/L)
- LDL-C ≥160 mg/dL (4.14 mmol/L) for HIGH-FH that enrolled patients who required a larger reduction in LDL-C

4.3.1.4 Comparative Summary of Trials

There are three trials specifically in patients Heterozygous Familial Hypercholesterolaemia (FH I, FH II and HIGH FH), which have all evaluated alirocumab as an add-on to maximally tolerated dose statin therapy, with or without other lipid-modifying therapy (LMT).

COMBO I and COMBO II evaluated alirocumab in high CV risk patients (excluding FH). COMBO I evaluated alirocumab as an add-on to maximal tolerated dose statin

therapy, with or without other lipid-lowering therapy, while COMBO II was a head-to-head comparison of alirocumab versus ezetimibe on top of maximally tolerated dose of statin.

The LONG TERM trial evaluated alirocumab in high CV risk patients (also including FH) as an add-on to maximally tolerated dose statin therapy, with or without other lipid-lowering therapy

There are two trials evaluating alirocumab in comparison to modulation of existing statin therapy in high CV risk patients (including FH). OPTIONS I compared alirocumab used as an add-on to atorvastatin with atorvastatin up-titration, switch to rosuvastatin, or addition of ezetimibe. OPTIONS II compared alirocumab used as an add-on to rosuvastatin with rosuvastatin up-titration and with addition of ezetimibe.

There is one study in statin intolerant patients. ALTERNATIVE compared alirocumab with ezetimibe, and with a calibrator arm of atorvastatin, in patients at moderate, high, and very high CV risk (including FH).

A further study (MONO) evaluated alirocumab monotherapy versus ezetimibe monotherapy in patients with moderate CV risk and no history of CV disease.

A comparative summary of the ODYSSEY trials can be found in Table 10 and Table 11.

Table 10 Comparative summary of ODYSSEY trial methodology (FHI, FHII, HIGH FH, COMBO I and COMBO II)

Trial number (acronym)	EFC12492 FH I	CL-1112 FH II	EFC12732 HIGH FH	EFC11568 COMBO I	EFC11569 COMBO II
Setting	Secondary care	Secondary care	Secondary care	Secondary care	Secondary care
Trial design	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, multinational study to assess the efficacy and safety of alirocumab in patients with HeFH who were not adequately controlled with their current LMT (i.e. stable maximally tolerated daily statin therapy with or without other LMT). Not adequately controlled was defined as an LDL-C ≥1.81 mmol/L at the screening visit (Week –3) in patients with a history of documented CVD, or LDL-C ≥100 mg/dL (≥2.59 mmol/L) at the screening visit (Week –3) in patients without a history of documented CVD. Randomisation was stratified according to prior history of MI or ischaemic stroke, statin treatment and geographic region.	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, multinational study to assess the efficacy and safety of alirocumab in patients with HeFH not adequately controlled on their LMT (i.e. stable, maximally tolerated daily statin therapy with or without other LMT). Not adequately controlled was defined, at the screening visit (Week –2), as an LDL-C ≥1.81 mmol/L in patients with a history of documented CVD or LDL-C ≥100 mg/dL (2.59 mmol/L) in patients without a history of documented CVD. Randomisation was stratified according to prior history of MI or ischaemic stroke and statin treatment.	Randomised, double-blind, placebo-controlled, parallel-group multicentre and multinational study to assess the efficacy and safety of alirocumab in patients with HeFH and LDL-C ≥4.14 mmol/Ldespite their LMT (i.e. stable maximally tolerated daily statin therapy with or without other LMT). Randomisation was stratified according to prior history of MI or ischaemic stroke and statin treatment.	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study conducted in the USA to assess the efficacy and safety of alirocumab in high CV risk patients with hypercholesterolaemia not adequately controlled on their LMT (i.e. stable maximally tolerated daily statin therapy with or without other LMT). Not adequately controlled was defined as an LDL-C ≥1.81 mmol/L at the screening visit (Week –2) in patients with a history of documented CVD or, LDL-C ≥ 2.59 mmol/L at the screening visit (Week –2) in patients without a history of documented CVD. Randomisation was stratified according to prior history of MI or ischaemic stroke and statin treatment.	Randomised, double-blind, parallel-group, double-dummy, ezetimibe-controlled, multicentre, multinational study to assess the efficacy and safety of alirocumab in patients with a history of CVD and LDL-C ≥1.81 mmol/L, or patients with moderate CKD or diabetes with additional risk factors and LDL-C ≥ 2.59 mmol/L with their current statin therapy. Randomisation was stratified according to prior history of MI or ischaemic stroke, statin treatment and geographic region.

Trial number (acronym)	EFC12492 FH I	CL-1112 FH II	EFC12732 HIGH FH	EFC11568 COMBO I	EFC11569 COMBO II
Eligibility criteria for participants	Patients ≥18 years of age with HeFH* who are not adequately controlled** with a maximally tolerated, stable, daily dose of statin^ for at least 4 weeks prior to the screening visit, with or without other LMTs.	Patients ≥18 years of age with HeFH* who are not adequately controlled** with a maximally tolerated, stable, daily dose of statin^ for at least 4 weeks prior to the screening visit, with or without other LMTs.	Patients ≥18 years of age with HeFH* who are not adequately controlled** with a maximally tolerated, stable, daily dose of statin^ for at least 4 weeks prior to the screening visit, with or without other LMTs.	Patients with hypercholesterolaemia and established CHD or CHD risk equivalents (see below) who are not adequately controlled** with a maximally tolerated daily dose of statin^ with or without other LMTs, both at stable dose for at least 4 weeks prior to the screening visit.	Patients with hypercholesterolaemia and established CHD or CHD risk equivalents (see below) who are not adequately controlled** with a maximally tolerated daily dose of statin^ with or without other LMTs, both at stable dose for at least 4 weeks prior to the screening visit.
Locations where the data were collected	89 study locations in 14 countries: Austria, Canada, Czech Republic, Denmark, France, Israel, Netherlands, Norway, Russia, South Africa, Spain, Sweden, UK and USA.	26 study locations in four countries: Czech Republic, Netherlands, Norway and UK.	33 study locations in five countries: Canada, Netherlands, Russia, South Africa and USA.	80 study locations all within the USA.	126 study locations in ten countries: Canada, Denmark, France, Hungary, Israel, Russia, South Africa, South Korea, USA and Ukraine.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=) and comparator(s)	Patients were randomised to one of the two arms, alirocumab or placebo (323:163), during the double-blind treatment period (78 weeks): **1. Alirocumab** • 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12 • 75 mg or 150 mg alirocumab SC Q2W	Patients were randomised to one of the two arms, alirocumab or placebo (167:82), during the double-blind treatment period (78 weeks): **1. Alirocumab** • 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12 • 75 mg or 150 mg alirocumab SC Q2W	Patients were randomised to one of the two arms, alirocumab or placebo (72:35), during the double-blind treatment period (78 weeks): **1. Alirocumab** • 150 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 76	Patients were randomised to one of the two arms, alirocumab or placebo (209:107), during the double-blind treatment period (52 weeks): **1. Alirocumab** • 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12	Patients were randomised to one of the two arms, alirocumab or ezetimibe (479:241), during the double-blind treatment period (104 weeks): **1. Alirocumab** • 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12

Trial number (acronym)	EFC12492 FH I	CL-1112 FH II	EFC12732 HIGH FH	EFC11568 COMBO I	EFC11569 COMBO II
(n=)	(based on their Week 8 LDL-C level), starting at Week 12, and continuing up to Week 76 **2. Placebo** • Placebo for alirocumab SC Q2W starting at Week 0 (randomisation), and continuing up to Week 76 Dose up-titration to alirocumab 150 mg Q2W occurred if the Week 8 LDL-C was ≥70 mg/dL (1.81 mmol/L). In the alirocumab group, among the 311 patients who received at least one injection after Week 12, 135 patients (43.4%) received automatic dose up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.	(based on their Week 8 LDL-C level), starting at Week 12, and continuing up to Week 76 **2. Placebo** • Placebo for alirocumab SC Q2W starting at Week 0 (randomisation), and continuing up to Week 76 Dose up-titration to alirocumab 150 mg Q2W occurred if the Week 8 LDL-C was ≥70 mg/dL (1.81 mmol/L). In the alirocumab group, among the 158 patients who received at least one injection after Week 12, 61 patients (38.6%) received automatic dose up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.	**2. Placebo** • Placebo for alirocumab SC Q2W starting at Week 0 (randomisation), and continuing up to Week 76	• 75 mg or 150 mg alirocumab SC Q2W (based on their Week 8 LDL-C level), starting at Week 12, and continuing up to Week 50 **2. Placebo** • Placebo for alirocumab SC Q2W starting at Week 0 (randomisation), and continuing up to Week 50 Dose up-titration to alirocumab 150 mg Q2W occurred if the Week 8 LDL-C was ≥70 mg/dL (1.81 mmol/L). In the alirocumab group, among the 191 patients who received at least one injection after Week 12, 32 patients (16.8%) received automatic up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.	• 75 mg or 150 mg alirocumab SC Q2W (based on their Week 8 LDL-C level), starting at Week 12, and continuing up to Week 102 **2. Ezetimibe** • Placebo for alirocumab SC Q2W starting at Week 0 (randomisation), and continuing up to the last injection (Week 102), i.e. 2 weeks before the end of the double-blind treatment period • 10 mg ezetimibe capsules once daily at approximately the same time of the day, with or without food from Week 0 to Week 104 Dose up-titration to alirocumab 150 mg Q2W occurred if the Week 8 LDL-C was ≥70 mg/dL (1.81 mmol/L). In the alirocumab group, among the 446 patients

Trial number (acronym)	EFC12492 FH I	CL-1112 FH II	EFC12732 HIGH FH	EFC11568 COMBO I	EFC11569 COMBO II
					who received at least one injection after Week 12, 82 patients (18.4%) received automatic up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.
Permitted and disallowed concomitant medication	Patients' current LMT was permitted as concomitant therapy with the exception of fibrates (other than fenofibrate) or a statin that is not simvastatin, atorvastatin or rosuvastatin. Red yeast rice products were also not permitted. The following classes of drugs were identified as non-investigational medicinal products because the medication was either a background therapy or a potential rescue medication: • Statins (rosuvastatin, atorvastatin, simvastatin) • Cholesterol absorption inhibitors (ezetimibe) • Bile acid-binding sequestrants (e.g. cholestyramine, colestipol, colesevelam) • Nicotinic acid • Fenofibrate • Omega-3 fatty acids (≥1000 mg daily)				
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint was the percent change in calculated LDL-C rom baseline to Week 24 in the ITT population. LDL-C was calculated according to the Friedewald formula. Measured LDL-C was assessed as a secondary endpoint.				
Secondary/ tertiary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints included the percentage change from baseline in calculated LDL-C at Weeks 12, 52 and 78, as well as the change in Apo B, non-HDL-C, Total-C, Lp(a),	Secondary efficacy endpoints included the percentage change from baseline in calculated LDL-C at Weeks 12, 52 and 78, as well as the change in Apo B, non-HDL-C, Total-C, Lp(a),	Secondary efficacy endpoints included the percentage change from baseline in calculated LDL-C at Weeks 12, 52 and 78, as well as the change in Apo B, non-HDL-C, Total-C, Lp(a),	Secondary efficacy endpoints included the percentage change from baseline in calculated LDL-C at Weeks 12 and 52, as well as the change in Apo B, non-HDL-C, Total-C, Lp (a),	Secondary efficacy endpoints included the percentage change from baseline in calculated LDL-C at Weeks 12 and 52, as well as the change in Apo B, non-HDL-C, Total-C, Lp(a),

Trial number (acronym)	EFC12492 FH I	CL-1112 FH II	EFC12732 HIGH FH	EFC11568 COMBO I	EFC11569 COMBO II
	HDL-C, triglycerides and Apo A1 at Weeks 12, 24, 52 and 78, and the proportions of patients achieving an LDL-C level of <100 mg/dL and <70 mg/dL at Weeks 12, 24, 52 and 78.^^ The EQ-5D questionnaire was assessed at baseline and at Weeks 12, 24, 36, 52 and 78.	HDL-C, triglycerides and Apo A1 at Weeks 12, 24, 52 and 78, and the proportions of patients achieving an LDL-C level of <100 mg/dL and <70 mg/dL at Weeks 12, 24, 52 and 78.^^ The EQ-5D questionnaire was assessed at baseline and at Weeks 12, 24, 36 and 52.	HDL-C, triglycerides and Apo A1 at Weeks 12, 24, 52 and 78, and the proportions of patients achieving an LDL-C level of <100 mg/dL and <70 mg/dL at Weeks 12, 24, 52 and 78.^^ The EQ-5D questionnaire was assessed at baseline and at Weeks 12, 24, 36, 52 and 78.	HDL-C, triglycerides and Apo A1 at Weeks 12 and 24, and the proportions of patients achieving an LDL-C level of <100 mg/dL and <70 mg/dL at Weeks 12, 24 and 52.^^ The EQ-5D questionnaire was assessed at baseline, at Week 12, Week 24, Week 36, and Week 52.	HDL-C, triglycerides and Apo A1 at Weeks 12 and 24, and the proportions of patients achieving an LDL-C level of <100 mg/dL and <70 mg/dL at Weeks 12, 24, 52 and 104.^^ The EQ-5D questionnaire was assessed at baseline, at Week 12, Week 24, Week 36 and Week 52.
Preplanned subgroups	See Section 5.9				

*Diagnosis of HeFH must be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis may be based on either the Simon Broome criteria for definite FH or the WHO/Dutch Lipid Network criteria with a score >8 points.

**Not adequately controlled was defined as an LDL-C ≥70 mg/dL (≥1.81 mmol/L) at screening (Week -3) in patients with a history of documented CV disease or LDL-C ≥100 mg/dL (≥2.59 mmol/L) at screening (Week -3) in patients without a history of documented CV disease.

^Definition of maximally-tolerated dose (any of the following are acceptable):

- Rosuvastatin 20 mg or 40 mg daily
- Atorvastatin 40 mg or 80 mg daily
- Simvastatin 80 mg daily (if already on this dose for >1 year)

Patients not able to be on any of the above statin doses should be treated with the dose of daily atorvastatin, rosuvastatin, or simvastatin that is considered appropriate for the patient as per the investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low BMI, regional practices, local prescribing information, concomitant medications, and comorbid conditions, such as impaired glucose tolerance/impaired fasting glucose

^^A full list of secondary outcomes can be found in Appendix 3

Note:

The definition of a documented history of CHD includes one or more of the following: Acute MI, Silent MI, Unstable angina, Coronary revascularisation procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]), Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)

The definition of CHD risk equivalents includes one or more of the following 4 criteria:

1. Documented PAD (one of the following criteria [a, b, or c] must be satisfied):
a) Current intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) of presumed atherosclerotic origin together with ankle-brachial index equal to or less than 0.90 in either leg at rest OR
b) History of intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) together with endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease OR
c) History of critical limb ischemia together with thrombolysis, endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease
2. Documented ischaemic stroke with a focal ischaemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or MRI must have been performed to rule out haemorrhage and nonischaemic neurological disease.
3. Documented chronic kidney disease (CKD) as defined by 30 ≤eGFR <60 mL/min/1.73 m2 for 3 months or more, including the screening visit
4. Known history of DM AND 2 or more additional risk factors (as listed below):
a) History of hypertension (established on antihypertensive medication)
b) Documented history of ankle-brachial index ≤0.90
c) Documented history of microalbuminuria or macroalbuminuria OR dipstick urinalysis at screening visit (Week-2) with >2+ protein.
d) Documented history of preproliferative or proliferative retinopathy or laser treatment for retinopathy) known family history of premature CHD (CHD in father or before 55 years of age; CHD in mother or sister before 65 years of age)

Table 11 Comparative summary of ODYSSEY trial methodology (LONG TERM, OPTIONS I, OPTIONS II, ALTERNATIVE, MONO)

Trial number (acronym)	**LTS11717 LONG TERM**	**CL-1110 OPTIONS I**	**CL-1118 OPTIONS II**	**CL-1119 ALTERNATIVE**	**EFC11716 MONO**
Setting	Secondary care	Secondary care	Secondary care	Secondary care	Secondary care
Trial design	Randomised, double-blind, placebo-controlled, multicentre, multinational study to assess the long-term safety and tolerability of alirocumab in high CV risk patients with hypercholesterolaemia who were not adequately controlled with a statin at a	Randomised, double-blind, active-comparator, parallel-group, multinational study in patients at high CV risk with non-FH or HeFH whose LDL-C levels were not adequately controlled with atorvastatin (20 mg or 40 mg QD) with or without other LMTs, excluding ezetimibe.	Randomised, double-blind, active-comparator, parallel-group, multinational study in patients at high CV risk with non-FH or HeFH whose LDL-C levels were not adequately controlled with rosuvastatin (10 mg or 20 mg QD) with or without other LMTs, excluding ezetimibe.	Randomised, double-blind, parallel-group, double-dummy, ezetimibe-controlled, multinational, multicentre study in statin intolerant patients with primary hypercholesterolaemia and moderate, high or very high CV risk. The double-blind period has	Randomised, double-blind, parallel-group, ezetimibe-controlled, multicentre, multinational study to assess the efficacy and safety of alirocumab in patients with LDL-C between 2.59 mmol/L and 4.91 mmol/L, with a moderate CV risk, defined as a 10-year risk

Trial number (acronym)	LTS11717 LONG TERM	CL-1110 OPTIONS I	CL-1118 OPTIONS II	CL-1119 ALTERNATIVE	EFC11716 MONO
	maximally tolerated daily dose with or without other LMTs. Randomisation was stratified according to diagnosed HeFH, prior history of MI or ischaemic stroke, statin treatment and geographic region.	Within each atorvastatin baseline regimen, randomisation was stratified according to a prior history of MI or ischaemic stroke.	Within each rosuvastatin baseline regimen, randomisation was stratified according to a prior history of MI or ischaemic stroke.	been completed, and the study is continuing with an ongoing open-label extension period. Randomisation was stratified according to a prior history of MI or ischaemic stroke.	of fatal CVD of ≥1% and <5% using SCORE. Randomisation was stratified according to DM status.
Eligibility criteria for participants	Patients with HeFH* with or without established CHD or CHD risk equivalents who are not adequately controlled** with a maximally tolerated daily dose of statin^ for at least 4 weeks prior to the screening visit with or without other LMTs OR Patients with hypercholesterolaemia and established CHD or CHD risk equivalents who are not adequately controlled** with a maximally tolerated daily dose of statin^ for at least 4 weeks prior to	Patients with screening LDL-C ≥1.81 mmol/L who were not adequately controlled** with a 20 mg or 40 mg stable daily dose of atorvastatin for at least 4 weeks prior to the screening visit with or without other LMTs (excluding ezetimibe). Patients with HeFH* or non-FH had to have a history of CHD, non-CHD CVD or DM with target organ damage. OR Patients with screening LDL-C ≥2.59 mmol/L who were not adequately controlled** with a 20 mg or 40 mg stable daily dose	Patients with screening LDL-C ≥1.81 mmol/L who were not adequately controlled** with a 10 mg or 20 mg stable daily dose of rosuvastatin for at least 4 weeks prior to the screening visit with or without other LMTs (excluding ezetimibe). Patients with HeFH* or non-FH had to have a history of CHD, non-CHD CVD or DM with target organ damage. OR Patients with screening LDL-C ≥2.59 mmol/L who were not adequately controlled** with a 10 mg or 20 mg stable daily dose	Patients with primary hypercholesterolaemia (HeFH* or non-FH) with a moderate, high or very high CV risk and a history of SI***	Patients with hypercholesterolaemia at moderate CV risk defined by a 10-year risk of fatal CVD of ≥1% and <5% using SCORE.

Trial number (acronym)	LTS11717 LONG TERM	CL-1110 OPTIONS I	CL-1118 OPTIONS II	CL-1119 ALTERNATIVE	EFC11716 MONO
	the screening visit with or without other LMTs	of atorvastatin for at least 4 weeks prior to the screening visit with or without other LMTs (excluding ezetimibe). Patients with HeFH* or non-FH had to have a history of CHD or non-CHD CVD but with a calculated 10-year fatal CVD risk SCORE ≥5%, or with moderate CKD or DM with target organ damage.	of rosuvastatin for at least 4 weeks prior to the screening visit with or without other LMTs (excluding ezetimibe). Patients also had to have HeFH* or non-FH without CHD, or non-CHD CVD but with a calculated 10-year fatal CVD risk SCORE ≥5%, or with moderate CKD or DM with target organ damage.		
Locations where the data were collected	320 study locations in 27 countries: Argentina, Belgium, Bulgaria, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, Norway, Poland, Portugal, Romania, Russia, South Africa, Spain, Sweden, Ukraine, UK and USA.	85 study locations in nine countries: Australia, Canada, France, Germany, Italy, Mexico, Spain, UK and USA.	79 study locations in eight countries: Australia, Canada, Germany, Italy, Mexico, Spain, UK and USA.	67 study locations in eight countries: Austria, Canada, France, Israel, Italy, Norway, UK and USA. Open-label extension: 65 study locations in seven countries: Austria, Canada, France, Israel, Italy, UK and USA.	Eight study locations in four countries: Belgium, Finland, Netherlands and USA.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they	Patients were randomised to one of the two arms, alirocumab or placebo (1553:788), during the double-blind treatment period (78 weeks):	Patients were randomised to one of the two atorvastatin baseline regimens: **1. Atorvastatin 20 mg baseline regimen** • Alirocumab Q2W +	Patients were randomised to one of the two rosuvastatin baseline regimens: **1. Rosuvastatin 10 mg baseline regimen** • Alirocumab Q2W +	A total of 314 patients were randomised to three treatment groups in the double-blind treatment period: **1. Alirocumab 75 mg Q2W + placebo atorvastatin/**	Patients were randomised to one of the two arms, alirocumab or ezetimibe (52:51), during the double-blind treatment period (24 weeks): **1. Alirocumab +**

Trial number (acronym)	LTS11717 LONG TERM	CL-1110 OPTIONS I	CL-1118 OPTIONS II	CL-1119 ALTERNATIVE	EFC11716 MONO
were administered) Intervention(s) (n=) and comparator(s) (n=)	**1. Alirocumab** • 150 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 76 **2. Placebo** • Placebo for alirocumab SC Q2W starting at Week 0 (randomisation), and continuing up to Week 76	atorvastatin 20 mg daily (57 patients) – 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12 – 75 mg or 150 mg alirocumab SC Q2W (based on their Week 8 LDL-C level), starting at Week 12 and continuing up to Week 24 • Atorvastatin 40 mg daily (57 patients) • Atorvastatin 20 mg + ezetimibe 10 mg daily (55 patients) **2. Atorvastatin 40 mg baseline regimen** • Alirocumab Q2W + atorvastatin 40 mg daily (47 patients) – 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12; – 75 mg or 150 mg alirocumab SC Q2W (based on their Week 8 LDL-C level), starting	rosuvastatin 10 mg daily (49 patients) – 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12; – 75 mg or 150 mg alirocumab SC Q2W (based on their Week 8 LDL-C level), starting at Week 12, and continuing up to Week 24 • Rosuvastatin 20 mg daily (48 patients) • Rosuvastatin 10 mg + ezetimibe 10 mg daily (48 patients) **2. Rosuvastatin 20 mg baseline regimen** • Alirocumab Q2W + rosuvastatin 20 mg daily (54 patients) – 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12; – 75 mg or 150 mg alirocumab SC Q2W (based on their Week 8 LDL-C level), starting	**ezetimibe PO QD (126 patients)** **2. Ezetimibe 10 mg PO QD + placebo alirocumab SC Q2W (125 patients)** **3. Atorvastatin 20 mg PO QD + placebo alirocumab SC Q2W (63 patients)** A total of 281 patients were treated with alirocumab during the open-label extension treatment period: 117 patients who had received alirocumab during the double-blind period, 59 patients who had received atorvastatin during the double-blind period and 105 patients who had received ezetimibe during the double-blind period. Among the 109 patients who received at least 1 alirocumab injection after week 12, 54 patients (49.5%) received automatic dose up-	**placebo for ezetimibe PO** • 75 mg alirocumab SC Q2W starting at Week 0 (randomisation) up to Week 12 • 75 mg or 150 mg alirocumab SC Q2W (based on their Week 8 LDL-C level), starting at Week 12, and continuing up to Week 24 **2. Ezetimibe 10 mg PO + placebo for alirocumab Q2W** Dose up-titration to alirocumab 150 mg Q2W occurred if the Week 8 LDL-C was ≥70 mg/dL (1.81 mmol/L). 14 patients received automatic up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.

Trial number (acronym)	LTS11717 LONG TERM	CL-1110 OPTIONS I	CL-1118 OPTIONS II	CL-1119 ALTERNATIVE	EFC11716 MONO
		at Week 12, and continuing up to Week 24 • Atorvastatin 80 mg daily (47 patients) • Rosuvastatin 40 mg daily (45 patients) • Atorvastatin 40 mg + ezetimibe 10 mg daily (47 patients) Dose up-titration to alirocumab 150 mg Q2W occurred if the Week 8 LDL-C was ≥70 mg/dL (1.81 mmol/L). Overall, 13 patients (14%) in the alirocumab add-on treatment group who received at least one injection after Week 12 received automatic dose up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner. Of these, four were in the atorvastatin 20 mg baseline regimen group.	at Week 12, and continuing up to Week 24 • Rosuvastatin 40 mg daily (53 patients) • Rosuvastatin 20 mg + ezetimibe 10 mg daily (53 patients) Dose up-titration to alirocumab 150 mg Q2W occurred if the Week 8 LDL-C was ≥70 mg/dL (1.81 mmol/L). Overall, 17 patients (18.5%) in the alirocumab add-on treatment group who received at least one injection after Week 12, received automatic dose up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner. Of these, seven were in the Rosuvastatin 10 mg baseline regimen group and ten in the rosuvastatin 20 mg group.	titration to 150 mg Q2W.	
Permitted and disallowed concomitant medication	Patients' current LMT was permitted as concomitant therapy with the exception of fibrates (other than fenofibrate) or a statin that is not	Prohibited concomitant medications from the initial screening visit until the end-of-study visit included the following:	Prohibited concomitant medications from the initial screening visit until the end-of-study visit included the following:	Prohibited concomitant medications from the initial screening visit until the follow-up visit (as applicable) included the	The following were forbidden from the screening period until the follow-up period: • Statins, ezetimibe,

Trial number (acronym)	LTS11717 LONG TERM	CL-1110 OPTIONS I	CL-1118 OPTIONS II	CL-1119 ALTERNATIVE	EFC11716 MONO
	simvastatin, atorvastatin or rosuvastatin. Red yeast rice products were also not permitted. The following classes of drugs were identified as non-investigational medicinal products because the medication was either a background therapy or a potential rescue medication: • Statins (rosuvastatin, atorvastatin, simvastatin) • Cholesterol absorption inhibitors (ezetimibe) • Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam) • Nicotinic acid • Fenofibrate • Omega-3 fatty acids (≥1000 mg daily)	• Statins (other than the atorvastatin and rosuvastatin provided as blinded study medication) • Ezetimibe (other than that provided as blinded study medication) • Fibrates, other than fenofibrate • Red yeast rice products LMTs that were allowed as background therapy included: • Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam) • Nicotinic acid • Fenofibrate • Omega-3 fatty acids (≥1000 mg daily)	• Statins (other than the rosuvastatin provided as blinded study medication) • Ezetimibe (other than that provided as blinded study medication) • Fibrates, other than fenofibrate • Red yeast rice products LMTs that were allowed as background therapy included: • Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam) • Nicotinic acid • Fenofibrate • Omega-3 fatty acids (≥1000 mg daily)	following: • Statins • Fibrates other than fenofibrate • Ezetimibe^^^ • Red yeast rice products Prohibited concomitant medications from the start of the open-label extension treatment period until the follow-up visit included the following: • Statins • Fibrates other than fenofibrate • Red yeast rice products LMTs that were allowed as background therapy included: • Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam) • Nicotinic acid • Fenofibrate • Omega-3 fatty acids (≥1000 mg daily)	bile acid sequestrants, Omega-3 fatty acids (≥1000 mg daily). • Fibrates (except fenofibrate if the patient met the pre-specified triglyceride alert (triglyceride >5.65 mmol/L)) • Red yeast rice products
Primary	The primary objective	The primary efficacy endpoint was the percent change in calculated LDL-C rom baseline to Week 24 in the			

Trial number (acronym)	LTS11717 LONG TERM	CL-1110 OPTIONS I	CL-1118 OPTIONS II	CL-1119 ALTERNATIVE	EFC11716 MONO
outcomes (including scoring methods and timings of assessments)	was to evaluate the long-term safety and tolerability of alirocumab in high CV risk patients with hypercholesterolaemia who were not adequately controlled with their LMT. The primary efficacy endpoint was the percent change in calculated LDL-C from baseline to Week 24 in the ITT population.	ITT population. LDL-C was calculated according to the Friedewald formula. Measured LDL-C was assessed as a secondary endpoint.			
Secondary/ tertiary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints included the percentage change from baseline in calculated LDL-C at Weeks 12, 52 and 78, as well as the change in Apo B, non-HDL-C, Total-C, lipoprotein(a), HDL-C, triglycerides and Apo A1 at Weeks 12, 24, 52 and 78, and the proportions of patients achieving an LDL-C level of <2.59mmol/L and <1.81mmol/L at Weeks 12, 24, 52 and 78^^ The EQ-5D	Secondary efficacy endpoints included the percentage change from baseline in calculated LDL-C at Weeks 12, as well as the change in Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, triglycerides and Apo A1 at Weeks 12 and 24, and the proportions of patients achieving an LDL-C level of <2.59mmol/L and <1.81mmol/L at Weeks 12 and 24.	Secondary efficacy endpoints included the percentage change from baseline in calculated LDL-C at Weeks 12, as well as the change in Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, triglycerides and Apo A1 at Weeks 12 and 24, and the proportions of patients achieving an LDL-C level of <2.59mmol/L and <1.81mmol/L at Weeks 12 and 24.	Secondary efficacy endpoints included the percentage change from baseline in calculated LDL-C at Weeks 12, as well as the change in Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, triglycerides, and Apo A1 at Weeks 12 and 24, and the proportions of patients achieving an LDL-C level of <2.59mmol/L and <1.81mmol/L at Weeks 12 and 24.	Secondary efficacy endpoints included the percentage change from baseline in calculated LDL-C at Weeks 12, as well as the change in Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, triglycerides and Apo A1 at Weeks 12 and 24, and the proportions of patients achieving an LDL-C level of <2.59mmol/L and <1.81mmol/L at Weeks 12 and 24.

Trial number (acronym)	LTS11717 LONG TERM	CL-1110 OPTIONS I	CL-1118 OPTIONS II	CL-1119 ALTERNATIVE	EFC11716 MONO
	questionnaire was assessed at baseline and at Weeks 12, 24, 36, 52, 64 and 78				
Preplanned subgroups	See Section 4.8				

*Diagnosis of HeFH must be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis may be based on either the Simon Broome criteria for definite FH or the WHO/Dutch Lipid Network criteria with a score >8 points.
**Not adequately controlled was defined as an LDL-C ≥70 mg/dL (≥1.81 mmol/L) at screening (Week -3) in patients with a history of documented CV disease or LDL-C ≥100 mg/dL (≥2.59 mmol/L) at screening (Week -3) in patients without a history of documented CV disease.
*** Definition of statin intolerance: the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued.
^Definition of maximally-tolerated dose (any of the following are acceptable):

- Rosuvastatin 20 mg or 40 mg daily
- Atorvastatin 40 mg or 80 mg daily
- Simvastatin 80 mg daily (if already on this dose for >1 year)

Patients not able to be on any of the above statin doses should be treated with the dose of daily atorvastatin, rosuvastatin, or simvastatin that is considered appropriate for the patient as per the investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low BMI, regional practices, local prescribing information, concomitant medications, and comorbid conditions, such as impaired glucose tolerance/impaired fasting glucose
^^A full list of secondary outcomes can be found in Appendix 3
^^^Patients who were discontinued from study drug during the double-blind treatment period due to skeletal muscle-related AEs were to be assessed. These patients could resume their pre-washout ezetimibe after the unscheduled visit took place.
Note:
The definition of a documented history of CHD includes one or more of the following: Acute MI, Silent MI, Unstable angina, Coronary revascularisation procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]), Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)
The definition of CHD risk equivalents includes one or more of the following 4 criteria:
1. Documented PAD (one of the following criteria [a, b, or c] must be satisfied):
a) Current intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) of presumed atherosclerotic origin together with ankle-brachial index equal to or less than 0.90 in either leg at rest OR
b) History of intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) together with endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease OR

c) History of critical limb ischemia together with thrombolysis, endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease
2. Documented ischaemic stroke with a focal ischaemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or MRI must have been performed to rule out haemorrhage and nonischaemic neurological disease.
3. Documented chronic kidney disease (CKD) as defined by 30 ≤eGFR <60 mL/min/1.73 m2 for 3 months or more, including the screening visit
4. Known history of DM AND 2 or more additional risk factors (as listed below):
a) History of hypertension (established on antihypertensive medication)
b) Documented history of ankle-brachial index ≤0.90
c) Documented history of microalbuminuria or macroalbuminuria OR dipstick urinalysis at screening visit (Week-2) with >2+ protein.
d) Documented history of preproliferative or proliferative retinopathy or laser treatment for retinopathye) known family history of premature CHD (CHD in father or before 55 years of age; CHD in mother or sister before 65 years of age)

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

Primary analyses of efficacy endpoints were conducted using an ITT approach including all lipid data collected within the pre-specified window, regardless of whether the patient was continuing therapy or not. In addition, analyses were also conducted using an on-treatment approach (based on the mITT population defined above), including lipid data collected during the treatment period.

The ITT population was defined as all randomised patients who had an evaluable primary efficacy endpoint. The primary efficacy endpoint was evaluable when the following conditions were met:

- Availability of baseline calculated LDL-C value;
- Availability of at least 1 calculated LDL-C value on or off-treatment within one of the analysis windows up to Week 24

Patients in the ITT population were analysed according to the treatment group allocated by randomisation (i.e., as-randomised treatment group).

The mITT population was defined as all randomised patients who took at least 1 dose or part of a dose of the double-blind injection and had an evaluable primary efficacy endpoint during the efficacy treatment period (defined as per in the ITT analysis).

The efficacy treatment period was defined as the time period from the first double-blind IMP injection up to the day of last injection +21 days. Patients in the mITT population were analysed according to the treatment group allocated by randomisation (ie, as-randomised treatment group). The analyses using the on-treatment estimand (on-treatment analyses) were performed on the mITT population.

A mixed effect model with repeated measures (MMRM) was used for primary efficacy analysis. Missing data were accounted for by the MMRM model which relied on the “missing-at-random” (MAR) assumption. In all Phase III studies sensitivity analyses, primarily a tipping-point approach and new pattern mixture model (PMM) approach using mixed imputation in the randomised population, were conducted to

assess the robustness of primary efficacy analysis with regards to handling of missing data [97]. Details of the sensitivity analyses can be found in Appendix 4.

In all Phase III studies, the MMRM included the fixed categorical effects of treatment group, randomisation strata, time point, treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction.

This model was run using SAS MIXED Procedure with an unstructured correlation matrix to model the within-patient errors. Parameters were estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom were estimated using Satterthwaite's approximation. This model provided baseline adjusted least-squares (LS) means estimates at Week 24 for both treatment groups with their corresponding standard errors (SEs) and 95% confidence intervals (CIs).

To compare the alirocumab group to the control group, an appropriate contrast statement was used to test the differences of these estimates, at the 2-sided 0.05 level in all studies, except in OPTIONS I study (2-sided 0.01 alpha level) and in the OPTIONS II study (2-sided 0.0125 alpha level). For OPTIONS I and OPTIONS II studies, the statistical testing of the primary efficacy endpoint was adjusted for multiplicity of pairwise comparisons (5 pairwise comparisons in OPTIONS I, 4 pairwise comparisons in OPTIONS II) using a Bonferroni approach.[98]

4.4.1 Sample Size Considerations

For all the Phase III studies except the LONG-TERM study (whose primary objective was to evaluate the long-term safety and tolerability of alirocumab), the sample size was determined to ensure sufficient power (90% to 95%) for the primary efficacy endpoint. Calculation of the sample size was based on the results observed in Phase II studies. In most studies, the sample size was increased in order to meet regulatory requirements regarding the size of the safety database (Table 12).

A summary of the statistical analyses conducted in the clinical trials can be found in Table 13. Note: in all trials a statistically significant decrease from baseline in LDL-C

was observed in the alirocumab group compared to controls at Week 24 (Section 4.7, Table 19 to Table 30).

Table 12 Sample size and power considerations for primary efficacy endpoint in Phase III studies

Study	Expected difference	Expected SD	Power	Sample size necessary for the primary efficacy endpoint	Sample size increased to assess safety of alirocumab?	Planned total sample size
FH I	30%	25%	95%	45 (30 alirocumab, 15 placebo)	Yes	471
FH II	30%	25%	95%	45 (30 alirocumab, 15 placebo)	Yes	250
HIGH FH	30%	25%	95%	45 (30 alirocumab, 15 placebo)	Yes	105
COMBO I	30%	25%	95%	45 (30 alirocumab, 15 placebo)	Yes	306
COMBO II	20%	25%	95%	96 (64 alirocumab, 32 ezetimibe)	Yes	660
LONG TERM	N/A[a]	N/A[a]	N/A[a]	N/A[a]	Yes	2100
OPTIONS I[b]	20%	25%	95%	350 (50 per group)	No	350
OPTIONS II[b]	20%	25%	95%	300 (50 per group)	No	300
ALTERNATIVE	20%	25%	95%	84 (42 alirocumab, 42 ezetimibe)	Yes	250
MONO[c]	20%	25%	95%	100 (50 alirocumab, 50 ezetimibe)	No	100

FH, familial hypercholesterolaemia; ITT, intention-to-treat; N/A, not available; SD, standard deviation
[a]Not applicable: sample size of study LONG TERM was driven by the size of the required safety database for the dossier.
[b]In OPTIONS I and OPTIONS II studies, sample size calculations included adjustment of alpha level due to multiple pairwise comparisons (alpha=0.01 in OPTIONS I and alpha=0.0125 in OPTIONS II).
[c]In the MONO study, an expected 5% exclusion rate from the modified ITT population was taken into account, and final sample size was rounded to 100 (50 per treatment arm

Table 13 Summary of statistical analyses in the RCTs

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
EFC12492 FH I	To demonstrate the superior reduction of calculated LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy with or without other LMTs in comparison with placebo after 24 weeks of treatment in patients with HeFH.	LS MD of percent change from in LDL-C from baseline to Week 24 with a 0.05 two-sided significance level.	A total sample size of 45 patients (30 on alirocumab and 15 on placebo) has 95% power to detect a difference in mean percent change in LDL-C of 30% with a 0.05 two-sided significance level and assuming a common SD of 25% and all these 45 patients having an evaluable primary endpoint. 485 patients were randomised and received study treatment.	Analysis using a mixed-effect model with repeated measures that accounted for missing data relying on “missing-at-random” assumption.
CL-1112 FH II	As above.	As above.	As above. 249 patients were randomised, and 248 patients received study treatment.	As above.
EFC12732 HIGH FH	As above.	As above.	As above. 107 patients were randomised and received study treatment.	As above.
EFC11568 COMBO I	To demonstrate the superior reduction of calculated LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy with or without other LMTs in comparison with placebo after 24 weeks of treatment in high CV risk patients with hypercholesterolaemia.	As above.	As above. 316 patients were randomised, and 314 patients received study treatment.	As above.
EFC11569 COMBO II	To demonstrate the superior reduction of calculated LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy in combination with ezetimibe 10 mg daily after	As above.	A total sample size of 96 patients (64 in alirocumab and 32 in ezetimibe) has 95% power to detect a difference in mean percent change in LDL-C of 20% with a 0.05 two-sided significance level and assuming a common SD of 25% and all	As above

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	24 weeks of treatment in patients with hypercholesterolaemia at high CV risk.		96 patients having an evaluable primary endpoint. 720 patients were randomised and received study treatment.	
LTS11717 LONG TERM	To evaluate the long-term safety and tolerability of alirocumab in high CV risk patients with hypercholesterolaemia not adequately controlled with their LMT.	As above for the primary efficacy endpoint (percentage change in calculated LDL-C from baseline to Week 24 in the ITT population).	For safety assessment a sample size of 2100 patients (randomised 2:1 to alirocumab) allows the collection of long-term safety data in a broad database (at least 1000 patients exposed to alirocumab for a minimum of 12 months, of which approximately 900 patients exposed to alirocumab for 78 weeks). Moreover, a sample size of 1400 patients treated with alirocumab allows detection of AEs at a rate of ≥0.002 with 95% confidence in the alirocumab group. 2341 patients were randomised, and 2338 received study treatment.	As above
CL-1110 OPTIONS I	To evaluate the reduction of LDL-C by alirocumab as add-on therapy to atorvastatin in comparison with ezetimibe as add-on therapy to atorvastatin, in comparison with doubling the atorvastatin dose, or in comparison with a therapy switch from atorvastatin to rosuvastatin, after 24 weeks of treatment in patients with hypercholesterolaemia at high CV risk.	The statistical testing of the five primary pairwise comparisons for the primary efficacy endpoint was evaluated at a two-sided significance level of 0.01 per comparison with adjustment for multiplicity, thereby maintaining an overall study alpha level of 0.05.	A sample size of 50 patients per group would have 90% power to detect a difference in means of at least 20% in any one pairwise comparison (i.e. alirocumab mean=50% and control mean=30%), assuming that the common SD was 25% using an independent group *t* test. The alpha level for each of the five pairwise comparisons was adjusted to a two-sided alpha level of 0.01, thereby maintaining an overall study alpha level of 0.05. 355 patients were randomised, and 354 received study treatment	As above

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
CL-1118 OPTIONS II	To evaluate the efficacy and safety of alirocumab as add-on therapy to submaximal doses of rosuvastatin in comparison with two other regimens: (1) ezetimibe as add-on therapy to submaximal doses of rosuvastatin; and (2) doubling of the rosuvastatin dose. The study was conducted in patients at high CV risk who had failed to reach their LDL-C treatment goal and required additional pharmacological management.	The statistical testing of the four primary pairwise comparisons for the primary efficacy endpoint was evaluated at a two-sided significance level of 0.0125 per comparison, adjusting for multiplicity, thereby maintaining an overall alpha level of 0.05.	A sample size of 47 patients per arm would have 90% power to detect a difference in means of at least 20% in any one pairwise comparison (i.e. alirocumab mean=50% and control mean=30%), assuming that the common SD was 25% using an independent group *t* test. The alpha level for each of the four pairwise comparisons was adjusted to a two-sided alpha level of 0.0125, thereby maintaining an overall study alpha level of 0.05. 305 patients were randomised and all received study treatment.	As above
CL-1119 ALTERNATIVE	To demonstrate superior reduction of LDL-C by alirocumab in comparison with ezetimibe in statin intolerant patients with primary hypercholesterolaemia.	LS MD of percent change in LDL-C from baseline to Week 24 with a 0.05 two-sided significance level.	A total sample size of 84 patients (42 patients in the alirocumab treatment group and 42 patients in the ezetimibe treatment group) was calculated to have 95% power to detect a difference in mean percent change from baseline to Week 24 in LDL-C of 20% with a two-sided significance level and assuming a SD of 25%. Of the 361 patients who completed the screening period, 314 patients (87.0%) completed the single-blind placebo run-in period, while 47 patients (13.0%) had run-in failures and were not randomised to a treatment group. Of the 314 patients who were randomised, 313 received study treatment.	As above
EFC11716 MONO	To demonstrate the superior reduction of calculated LDL-C by alirocumab as monotherapy in comparison with ezetimibe 10 mg daily after 24 weeks of treatment in patients with	As above.	A total sample size of 90 patients (45 in each arm) has 96% power to detect a 20% MD between alirocumab and ezetimibe in percent change from baseline at a 0.05 two-sided significance level and assuming a common SD of 25%.	As above

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	hypercholesterolaemia at moderate CV risk.		103 patients were randomised and received study treatment.	

AE, adverse event; CV, cardiovascular; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; LS, least-squares; MD, mean difference; RCT, randomised controlled trial; SD, standard deviation.

4.5 Participant flow in the relevant randomised controlled trials

Key points

- The ODYSSEY programme included 36 NHS centres excluding CVOT, with 30 UK centres participating in the ongoing CVOT outcomes trial
- In total, in Phase III trials, 5,296 patients were randomised; 3188 to alirocumab and 2108 to controls
    - 26% (1377) had HeFH
    - 97.0% (5138) were at high/very high CV risk, with 78.5% at very high CV risk.
    - 64.1% (3392) patients had a history of any CHD
    - 34.3% (1816) patients had prior MI
    - 7.9% (416) had prior ischaemic stroke
    - 30.8% (1629) had Type 2 diabetes
- A majority of patients treated were on maximal tolerated dose statins (79.7%), and significant numbers treated with statins plus ezetimibe (particularly in the FH trials) (Table 16)

The data from the Phase III studies were collected in 30 countries worldwide. This included North America (2017 patients) and 20 countries in Europe (1741 patients from Western EU, 824 patients from Eastern EU and 714 patients from the rest of the world). In the UK there were 36 NHS centres involved in 6 of the trials (FHI, FHII, LONG TERM, OPTIONS I, OPTIONS II and ALTERNATIVE).

A total of 5296 patients were randomised in the 10 Phase III studies (3188 randomised to alirocumab group, 1175 randomised to placebo group, 620 randomised to ezetimibe group, and 313 randomised to statin). Of these 5296 patients, 9 patients were randomised but not treated; 5222 patients (98.6%) were included in the ITT population and 5180 patients (97.8%) were included in the mITT population (population for on-treatment analyses).

A summary of reasons for not completing study treatment periods across Phase III studies can be found in Table 14. CONSORT flow diagrams can be found in Appendix 5.

An overview of the ODYSSEY trial populations is shown in Table 15 and Table 16.

Tables of baseline characteristics for each trial can be found in Appendix 5. As intended, the patients included in ODYSSEY were at high CV risk and had elevated LDL-C despite treatment. Overall, 26% (1377) had HeFH. 97.0% (5138) were at high/very high CV risk, with 78.5% at very high CV risk, including 64.1% with a history of any CHD. 34.3% had prior MI and 7.9% had a history of ischaemic stroke. The majority of patients treated were on maximal tolerated dose statins (79.7%). The majority of patients in trials where statins were a background therapy were receiving high dose high intensity statins. A lower proportion (44%) was observed in LONG-TERM, with previous muscle symptoms or creatine kinase elevations during receipt of a high-dose statin accounting for 17% of study patients and regional practices or local labelling accounting for 28%. Approximately 50% of patients in the FH trials received statins plus ezetimibe as background therapy, as did approximately 14% of patients in LONG-TERM.

An analysis of UK patients was performed to inform the cost-effectiveness model. In comparison, ODYSSEY patients were on the whole younger, with a mean age of around 60 – 63 in non-FH populations, compared with an average age of 72 for patients with CHD observed in THIN (Appendix 11). The proportion of males was similar (~60% in both for non-FH populations). Mean LDL-C levels were similar.

Table 14 Patient Disposition: Reasons for not completing study treatment period (Randomised population) - Phase III studies

Study treatment	Randomised and treated	Did not complete study treatment period[a]	Discontinued due to:		
			AE	Poor protocol compliance	Other reasons
FH I – EFC12492					
Placebo	163	18 (11.0%)	8 (4.9%)	4 (2.5%)	6 (3.7%)
Alirocumab 75 mg Q2W up to 150 mg Q2W	322	36 (11.1%)	12 (3.7%)	8 (2.5%)	16 (5.0%)
FH II – CL1112					
Placebo	81	3 (3.7%)	1 (1.2%)	1 (1.2%)	1 (1.2%)
Alirocumab 75 mg Q2W up to 150 mg Q2W	167	11 (6.6%)	5 (3.0%)	2 (1.2%)	4 (2.4%)
HIGH FH – EFC12732					
Placebo	35	6 (17.1%)	1 (2.9%)	1 (2.9%)	4 (11.4%)
Alirocumab 75 mg Q2W up to 150 mg Q2W	72	15 (20.8%)	3 (4.12%)	4 (5.6%)	8 (11.1%)
COMBO I – EFC11568					
Placebo	107	32 (29.9%)	8 (7.5%)	9 (8.4%)	15 (14.0%)
Alirocumab 75 mg Q2W up to 150 mg Q2W	207	51 (24.4%)	13 (6.2%)	10 (4.8%)	28 (13.4%)
COMBO II – EFC11569					
Placebo	241	35 (14.5%)	13 (5.4%)	7 (2.9%)	15 (6.2%)
Alirocumab 75 mg Q2W up to 150 mg Q2W	479	73 (15.2%)	36 (7.5%)	13 (2.7%)	24 (5.0%)
LONG TERM – LTS11717					
Placebo	788	146 (18.5%)	44 (5.6%)	34 (4.3%)	67 (8.5%)
Alirocumab 150 mg Q2W	1550 (99.8%)	311 (20.0%)	98 (6.3%)	54 (3.5%)	159 (10.2%)
OPTIONS I – CL1110: **Patients on atorvastatin 20 mg before randomisation**					

Study treatment	Randomised and treated	Did not complete study treatment period[a]	Discontinued due to:		
			AE	Poor protocol compliance	Other reasons
Atorvastatin 40 mg	57	13 (22.8%)	4 (7.0%)	2 (3.5%)	7 (12.3%)
Ezetimibe 10 mg + atorvastatin 20 mg	55	15 (27.3%)	3 (5.5%)	4 (7.3%)	8 (14.5%)
Alirocumab 75 mg Q2W up to 150 mg Q2W + atorvastatin 20 mg	57	11 (19.3%)	5 (8.8%)	0	6 (10.5%)
Patients on atorvastatin 40 mg before randomisation					
Atorvastatin 80 mg	47	8 (17.0%)	3 (6.4%)	0	5 (10.6%)
Rosuvastatin 40 mg	45	6 (13.3%)	1 (2.2%)	0	5 (11.1%)
Ezetimibe 10 mg + atorvastatin 40 mg	46	6 (12.8%)	1 (2.1%)	0	5 (10.6%)
Alirocumab 75 mg Q2W up to 150 mg Q2W + atorvastatin 40 mg	47	9 (19.1%)	2 (4.3%)	1 (2.1%)	6 (12.8%)
OPTIONS II – CL1118: **Patients on rosuvastatin 10 mg before randomisation**					
Rosuvastatin 20 mg	48	5 (10.4%)	2 (4.2%)	1 (2.1%)	2 (4.2%)
Ezetimibe 10 mg + rosuvastatin 10 mg	48	14 (29.2%)	6 (12.5%)	2 (4.2%)	6 (12.5%)
Alirocumab 75 mg Q2W up to 150 mg Q2W + rosuvastatin 10 mg	49	11 (22.4%)	3 (6.1%)	2 (4.1%)	6 (12.2%)
Patients on rosuvastatin 20 mg before randomisation					
Rosuvastatin 40 mg	53	8 (15.1%)	3 (5.7%)	0	5 (9.4%)
Ezetimibe 10 mg + rosuvastatin 20 mg	53	9 (17.0%)	2 (3.8%)	0	7 (13.2%)
Alirocumab 75 mg Q2W up to 150 mg Q2W + rosuvastatin 20 mg	54	13 (24.1%)	2 (3.7%)	2 (3.7%)	9 (16.7%)
ALTERNATIVE – CL1119					
Atorvastatin 20 mg	63	21 (33.3%)	16 (25.4%)	2 (3.2%)	3 (4.8%)
Ezetimibe 10 mg	124	42 (33.6%)	31 (24.8%)	0	11 (8.8%)
Alirocumab 75 mg Q2W up to 150 mg Q2W	126	30 (23.8%)	23 (18.3%)	0	7 (5.6%)
MONO – EFC11716					
Ezetimibe 10 mg	51	7 (13.7%)	4 (7.8%)	1 (2.0%)	2 (3.9%)

Study treatment	Randomised and treated	Did not complete study treatment period[a]	Discontinued due to:		
			AE	Poor protocol compliance	Other reasons
Alirocumab 75 mg Q2W up to 150 mg Q2W	52	8 (15.4%)	5 (9.6%)	0	3 (5.8%)

AE, adverse event; e-CRF, electronic case report form; FH, familial hypercholesterolaemia; Q2W, every 2 weeks; [a] As per e-CRF

Table 15 Overview of ODYSSEY programme trial populations at baseline by CV risk and background therapy

Study	Age (mean [SD])	Males (%)	Mean calculated LDL-C, mmol/L	High CV risk patients (%)	Very high CV risk patients (%)	High/very high CV risk patients (%)	Treatment with high-intensity statin (%)	Treatment with ezetimibe (%)	Proportion of patients with FH (%)
EFC12492 FH I	51.9 (12.7)	56.4	3.746	48.8	51.2	100	81.5	57.0	100
CL1112 FH II	53.2 (12.8)	52.6	3.480	61.4	38.6	100	86.3	66.3	100
EFC12732 HIGH FH	50.6 (13.3)	53.3	5.123	43.0	57.0	100	72.9	24.3	100
EFC11568 COMBO I	63.0 (9.3)	65.8	2.646	0	100	100	57.6	8.2	0
EFC11569 COMBO II	61.6 (9.3)	73.6	2.778	0	100	100	66.7	N/A	0
LTS11717 LONG TERM	60.5 (10.4)	62.2	3.171	8.5	91.5	100	44.1	14.3	17.7
CL1110 OPTIONS I	62.9 (10.2)	65.1	2.723	39.7	60.3	100	N/A	N/A	9.0
CL1118 OPTIONS II	60.9 (10.4)	61.3	2.882	37.0	63.0	100	N/A	N/A	13.4

Study	Age (mean [SD])	Males (%)	Mean calculated LDL-C, mmol/L	High CV risk patients (%)	Very high CV risk patients (%)	High/very high CV risk patients (%)	Treatment with high-intensity statin (%)	Treatment with ezetimibe (%)	Proportion of patients with FH (%)
CL1119 ALTERNATIVE	63.4 (9.5)	54.8	4.954	28.3	54.1	82.4	N/A	N/A	15.0
EFC11716 MONO	60.2 (5.0)	53.4	3.619	0*	0*	0	N/A	N/A	0

CV, cardiovascular; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; N/A, not available; SD, standard deviation

*All patients had moderate CV risk

Table 16 Summary of key baseline demographics in the ODYSSEY Phase III programme

	FHI	FHII	HIGH-FH	LONG TERM	COMBO-I	COMBO-II	OPTIONS I	OPTIONS II	ALTERNATIVE	MONO
N	496	249	107	2341	316	720	355	305	314	103
Age (years)means (SD)	52(13)	53(13)	51(13)	61(10)	63(9)	62(9)	63(10)	61(10)	63(10)	60(5)
Age Group [n(%)]										
<45	142(29%)	59(24%)	31(29%)	157 (7%)	13 (4%)	24 (3%)	18 (5%)	15 (5%)	9 (3)	0
≥45 to <65	263(54%)	139(56%)	62(58%)	1317(56%)	172 (54%)	410 (57%)	174 (49%)	173 (57%)	161 (51%)	84 (82%)
≥65 to <75	72(15%)	43(17%)	13(12%)	678 (29%)	99 (31%)	229 (32%)	125 (35%)	93 (31%)	100 (32%)	19 (18%)
≥75	9(2%)	8(3%)	1 (1%)	189 (8%)	32 (10%)	57 (8%)	38 (11%)	24 (8%)	44 (14%)	0
Male [n(%)]	274(56%)	131(53%)	57(53%)	1457 (62%)	208 (66%)	530 (74%)	231 (65%)	187 (61%)	172 (55%)	55 (53%)
Weight (kg) mean (SD)	85 (17)	85 (16)	83 (16)	87 (18)	95 (21)	89 (18)	90 (22)	89 (20)	84 (19)	86 (18)
BMI (kg/m2) Mean (SD)	29 (5)	28 (5)	29 (5)	30 (6)	32 (7)	30 (5)	31 (6)	31 (7)	29 (6)	29 (6)
Race [n(%)]										
White	444(91%)	244(98%)	94(88%)	2171(93%)	258 (82%)	610 (85%)	306 (86%)	256 (84%)	295 (94%)	93 (90%)
Black or African American	5 (1%)	2 (1%)	2 (2%)	77 (3%)	51 (16%	28 (4%)	38 (11%)	27 (9%)	12 (4%)	10 (10%)

	FHI	FHII	HIGH-FH	LONG TERM	COMBO-I	COMBO-II	OPTIONS I	OPTIONS II	ALTERNATIVE	MONO
Asian	6 (1%)	3 (1%)	6 (6%)	18 (1%)	3 (1%)	53 (7%)	6 (2%)	11 (4%)	4 (1%)	0
American Indian or Alaska native	2 (0.4%)	0	0	46 (2%)	3 (1%)	2 (0.3%)	3 (0.8%)	10 (3%)	0	0
Native Hawaiian or other Pacific Islander	1 (0.2%)	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0
Other	28 (6%)	0	5 (5%)	29 (1%)	1 (0.3%)	27 (4%)	1 (0.3%)	1 (0.3%)	2 (0.6%)	0
Any cardiovascular history /risk factors	249(51%)	96(39%)	61(57%)	2121(91%)	312 (99%)	718(100%)	355(100%)	305 (100%)	314 (100%)	102 (99%)
Coronary heart disease[a]	225 (46%)	88(35%)	53 (50%)	1607 (69%)	247 (78%)	649 (90%)	200 (56%)	177 (58%)	146 (47%)	0
Acute myocardial infarction	114 (24%)	41(17%)	24(22%)	872 (37%)	130 (41%)	416 (58%)	92 (26%)	84 (28%)	43 (14%)	0
Silent myocardial	10 (2%)	3 (1%)	1 (1%)	69 (3%)	14 (4%)	15 (2%)	16 (5)	11 (4%)	11 (4%)	0

	FHI	FHII	HIGH-FH	LONG TERM	COMBO-I	COMBO-II	OPTIONS I	OPTIONS II	ALTERNATIVE	MONO
infarction										
Unstable angina	61 (13%)	23 (9%)	13(12%)	291 (12%)	54 (17%)	152 (21%)	32 (9%)	40 (13%)	27 (9%)	0
Coronary revascularisation procedures	158 (33%)	70(28%)	25(23%)	1081(46%)	193 (61%)	495 (69%)	136 (38%)	130 (43%)	102 (33%)	0
Other clinically significant CHD[b]	135 (28%)	44(18%)	30(28%)	678 (29%)	52 (17%)	266 (37%)	143 (40%)	139 (46%)	89 (28%)	0
Coronary heart disease risk equivalents										
Ischaemic stroke	79 (16%)	19 (8%)	18(17%)	962 (41%)	136 (43%)	223 (31%)	100 (28%)	79 (26%)	73 (23%)	0
Peripheral arterial disease	16 (3%)	6 (2%)	4 (4%)	232 (10%)	27 (9%)	60 (8)	26 (7%)	16 (5%)	29 (9%)	0
Moderate chronic kidney disease	13 (3%)	6 (2%)	1 (1%)	122 (5%)	11 (4%)	35 (5%)	11 (3%)	12 (4%)	6 (2%)	0
Known history of	29 (6%)	3 (1%)	5 (5%)	326 (14%)	61 (19%)	84 (12%)	n.a.	n.a.		

	FHI	FHII	HIGH-FH	LONG TERM	COMBO-I	COMBO-II	OPTIONS I	OPTIONS II	ALTERNATIVE	MONO
DM(T 1 or 2) or more additional risk factors										
Abdominal aortic aneurysm	29 (6%)	7 (3%)	9 (8%)	482 (21%)	67 (21%)	90 (13%)	n.a.	n.a.		
Carotid artery occlusion > 50% without symptoms	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	8 (2%)	10 (3%)	8 (3%)	0
Carotid endarterectomy of	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	0	22 (7%)	0
carotid artery stent procedure	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1 (0.3%)	2 (1%)	11 (4%)	0
Renal artery stenosis	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	0	1 (0.3%)	0
Renal artery stent procedure	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	0	1 (0.3%)	0

	FHI	FHII	HIGH-FH	LONG TERM	COMBO-I	COMBO-II	OPTIONS I	OPTIONS II	ALTERNATIVE	MONO
Type 1 or 2 DM with target organ damage	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	43 (12.1)	32 (11%)	11 (4%)	0
Very high CV risk	249 (51%)	96(39%)	61(57%)	2141(92%)	316(100%)	720(100%)	214 (60%)	192 (63%)	170 (54%)	0
High CV risk	237 (49%)	153(61%)	46(43%)	200 (9%)	0	0	141 (40%)	11 (37%)	89 (28%)	0
Moderate CV risk	0	0	0	0	0	0	0	0	43 (14%)	103(100%)
Hypertension	210(43%)	81(33%)	61(57%)	1762(75%)	280 (89%)	580 (81%)	278 (78%)	221 (73%)	197 (63%)	32 (31%)
Type 1 Diabetes	0	1(0.4%)	0	23(1%)	0	2(0.3%)	1(0.3%)	2(0.7%)	0	0
Type 2 Diabetes	56(12%)	10 (4%)	15(14%)	809 (35%)	136 (43%)	221 (31%)	177 (50%)	126 (41%)	75 (24%)	4 (4%)
Family history of premature CHD	218 (45%)	122(49%)	61(57%)	762 (33%)	109 (35%)	153 (21%)	85 (24%)	88 (30%)	114 (36%)	4 (4%)
Current Smoker	69(14%)	49(20%)	21(20%)	484 (21%)	60 (19%)	155 (22%)	66 (19%)	56 (18%)	21 (7%)	11 (11%)
HeFH	486(100%)	249(100%)	107 (100%)	415 (18%)	0	0	32 (9%)	41 (13%)	47 (15%)	0
non-FH	0	0	0	1926(82%)	316(100%)	720(100%)	323 (91%)	264 (87%)	267 (85%)	103(100%)
Taking	405(83%)	219(88%)	85(79%)	1096(47%)	198 (63%)	494 (69%)	355(100%)	305(100%)	17 (5%)	0

	FHI	FHII	HIGH-FH	LONG TERM	COMBO-I	COMBO-II	OPTIONS I	OPTIONS II	ALTERNATIVE	MONO
statins										
Free PCSK9 level (ng/mL)	315(128)	n.a.	n.a.	305 (122)	n.a.	283 (99)	n.a.	n.a.	n.a.	186 (56)
Total PCSK9 level (ng/mL)	853(293)	n.a.	n.a.	679 (298)	n.a.	620(187)	n.a	n.a.	n.a.	498 (154)
Calculated LDL-C (mg/dL)Mean (SD)	145(50)	134 (41)	198 (53)	122 (42)	102 (32)	107 (36)	105 (34)	111 (39)	191 (69)	140 (26)
Calculated LDL-C (mmol/L) Mean (SD)	3.7 (1.3)	3.5 (1.1)	5.1 (1.4)	3.2 (1.1)	2.6 (0.8)	2.8 (0.9)	2.7 (0.9)	2.9 (1.0)	5.0 (1.8)	3.6 (0.7)

4.6 Quality assessment of the relevant randomised controlled trials

The quality of included RCTs was examined following The Cochrane Collaboration's tool for assessing risk of bias [79 99]

All studies were deemed to have a low risk of bias or unclear risk of bias. A summary can be found in Table 17 and full details in Appendix 6. Studies were double-blind with objective endpoints, and the analysis was conducted as both ITT and on-treatment with a good degree of alignment. One quality issue was observed in High FH, where two sites had protocol violations (did not meet GCP requirements); these sites were shut down.

Table 17 Quality assessment of the randomised controlled trials

Author (RefID), year		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other potential threats to validity
		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective outcome reporting	Imbalance in baseline characteristics
Ginsberg HIGH FH	**Judgement**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Kastelein ODYSSEY FH I	**Judgement**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Kastelein ODYSSEY FH II	**Judgement**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Robinson ODYSSEY LONG TERM	**Judgement**	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Keriakes COMBO I	**Judgement**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Cannon COMBO II	**Judgement**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Bays OPTIONS I	**Judgement**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Bays OPTIONS II	**Judgement**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Roth ODYSSEY MONO	**Judgement**	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk

Author (RefID), year		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other potential threats to validity
		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective outcome reporting	Imbalance in baseline characteristics
Moriarty ODYSSEY ALTERNATIVE	**Judgement**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Total low risk		**2**	**1**	**10**	**1**	**10**	**10**	**9**
Total unclear risk		**8**	**9**	**0**	**9**	**0**	**0**	**1**
Total high risk		**0**	**0**	**0**	**0**	**0**	**0**	**0**
TOTAL		**10**	**10**	**10**	**10**	**10**	**10**	**10**

FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; IS, ischaemic stroke; MI, myocardial infarction; RCT, randomised controlled trial

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Key Points

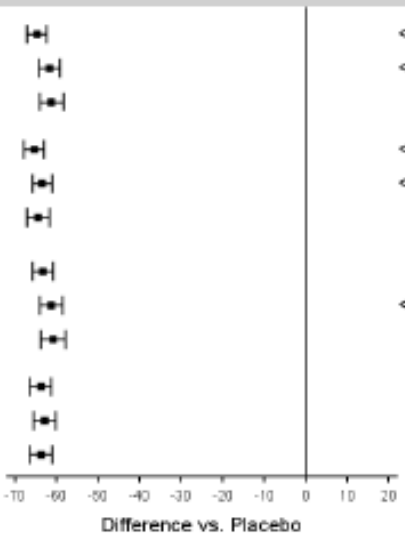
- **Alirocumab demonstrates a substantial and consistent reduction in LDL-C levels across the ODYSSEY programme**
    - **From 39% and 62% compared to placebo (Week 24 values)**
- **The effect was maintained over the duration of the trials (cut-off at 52 weeks for most trials, up to 78 weeks for LONG-TERM)**
- **Alirocumab also exerts a consistent and expected impact on other key lipid parameters (lowering non-HDL-C, ApoB, ApoA-1, Lp(a) and increasing HDL-C**
- **Calculated LDL-C measurement was used for the primary efficacy parameters. Directly measured LDL-C showed very comparable results**
- **In almost all cases a significantly higher proportion of patients reach pre-defined treatment goals with alirocumab than vs active or no-active comparator**
- **A post-hoc analysis of the LONG TERM study provides preliminary indication of a reduction in cardiovascular events with alirocumab**

A summary of the ODYSSEY trial programme efficacy data is presented below. The trial programme covers a wide range of clinical end points which are in line with UK monitoring in clinical practice (total cholesterol, non-HDL-C, triglycerides, combined lipid profile [100] As detailed below, the effect of alirocumab on LDL-C levels is substantial, consistent and maintained throught the duration of the trials in each case. The impact of alirocumab on other lipid parameters was also consistent and directionally in line with what would be expected to be associated with a decrease in CV risk. The proportion of patients achieving pre-defined ODYSSEY LDL-C goals is clearly influenced by the starting baseline LDL-C of patients which varies across the ODYSSEY trials (Section 4.5).

Calculated LDL-C measurement according to the Friedewald method was used for the primary efficacy parameters for LDL-C and at all-time points where LDL-C was determined. The programme also included measured LDL-C using the beta quantification method at certain key time points. This was assessed at Week 12, Week 24, and Week 52 in the LONG TERM study. In addition, measured LDL-C at baseline and Week 24 was also implemented during the course of 7 other studies (FH I, FH II, COMBO I, COMBO II, OPTIONS I, OPTIONS II, and ALTERNATIVE) to further assess the possible differences between the two measurement modalities and confirm the robustness of the results regardless of the method used to obtain LDL-C level. The comparability of the calculated and directly measured LDL-C efficacy of alirocumab was confirmed in the LONG TERM study where a similar magnitude of reduction in LDL-C at Week 24 was observed. Similar results were seen at Week 12 and Week 52 and regardless of the analysis performed (ITT or on-treatment analysis) as illustrated in Figure 9.

Figure 9 Summary of percent change from baseline in calculated LDL-C and measured LDL-C - Study LONG TERM

Endpoint	Analysis	Time	% change from baseline LS means (SE) Placebo	Alirocumab 150 Q2W	LS means difference (95% CI)	P-value	
Calculated LDL-C	ITT	Week 12	1.5 (1.0)	-63.3 (0.7)		<0.0001*	K
		Week 24	0.8 (1.0)	-61.0 (0.7)		<0.0001*	P
		Week 52	4.4 (1.2)	-56.8 (0.8)		<0.0001	
	On-treatment	Week 12	1.4 (1.0)	-64.2 (0.7)		<0.0001*	K
		Week 24	0.7 (1.0)	-62.8 (0.7)		<0.0001*	K
		Week 52	4.6 (1.1)	-59.9 (0.8)		<0.0001	
Measured LDL-C	ITT	Week 12	2.8 (1.1)	-60.6 (0.8)		<0.0001	
		Week 24	3.5 (1.1)	-57.8 (0.8)		<0.0001*	K
		Week 52	6.5 (1.2)	-54.4 (0.9)		<0.0001	
	On-treatment	Week 12	2.8 (1.1)	-61.2 (0.8)		<0.0001	
		Week 24	3.4 (1.1)	-59.6 (0.8)		<0.0001	
		Week 52	6.5 (1.1)	-57.4 (0.8)		<0.0001	



P: Primary efficacy endpoint
K: Key secondary efficacy endpoint
For primary and key secondary efficacy endpoints, the p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

4.7.1 FHI – EFC12492

In the ITT analysis, at Week 24, a significant LS mean percent reduction from baseline in calculated LDL-C was observed in the alirocumab 75/150 mg group as compared with an increase in the placebo group (LS mean difference versus placebo of -57.9%, p<0.0001).

Statistical significance was also reached at Week 12 on 75 mg, before possible up-titration to 150 mg (LS mean difference versus placebo of -49.2%; p<0.0001 - ITT analysis). The on-treatment analysis of the LDL-C percent change from baseline to Week 24 and to Week 12 showed very consistent results with the ITT analysis.

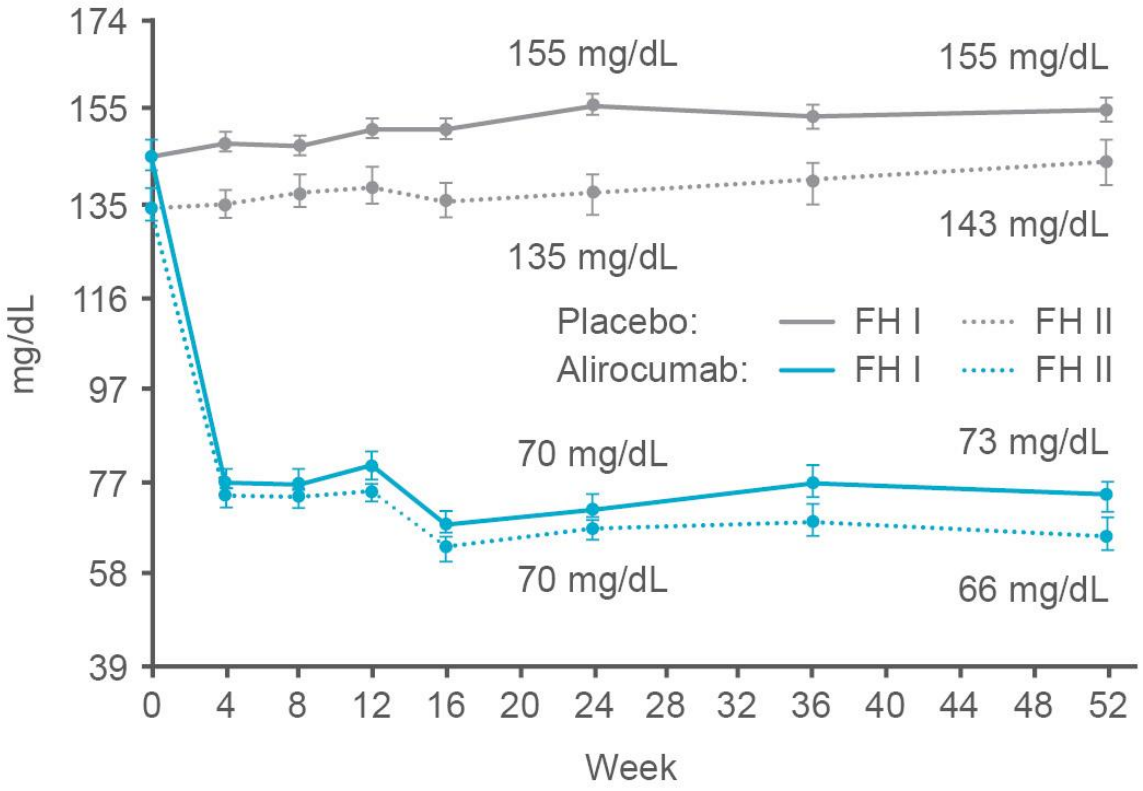
Effects of alirocumab on all key secondary endpoints including Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, fasting TGs, and Apo A-1 were statistically significant at both Week 24 and Week 12 (Table 19).

At all time points, the majority of patients in the alirocumab group reached all pre-specified LDL-C targets, with a highly significant difference versus placebo (eg, at Week 24, for alirocumab 72.2% of patients at very high CV risk with calculated LDL-C <70 mg/dL [<1.81 mmol/L] or at high CV risk with calculated LDL-C <100 mg/dL [<2.59 mmol/L] versus 2.4% for placebo [p<0.0001])).

The mean LDL-C concentrations dropped rapidly in the first 4 weeks with alirocumab. This reduction alirocumab. This reduction achieved by 4 weeks was maintained at all time points throughout throughout the study up to Week 52 with very consistent results over time regardless of the of the analysis (ITT or on-treatment analysis) (

Figure 10).

Figure 10 Calculated LDL-C LS mean (+/- SE) percent change from baseline: FHI and FHII - Time profile – ITT analysis



4.7.2 FHII – CL1112

In the ITT analysis, at Week 24, a significant LS mean percent reduction from baseline in calculated LDL-C was observed in the alirocumab 75/150 mg group as compared to an increase in the placebo group (LS mean difference versus placebo of -51.4%, p<0.0001).

Statistical significance was also reached at Week 12 on 75 mg, before possible up-titration to 150 mg (LS mean difference versus placebo of -48.4%; p<0.0001 - ITT analysis). The on-treatment analysis of the LDL-C percent change from baseline to Week 24 and to Week 12 showed very consistent results with the ITT analysis. Effects of alirocumab on all key secondary endpoints were statistically significant at Week 12 and Week 24, except Apo A-1 at Week 12 (
Table **20**).

At all time points, the majority of patients in the alirocumab group reached all pre-specified LDL-C targets, with highly significant difference versus placebo (eg, at Week 24 for alirocumab, 81.4% of patients at very high CV risk with calculated LDL-C <70 mg/dL [<1.81 mmol/L] or at high CV risk with calculated LDL-C <100 mg/dL [<2.59 mmol/L] versus 11.3% for placebo [p<0.0001].

Following a rapid drop in LDL-C concentrations in the first 4 weeks induced by alirocumab, this reduction achieved by 4 weeks was well maintained at all time points throughout the study up to Week 52 with very consistent results over time regardless of the analysis (ITT or on-treatment analysis) (

Figure 10).

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4.7.3 HIGH FH – EFC12732

In the ITT analysis, at Week 24, a significant LS mean percent reduction from baseline in calculated LDL-C was observed in the alirocumab group compared to the placebo group (LS mean difference versus placebo of -39.1%, p<0.0001).

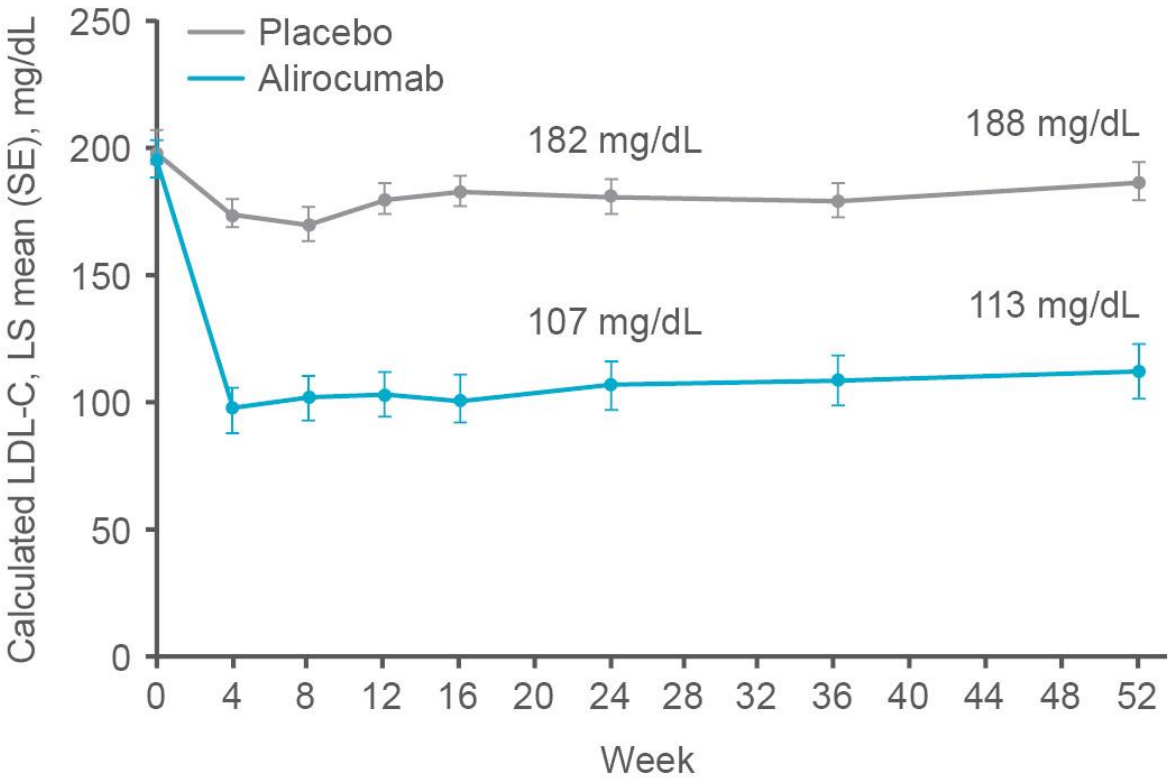
Statistical significance was also reached at Week 12 on 150 mg (LS mean difference versus placebo of -40.3%; p<0.0001 - ITT analysis). The on-treatment analysis of the LDL-C percent change from baseline to Week 24 and to Week 12 showed very consistent results.

Effects of alirocumab on key secondary endpoints including Apo B, non-HDL-C, Total-C at Week 24 and Week 12, and Lp(a) at Week 24 were statistically significant. Numerical reduction in fasting TGs as well as numerical increase in HDL-C and Apo A-1 were also seen (Table 21).

At all time points, the majority of patients in the alirocumab group reached all pre-specified LDL-C targets, with highly significant difference versus placebo (e.g., at Week 24, for alirocumab 41.0% of patients at very high CV risk with calculated LDL-C <70 mg/dL [<1.81 mmol/L] or at high CV risk with calculated LDL-C <100 mg/dL [<2.59 mmol/L] versus 5.7% for placebo [p=0.0016]).

The mean reduction in calculated LDL-C observed with alirocumab 150 mg was achieved from Week 4 and maintained at all time points throughout the study up to Week 52 with consistency in the effect over time regardless of the analysis (ITT or on-treatment analysis) (Figure 11).

Figure 11 LDL-C LS mean (+/- SE) percent change from baseline: Time profile - ITT analysis – ITT population



4.7.4 COMBO I – EFC11568

In the ITT analysis, at Week 24, the LS mean percent reduction from baseline in calculated LDL-C was significantly greater in the alirocumab 75/150 mg group compared to the placebo group (LS mean difference versus placebo of -45.9%, $p<0.0001$).

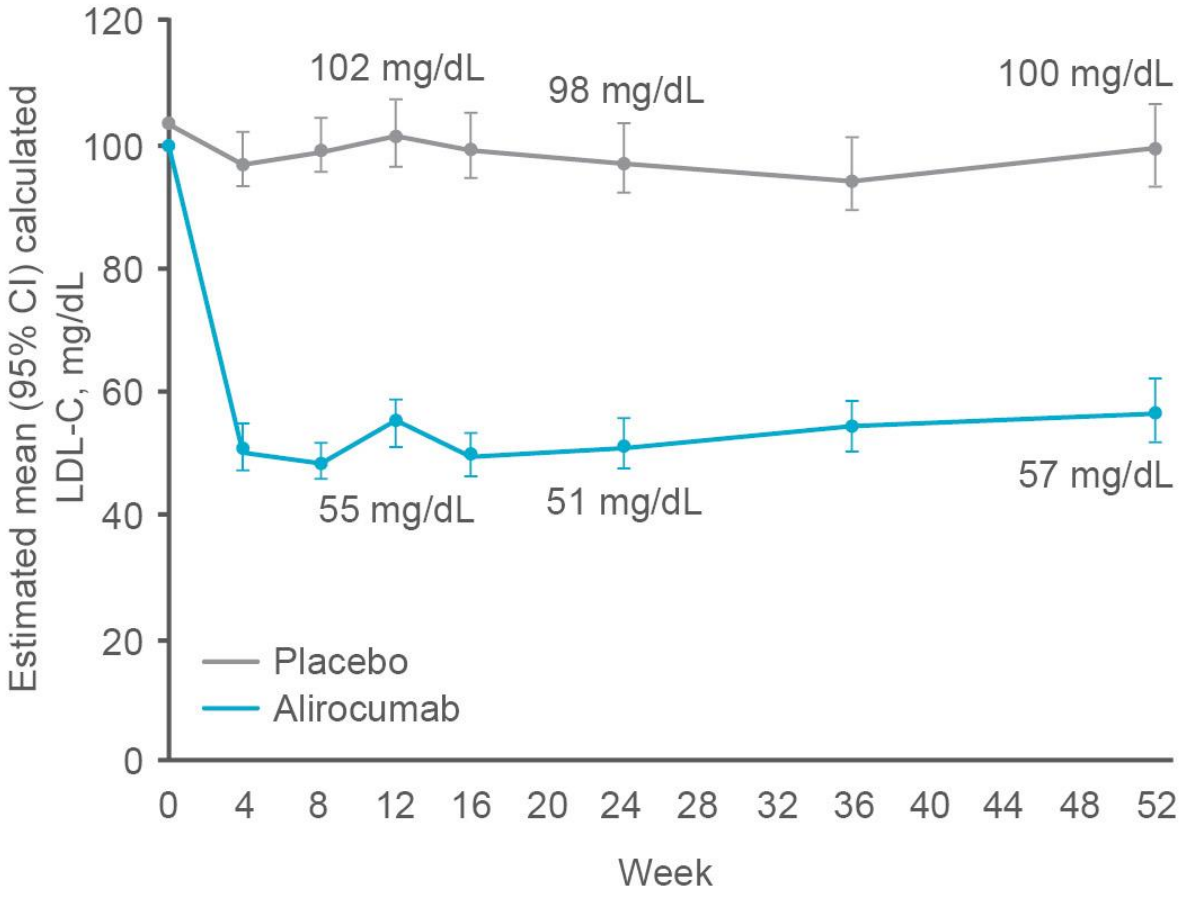
Statistical significance was also reached at Week 12, on the dose of 75 mg, before possible up-titration to 150 mg (LS mean difference versus placebo of -47.4%; $p<0.0001$). The on-treatment analysis of the LDL-C percent change form baseline to Week 24 and Week 12 showed very consistent results with the ITT analysis.

Effects of alirocumab on key secondary endpoints including Apo B, non-HDL-C, Total-C at Week 24 and Week 12, and Lp(a) and HDL-C at Week 24 were statistically significant. Numerical reduction in fasting TGs was also observed as well as a numerical increase in Apo A-1 (Table 22).

At all time points, the majority of patients in the alirocumab group reached all pre-specified LDL-C targets, with highly significant difference versus placebo (eg, at Week 24 for alirocumab, 75.0% of patients with calculated LDL-C <70 mg/dL [<1.81 mmol/L] versus 9.0% for placebo [p<0.0001]). In the alirocumab group, LDL-C reduction from baseline was observed from Week 4 to Week 52. In the ITT analysis, a significant reduction was also seen for alirocumab as compared with placebo, however a slight diminution over time in LDL-C reduction was observed in alirocumab group (LS mean versus baseline at Week 52 of -42.5% versus -48.2% at Week 24).

Within the on-treatment analysis the same magnitude of effect was seen at Week 52 as compared with Week 24 (LS mean versus baseline at Week 52 of -47.5% versus -48.2% at Week 24), thus confirming the consistency of the effect in patients who maintain treatment with alirocumab (Figure 12).

Figure 12 LDL-C LS mean (+/- SE) percent change from baseline: Time profile - ITT analysis – ITT population



4.7.5 COMBO II – EFC11569

In the ITT analysis, at Week 24, the LS mean percent reduction from baseline in calculated LDL-C was significantly greater in the alirocumab group 75/150 mg compared to the ezetimibe group (LS mean difference versus ezetimibe of -29.8%, p<0.0001).

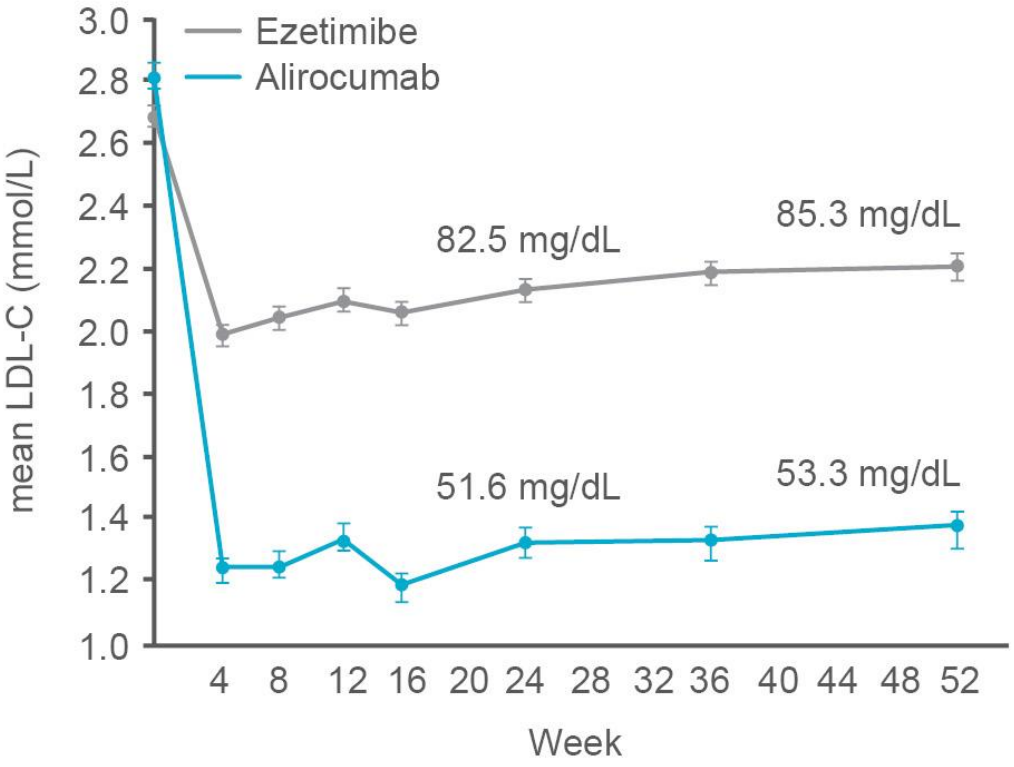
Statistical significance was also reached at Week 12, on the dose of 75 mg, before possible up-titration to 150 mg (LS mean difference versus ezetimibe of -29.4%; p<0.0001). The on-treatment analysis of the LDL-C percent change from baseline to Week 24 and Week 12 showed very consistent results with the ITT analysis.

Effects of alirocumab on key secondary endpoints including Apo B, non-HDL-C, Total-C at Week 24 and Week 12, and Lp(a) and HDL-C at Week 24 were statistically significant. Numerical reduction in fasting TGs as well as numerical increase in Apo A-1 were also seen (

Table 23).

At all time points, a significantly higher proportion of patients in the alirocumab group versus the ezetimibe group reached all pre-specified LDL-C targets, (eg, at Week 24 for alirocumab, 77.0% of patients with calculated LDL-C <70 mg/dL [<1.81 mmol/L] versus 45.6% for ezetimibe [p<0.0001]). The large percent decrease in calculated LDL-C observed with alirocumab was achieved from Week 4 and maintained at all time points throughout the study up to Week 52 (Figure 13).

Figure 13 LDL-C LS mean (+/- SE) percent change from baseline: Time profile - ITT analysis – ITT population



4.7.6 LONG TERM – LTS11717

4.7.6.1 Efficacy Data

In the ITT analysis, at Week 24, a significant LS mean percent reduction from baseline in calculated LDL-C was observed with alirocumab 150 mg compared to an increase in the placebo group (LS mean difference versus placebo of -61.9%, p<0.0001).

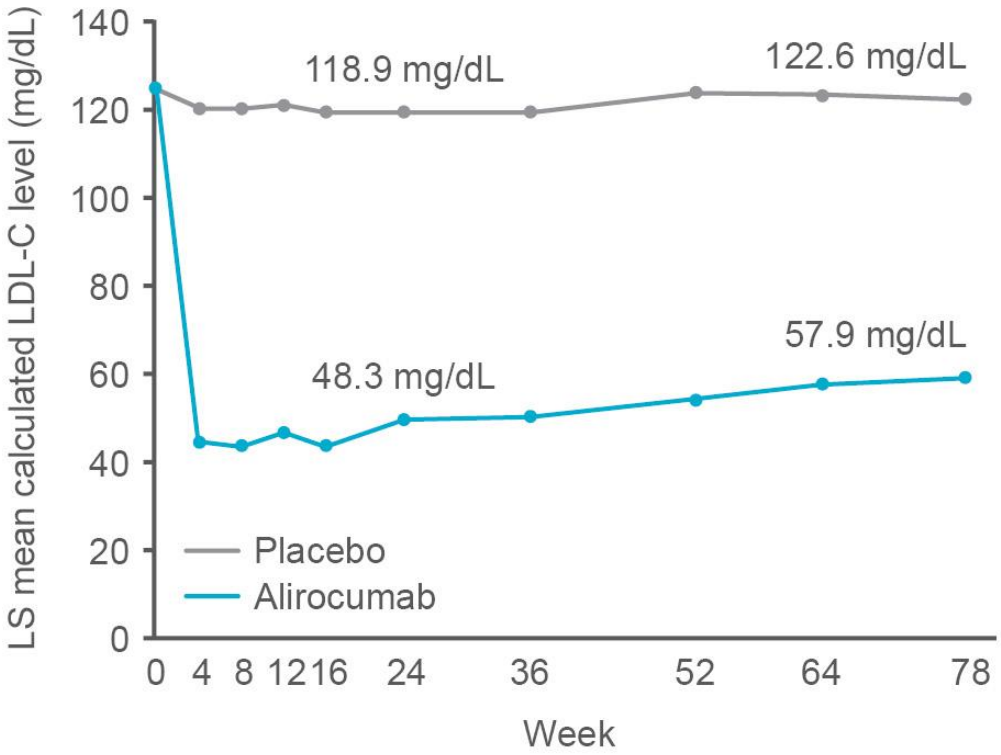
Statistical significance was also reached at Week 12 on 150 mg (LS mean difference versus placebo of -64.8%; p<0.0001 – ITT population). The on-treatment analysis of the LDL-C percent change from baseline to Week 24 and Week 12 showed very consistent results with the ITT analysis.

Effects of alirocumab on all key secondary endpoints including Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, fasting TGs, and Apo A-1 at Week 12 and Week 24 were statistically significant. (Table 24)

At all time points, the majority of patients in the alirocumab group reached all pre-specified LDL-C specified LDL-C targets, with highly significant difference versus placebo (eg, at Week 24 Week 24 for alirocumab, 79.3% of patients with calculated LDL-C <70 mg/dL [<1.81 mmol/L] mmol/L] versus 8.0% for placebo [p<0.0001]). The large percent decrease in calculated LDL-calculated LDL-C observed with alirocumab 150 mg was achieved from Week 4 and maintained at all time points throughout the study up to Week 52. (

Figure 14)

Figure 14 LDL-C LS mean (+/- SE) percent change from baseline: Time profile - ITT analysis – ITT population



4.7.6.2 LONG TERM Post-Hoc MACE Analysis

As the largest and longest of the Phase III studies, a post-hoc analysis of the LONG TERM study was undertaken assessing major adverse cardiac events (MACE), comprising CHD death, non-fatal MI, fatal or non-fatal ischaemic stroke, and

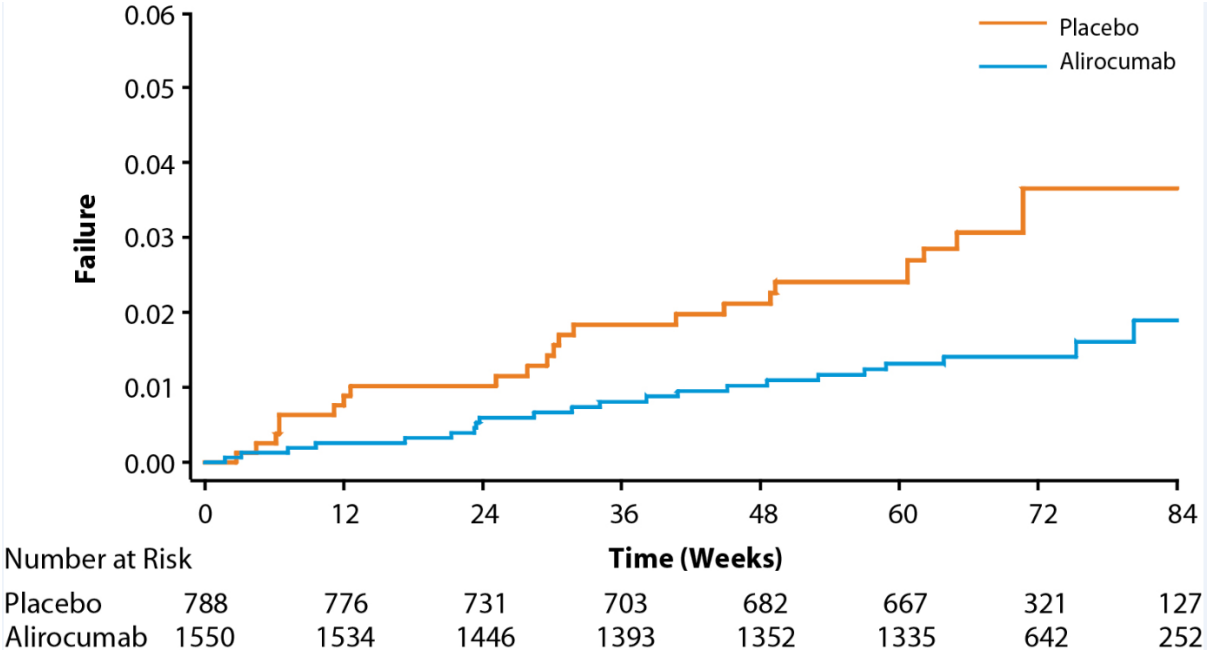
unstable angina requiring hospitalisation, which is generally considered the most appropriate and rigorous to assess cardiovascular outcomes and is the endpoint for the CVOT. 2020 patients with high and very high CV risk were treated for at least 12 months [817 patients were treated for up to 18 months (78 weeks)], with an overall patient-years exposure of 2892 (1918 in the Alirocumab group).

The rate of MACE was 48% lower with alirocumab than with placebo (27 (1.7%) vs. 26 (3.3%); hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal P = 0.02) (Table 18 and Figure 15).

Table 18 Summary of LONG TERM cardiovascular TEAEs according to adjudication (MACE endpoint) – Safety population

Category of adjudication n(%)	Placebo (N=788)	Alirocumab 150 Q2W (N=1550)
Any patients with treatment emergent cardiovascular events confirmed by adjudication (MACE event)	26 (3.3%)	27 (1.7%)
CHD death (including undetermined cause)	7 (0.9%)	4 (0.3%)
Non-fatal MI	18 (2.3%)	14 (0.9%)
Fatal and non-fatal ischaemic stroke (including stroke not otherwise specified)	2 (0.3%)	9 (0.56
Unstable angina requiring hospitalisation	1 (0.1%)	0

Figure 15 Summary of LONG TERM cardiovascular TEAEs according to adjudication (MACE endpoint) – Safety population



Failure = Cumulative incidence of event

When all adjudicated cardiovascular events were included (i.e., with the addition of congestive heart failure requiring hospitalisation and ischemia-driven coronary revascularisation), the difference between groups was not significant (72 (4.6%) vs. 40 (5.1%); nominal P = 0.68).

This is a post-hoc analysis where there are a relatively small number of cardiovascular events. Nevertheless, the analysis provides initial evidence of a reduction in MACE with alirocumab, in line with the rationale for PCSK9 inhibitor development. Analyses of MACE in the Global pool of Phase III trials are discussed further in Section 4.12

4.7.7 OPTIONS I – CL1110

In the ITT analysis, a statistically significant difference in the LS mean percent change from baseline in change from baseline in calculated LDL-C at Week 24 was observed for all pre-specified specified comparisons between alirocumab 75/150 mg versus ezetimibe or versus statin statin intensification, and whatever the atorvastatin regimen (20 mg or 40 mg) (Figure 16 and

Figure 17).

Treatment effects were consistent across all subgroups examined. In the pooled alirocumab groups, 13 (14.0%) patients (4 in the atorvastatin 20 mg regimen and 9 in the atorvastatin 40 mg regimen) received an automatic up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.

Statistical significance was also reached at Week 12 for all pre-specified comparisons on the dose of 75 mg, before possible up-titration to 150 mg. The on-treatment analysis of the LDL-C percent change from baseline to Week 24 and Week 12 showed very consistent results with the ITT analysis.

Alirocumab also demonstrated a consistent treatment effect across a number of key secondary endpoints, including Apo B, non-HDL-C, Total-C. Because of the numerous pairwise comparisons and the variability observed in this study across groups, a statistically significant difference was not reached for some comparisons. However, clinically meaningful changes were systematically seen with alirocumab. (Table 25 and

Table 26).

At all time points, a higher proportion of patients in the alirocumab group reached all pre-specified LDL-C target, with a consistent significant difference versus atorvastatin intensification or ezetimibe.

Figure 16 Calculated LDL-C LS Mean (+/-SE) Percent Change from Baseline: Time Profile – ITT Analysis – Atorvastatin 20 mg Baseline Regimen-ITT Population

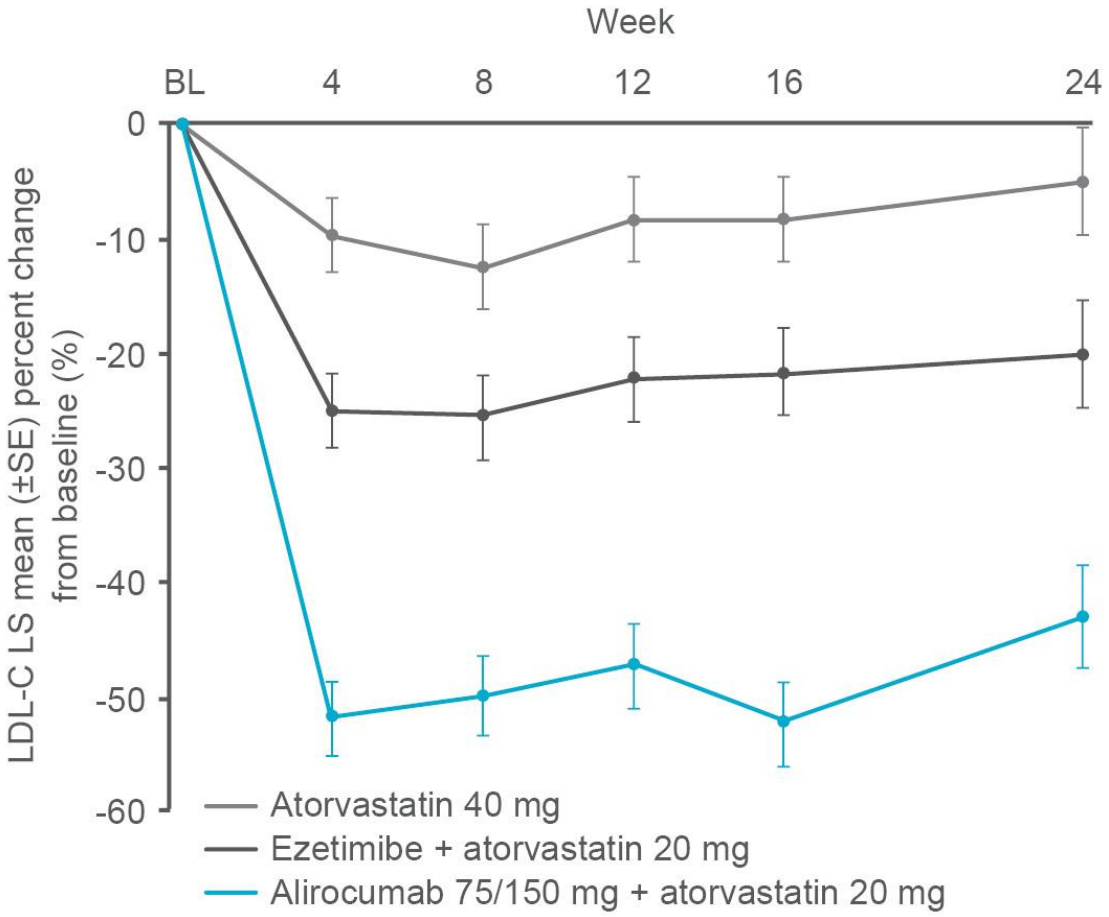
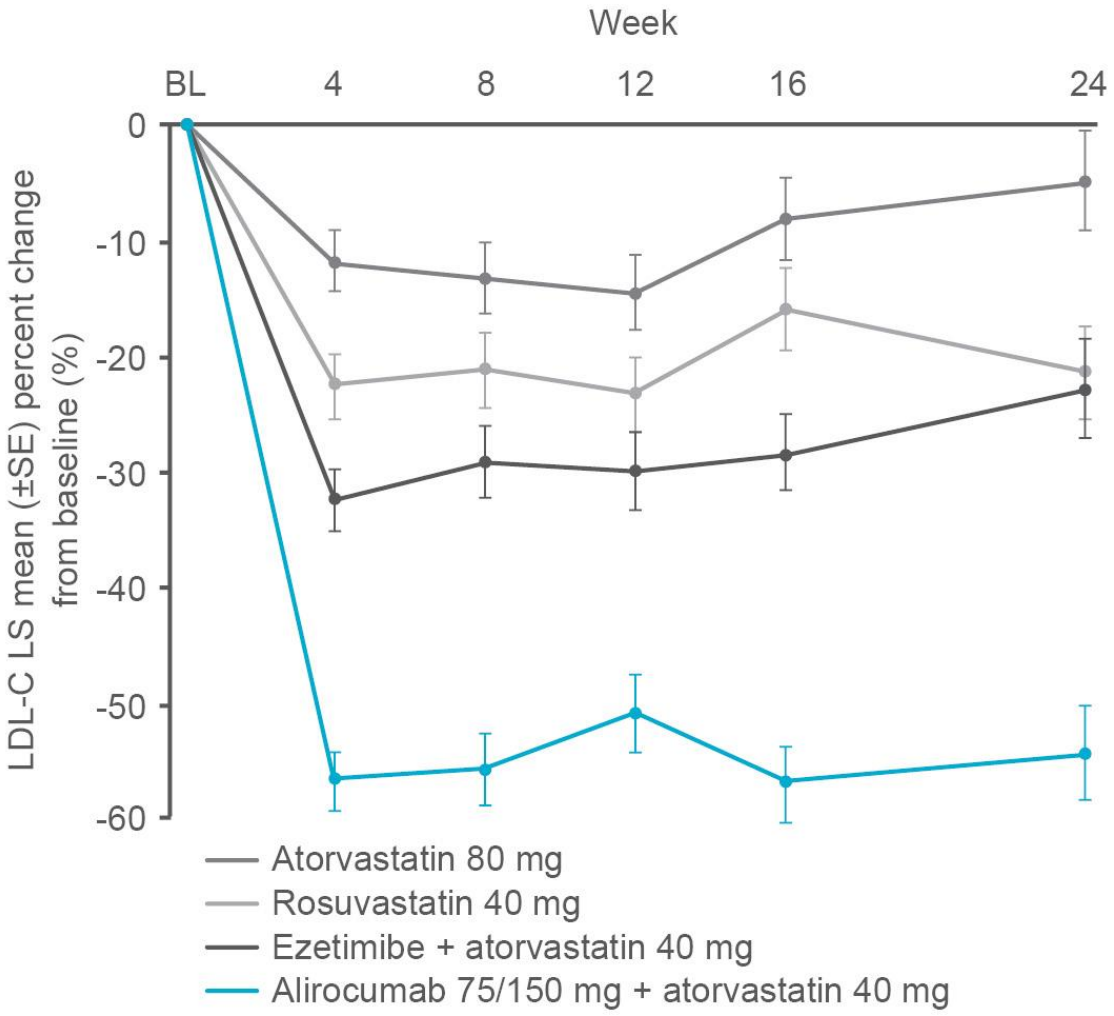


Figure 17 Calculated LDL-C LS Mean (+/-SE) Percent Change from Baseline: Time Profile – ITT Analysis – Atorvastatin 40 mg Baseline Regimen-ITT Population



4.7.8 OPTIONS II – CL1118

In the rosuvastatin 10 mg regimen (baseline stratum), alirocumab 75/150 mg demonstrated a statistically significant greater LS mean percent reduction in calculated LDL-C from baseline to Week 24 as compared with ezetimibe and rosuvastatin intensification to 20 mg ($p<0.0001$; ITT analysis).

In the rosuvastatin 20 mg regimen (baseline stratum), the LS mean percent reduction from baseline in LDL-C at week 24 was numerically greater with alirocumab 75/150 mg as compared with ezetimibe and rosuvastatin intensification to 40 mg, however in this stratum where larger variability was noted statistical significance was not reached at the 2-sided significance level of 0.0125.

Similar results to Week 24 were seen at Week 12 for both dose regimens. The on treatment analysis performed for both dose regimens showed consistent results as compared with the ITT analysis at both Week 24 and Week 12 (Figure 18 and

Figure 19).

Statistical significance was reached for many of the key secondary endpoints in the rosuvastatin 10 mg regimen (baseline stratum). In the rosuvastatin 20 mg regimen (baseline stratum) since statistical significance for the primary endpoint was not reached, p-values for the key secondary endpoints are presented for descriptive purposes. However, in both regimens, positive changes produced by alirocumab on the different key endpoints were overall numerically greater than those seen with ezetimibe or rosuvastatin intensification. (

Table 27 and Table 28).

At all time points a greater proportion of patients in the alirocumab group reached all pre-specified LDL-C targets versus ezetimibe or rosuvastatin intensification to 20 mg or 40 mg, although statistical significance was not systematically reached.

Figure 18 Calculated LDL-C Mean (±SE) Percent Change from Baseline: Time Profile-Rosuvastatin 10 mg Baseline Regimen - ITT Population

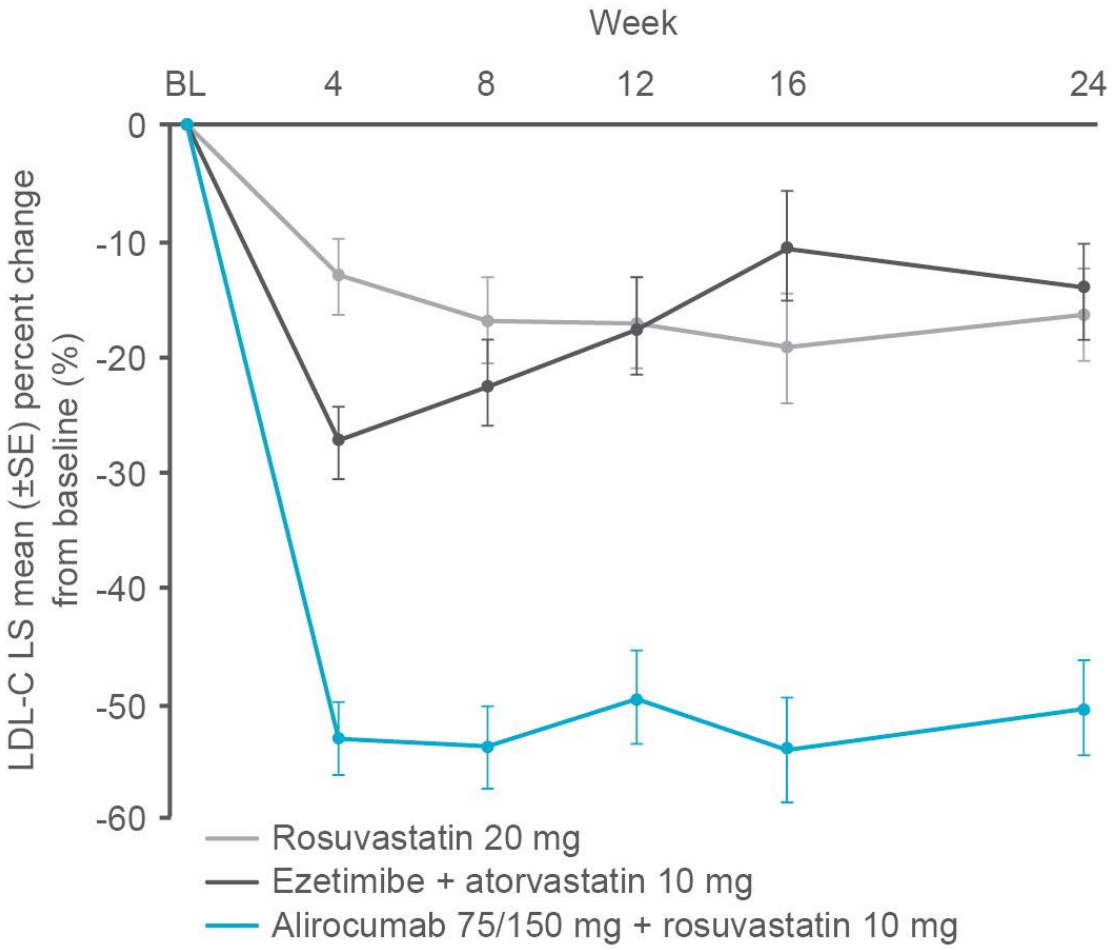
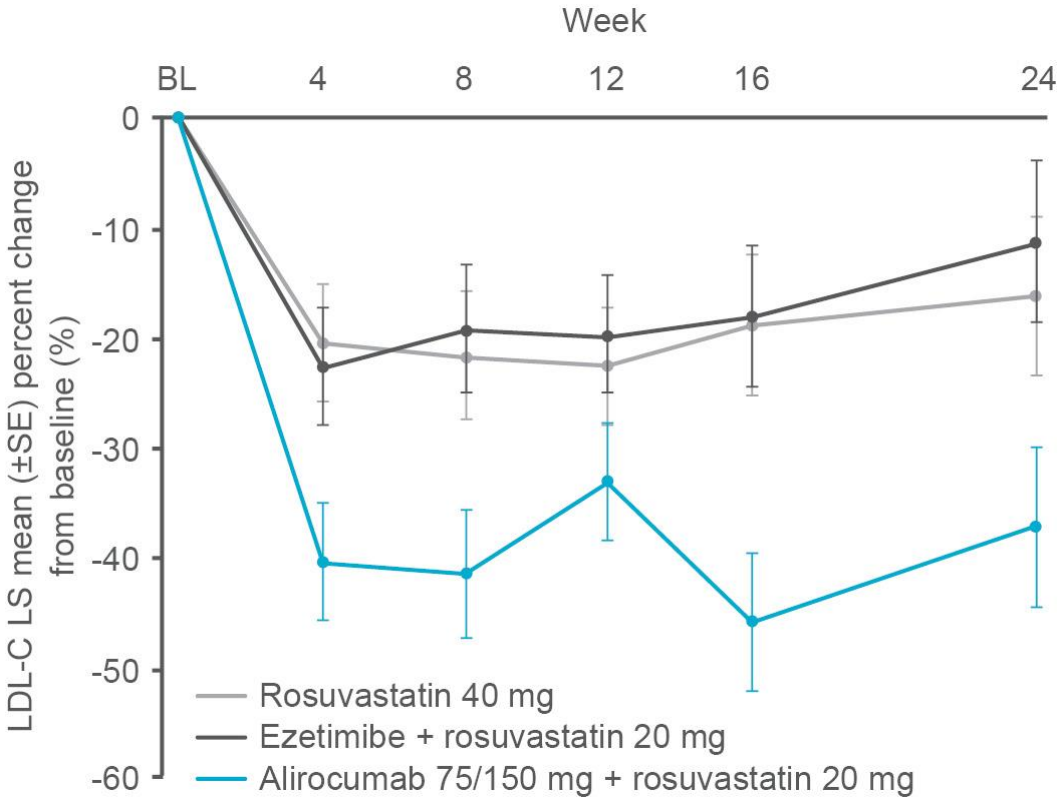


Figure 19 Calculated LDL-C Mean (±SE) Percent Change from Baseline: Time Profile-Rosuvastatin 20 mg Baseline Regimen - ITT Population



4.7.9 ALTERNATIVE – CL1119

In the ITT analysis, at Week 24, a significant LS mean percent reduction from baseline in calculated LDL-C was observed in the alirocumab 75/150 mg group compared to the ezetimibe group (LS mean difference versus ezetimibe of -30.4%, p<0.0001).

In the alirocumab group, 54 (49.5%) patients received an automatic up-titration from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner, resulting in an additional mean reduction of -3.6% between Week 12 and Week 24 (Table 58).

Statistical significance was also reached at Week 12, on the dose of 75 mg, before possible up-titration to 150 mg (LS mean difference versus ezetimibe of -31.5%). The on-treatment analysis of the LDL-C percent change from baseline to Week 24 and Week 12 showed very consistent results with the ITT analysis.

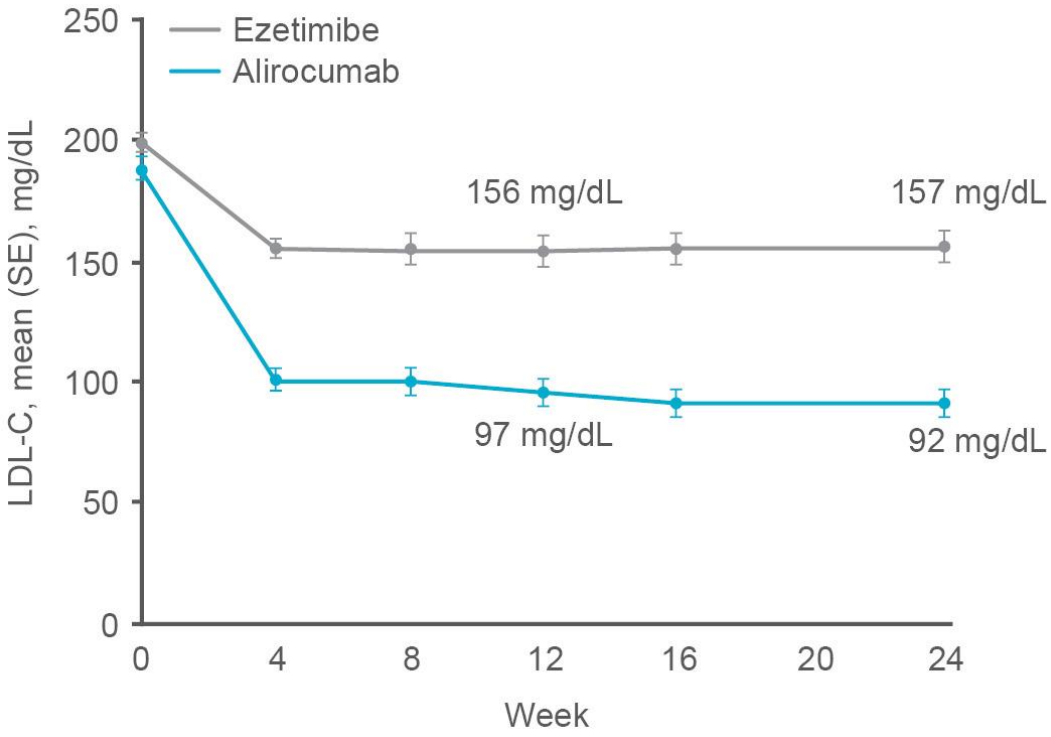
Alirocumab induced a greater statistically significant mean percent reduction for Apo B, non-HDL-C, Total-C at Week 24 and Week 12 and Lp(a) at Week 24 versus

ezetimibe. For the other key secondary endpoints, although no statistical significance was reached, there was a consistently a greater improvement with alirocumab as compared with ezetimibe, with the exception of TGs. (

Table **29**)

The large percent decrease in calculated LDL-C observed with alirocumab was achieved from Week 4 and maintained at all time points throughout the study set up to Week 24 (Figure 20).

Figure 20 Calculated LDL-C LS Mean (±SE) Percent Change from Baseline (ITT Analysis): Time Profile - ITT Population



4.7.10 MONO – EFC11716

In the ITT analysis, at Week 24, a significant LS mean percent reduction from baseline in calculated LDL-C was observed in the alirocumab 75/150 mg group as compared to the ezetimibe group (LS mean difference versus ezetimibe of -31.6%, p<0.0001).

Statistical significance was also reached at Week 12, on the dose of 75 mg, before possible up-titration to 150 mg (LS mean difference versus ezetimibe of -28.5%, p<0.0001). The on-treatment analysis of the LDL-C percent change form baseline to Week 24 and Week 12 showed very consistent results with the ITT analysis.

Alirocumab induced a greater statistically significant mean percent reduction for Apo B, non-HDL-C, Total-C at Week 24 and Week 12 versus ezetimibe. For the other key secondary endpoints, although no statistical significance was reached, there was a consistently greater improvement with alirocumab as compared with ezetimibe (

Table 30).

The large percent decrease in calculated LDL-C observed with alirocumab was achieved from Week 4 and maintained at all time points throughout the study up to Week 24 (Figure 21).

Figure 21 Calculated LDL-C LS Mean (±SE) Percent Change from Baseline (ITT Analysis): Time Profile - ITT Population

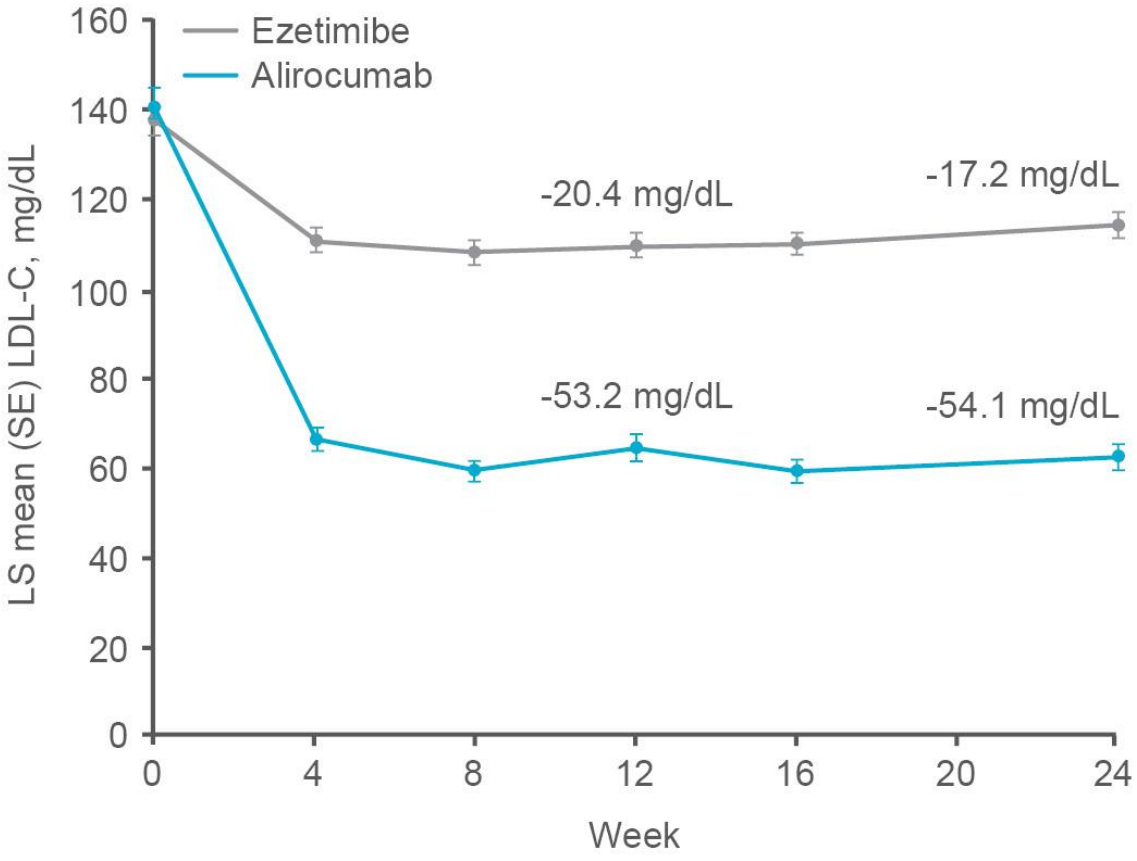

Ezetimibe
Alirocumab
LS mean (SE) LDL-C, mg/dL
160
140
120
100
80
60
40
20
0
-20.4 mg/dL
-17.2 mg/dL
-53.2 mg/dL
-54.1 mg/dL
0
4
8
12
16
20
24
Week

Table 19 Efficacy endpoints (mean percent change from baseline) in the ITT analysis - FH I

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12													
Placebo	163	5.7	5.7	NR	4.1	5.3	3.1	–3.9	1.7	2.1	0.1	0.0%	15.4%
Alirocumab (75 mg)	322	–43.5	–43.9	NR	–28.3	–38.4	–34.5	–21.2	–8.0	6.4	2.9	49.1%	76.7%
p-value		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0003*	0.0031*	0.0187*	<0.0001	<0.0001
Week 24													
Placebo	163	9.1	8.8	12.6	7.3	9.6	4.7	-7.5	6.3	0.8	0.3	0.8%	11.6%
Alirocumab (75/150 mg)	322	–48.8	–49.3	–50.1	–31.4	–42.8	–41.1	–25.2	–9.6	8.8	5.0	59.8%	83.7%
p-value		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0002*	<0.0001*	<0.0001
Week 52													
Placebo	148	9.0	9.1	NR	NR	NR	NR	NR	NR	NR	NR	0.0%	13.0%
Alirocumab (75/150 mg)	289	–47.1	–48.1	NR	NR	NR	NR	NR	NR	NR	NR	56.2%	77.0%
p-value		<0.0001*	<0.0001	NR	NR	NR	NR	NR	NR	NR	NR	<0.0001	<0.0001

Apo, apolipoprotein; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a); Lipoprotein(a); NR, not recorded; Total-C, total cholesterol; TG, Triglycerides

[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment (n=321 patients for alirocumab).

* Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

Table 20 Efficacy endpoints (mean percent change from baseline) in the ITT analysis - FH II

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12													
Placebo	81	4.6	4.6	NR	3.4	4.1	–0.9	–5.6	0.6	1.7	–1.9	1.4%	18.9%
Alirocumab (75 mg)	166	–43.8	–44.2	NR	–26.6	–37.9	–35.4	–24.7	–8.1	6.0	0.4	54.0%	79.5%
p-value		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0240*	0.0147*	0.1475	<0.0001	<0.0001
Week 24													
Placebo	81	2.8	2.7	0.7	2.1	3.1	–3.5	–10.0	0.5	–0.8	–1.6	1.2%	18.7%
Alirocumab (75/150 mg)	166	–48.7	–49.4	–49.2	–30.6	–42.6	–42.8	–30.3	–10.4	6.0	2.8	68.2%	85.4%
p-value		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0012*	0.0009*	0.0062*	<0.0001*	<0.0001
Week 52													
Placebo	80	8.4	8.4	NR	NR	NR	NR	NR	NR	NR	NR	0.0%	15.3%
Alirocumab (75/150 mg)	156	–50.3	–51.7	NR	NR	NR	NR	NR	NR	NR	NR	68.1%	88.0%
p-value		<0.0001*	<0.0001	NR	NR	NR	NR	NR	NR	NR	NR	<0.0001	<0.0001

Apo, apolipoprotein; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a); Lipoprotein(a); NR, not recorded; Total-C, total cholesterol; TG, Triglycerides

[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment.

*Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

Table 21 Efficacy endpoints (mean percent change from baseline) in the ITT analysis – HIGH FH

Treatment (daily dose)	n	Mean percentage change from baseline (%)									Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12												
Placebo	35	–6.6	–6.6	–5.2	–6.9	–9.0	–1.5	–4.4	8.0	1.1	0.0%	0.0%
Alirocumab (150 mg)	71	–46.9	–46.9	–33.0	–41.4	–39.2	–23.2	–9.4	7.9	4.6	31.0%	63.4%
p-value		<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0005	0.4195	0.9727	0.1845	0.0001	<0.0001
Week 24												
Placebo	35	–6.6	–6.6	–4.8	–6.2	–8.7	–8.7	–1.9	3.9	2.0	2.9%	11.4%
Alirocumab (150 mg)	71	–45.7	–45.5	–33.2	–41.9	–39	–23.5	–10.5	7.5	5.6	32.4%	57.0%
p-value		<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0164*	0.1386	0.2745	0.1715	0.0082	<0.0001
Week 52												
Placebo	29	–3.0	–2.9	NR	NR	NR	NR	NR	NR	NR	5.7%	5.8%
Alirocumab (150 mg)	57	–42.1	–42	NR	NR	NR	NR	NR	NR	NR	31.0%	53.7%
p-value		<0.0001*	<0.0001	NR	NR	NR	NR	NR	NR	NR	0.0052	0.0012

Apo, apolipoprotein; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lipoprotein(a); NR, not recorded; Total-C, total cholesterol; TG, Triglycerides

[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment.

*Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

Table 22 Efficacy endpoints (mean percent change from baseline) in the ITT analysis - COMBO I

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12													
Placebo	106	1.1	1.7	NR	0.9	2.6	3.4	0.0	3.0	–2.4	–1.8	11.3%	53.2%
Alirocumab (75 mg)	205	–46.3	–47.6	NR	–25.4	–37.4	–34.8	–19.7	–11.3	6.7	3.8	76.0%	90.6%
p-value		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001	<0.0001	<0.0001	<0.0001	0.0006	<0.0001	<0.0001
Week 24													
Placebo	106	–2.3	–0.8	–0.2	–2.9	–1.6	–0.9	–5.9	–5.4	–3.8	–2.5	9.0%	64.1%
Alirocumab (75/150 mg)	205	–48.2	–50.7	–46.1	–27.9	–39.1	–36.7	–20.5	–6.0	3.5	3.3	75.0%	93.8%
p-value		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.8699	0.0001*	0.0002	<0.0001*	<0.0001
Week 52													
Placebo	75	0.5	2.6	NR	NR	NR	NR	NR	NR	NR	NR	10.5%	59.1%
Alirocumab (75/150 mg)	158	–42.5	–47.5	NR	NR	NR	NR	NR	NR	NR	NR	75.0%	89.5%
p-value		<0.0001*	<0.0001	NR	NR	NR	NR	NR	NR	NR	NR	<0.0001	<0.0001

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lipoprotein(a); NR, not recorded; Total-C, total cholesterol; TG, Triglycerides

[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment (n=105 for placebo and n=204 for alirocumab).

*Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

Table 23 Efficacy endpoints (mean percent change from baseline) in the ITT analysis – COMBO II

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12													
Ezetimibe	240	–21.8	–22.7	NR	–15.1	–20.6	–17.2	1.1	–15.3	2.8	–2.9	46.2%	79.6%
Alirocumab (75 mg)	467	–51.2	–52.4	NR	–29.4	–42.6	–39.7	–22.1	–13.5	8.7	1.5	77.2%	90.9%
p-value		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	<0.0001	0.3912	<0.0001	<0.0001	<0.0001	<0.0001
Week 24													
Ezetimibe	240	–20.7	–21.8	–18.9	–14.6	–19.2	–18.3	–6.1	–12.8	0.5	–1.3	45.6%	76.4%
Alirocumab (75/150 mg)	467	–50.6	–52.4	–47.7	–29.3	–42.1	–40.7	–27.8	–13.0	8.6	5.0	77.0%	91.0%
p-value		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.9117	<0.0001*	<0.0001	<0.0001	<0.0001
Week 52													
Ezetimibe	208	–18.3	–19.7	NR	NR	NR	NR	NR	NR	NR	NR	41.5%	74.3%
Alirocumab (75/150 mg)	408	–49.5	–51.8	NR	NR	NR	NR	NR	NR	NR	NR	75.4%	88.3%
p-value		<0.0001*	<0.0001	NR	NR	NR	NR	NR	NR	NR	NR	<0.0001	<0.0001

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lipoprotein(a); NR, not recorded; Total-C, total cholesterol; TG, Triglycerides.

[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment (n=235 for ezetimibe and n=464 for alirocumab).

*Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

Table 24 Efficacy endpoints (mean percent change from baseline) in the ITT analysis – LONG TERM

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12													
Placebo	780	1.5	1.4	NR	0.2	0.9	0.5	–3.1	1.2	0.2	0.6	7.2%	34.8%
Alirocumab (150 mg)	1530	–63.3	–64.2	NR	–38.8	–53.7	–55.5	–28.2	–16.7	5.8	4.6	82.1%	92.1%
p-value		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001	<0.0001
Week 24													
Placebo	780	0.8	0.7	3.5	–0.3	0.7	1.2	–3.7	1.8	–0.6	1.2	8.0%	35.5%
Alirocumab (150 mg)	1530	–61	–62.8	–57.8	–37.8	–51.6	–52.8	–29.3	–15.6	4.0	4.0	79.3%	90.3%
p-value		<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001
Week 52													
Placebo	676	4.4	4.6	NR	NR	NR	NR	NR	NR	NR	NR	4.5%	34.0%
Alirocumab (150 mg)	1333	–56.8	–59.9	NR	NR	NR	NR	NR	NR	NR	NR	75.0%	87.4%
p-value		<0.0001	<0.0001	NR	NR	NR	NR	NR	NR	NR	NR	<0.0001	<0.0001

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lipoprotein(a); NR, not recorded; Total-C, total cholesterol; TG, Triglycerides

[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment (n=777 for placebo and n=1523 for alirocumab).

*Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

Table 25 Efficacy endpoints (mean percent change from baseline) in the ITT analysis; Atorvastatin 20 mg regimen - OPTIONS I

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12													
Atorvastatin 40 mg	53	–8.5	–9.2	NR	–6.5	–7.1	–6.9	–11.7	–4.7	–3.2	–0.8	25.4%	69.6%
Ezetimibe + atorvastatin 20 mg	53	–22.6	–27.1	NR	–13.2	–17.2	–13.1	–5.4	0.5	–1.7	1.7	52.8%	85.3%
Alirocumab 75 mg + atorvastatin 20 mg	55	–48.4	–53.7	NR	–29.0	–40.6	–38.4	–24.0	–12.4	4.1	5.4	78.7%	91.4%
p-value alirocumab + atorvastatin vs Atorvastatin alone		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	0.0300	0.1946	0.0042	0.0036	<0.0001	0.0035
p-value alirocumab + atorvastatin vs ezetimibe + atorvastatin		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	0.0010	0.0286	0.0220	0.0705	0.0024	0.1734
Week 24													
Atorvastatin 40 mg	53	–5.0	–6.1	8.1	–4.0	–6.3	–4.4	–20.2	–6.7	1.9	1.2	16.0%	67.0%
Ezetimibe + atorvastatin 20 mg	53	–20.5	–23.7	–10.3	–11.2	–15.1	–10.1	–10.6	–3.3	–0.1	1.0	50.3%	84.2%

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Alirocumab 75/150 mg + atorvastatin 20 mg	55	–44.1	–48.6	–44.7	–27.1	–36.7	–33.7	–23.6	–12.0	4.8	7.6	79.2%	89.9%
p-value alirocumab + atorvastatin vs Atorvastatin alone		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	0.5520	0.3054	0.3152	0.0034	<0.0001	<0.003
p-value alirocumab + atorvastatin vs ezetimibe + atorvastatin		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	0.0294	0.1116	0.0973	0.0029	0.0018	0.2543

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lipoprotein(a); NR, not recorded; Total-C, total cholesterol; TG, Triglycerides.

[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment (n=52 for atorvastatin, n=52 for ezetimibe and n=52 for alirocumab).

*Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.01 level (Bonferroni adjustment for multiple pairwise comparisons).

Table 26 Efficacy endpoints (mean percent change from baseline) in the ITT analysis; Atorvastatin 40 mg regimen - OPTIONS I

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12													
Atorvastatin 80 mg	47	–14.5	–14.6	NR	–9.9	–13.0	–9.5	–1.6	–4.6	3.0	1.6	10.2%	69.8%
Rosuvastatin 40 mg	45	–23.3	–23.3	NR	–13.5	–19.8	–14.1	11.5	–3.7	4.6	5.6	42.2%	70.7%
Ezetimibe + atorvastatin 40 mg	46	–29.7	–30.7	NR	–19.2	–27.5	–20.3	7.9	–16.8	4.6	1.6	54.2%	89.6%
Alirocumab 75 mg + atorvastatin 40 mg	46	–50.5	–50.9	NR	–29.0	–42.3	–36.2	–27.9	–12.1	8.5	9.4	77.2%	88.2%
p-value alirocumab vs atorvastatin		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	<0.0001	0.1831	0.1458	0.0012	<0.0001	0.0031
p-value alirocumab vs rosuvastatin		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	<0.0001	0.1429	0.3087	0.1189	<0.0001	0.0055
p-value alirocumab vs ezetimibe		<0.0001*	<0.0001*	NR	0.0015	<0.0001*	<0.0001*	<0.0001	0.4011	0.3083	0.0012	0.0004	0.2782
Week 24													
Atorvastatin 80 mg	47	–4.8	–5.0	2.8	–4.8	–6.5	–3.5	–9.7	–7.3	4.7	2.2	24.6%	61.4%
Rosuvastatin 40 mg	45	–21.4	–22.9	–14.3	–11.7	–17.4	–10.9	–4.9	–0.5	5.7	4.7	45.6%	71.1%
Ezetimibe + atorvastatin 40 mg	46	–22.6	–24.5	–16.1	–15.2	–21.0	–14.3	0.2	–13.9	2.0	–1.8	52.0%	80.7%
Alirocumab 75/150 mg +	46	–54.0	–57.8	–48.0	–33.6	–47.6	–41.9	–30.8	–19.1	7.7	5.8	74.5%	90.1%

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
atorvastatin 40 mg													
p-value alirocumab vs atorvastatin		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	0.0004*	0.0403	0.4456	0.1986	<0.0001	<0.0001
p-value alirocumab vs rosuvastatin		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0011	0.6086	0.6745	0.0002	0.0025
p-value alirocumab vs ezetimibe		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.3652	0.1426	0.0066	0.0002	0.0074

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NR, not recorded; Total-C, total cholesterol; TG, Triglycerides.

[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment.

*Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.01 level (Bonferroni adjustment for multiple pairwise comparisons).

Table 27 Efficacy endpoints (mean percent change from baseline) in the ITT analysis; Rosuvastatin 10 mg regimen - OPTIONS II

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting tTG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12													
Rosuvastatin 20 mg	48	–17.1	–17.2	NR	–8.9	–11.7	–8.1	–0.7	8.1	0.7	4.0	37.5%	77.7%
Ezetimibe + rosuvastatin 10 mg	47	–17.4	–20.3	NR	–11.8	–16.3	–12.1	–3.9	–8.2	0.2	2.6	46.5%	76.4%
Alirocumab 75 mg + rosuvastatin 10 mg	48	–49.6	–52.6	NR	–29.0	–41.2	–36.1	–20.7	–14.0	5.9	4.3	77.4%	91.4%
p-value alirocumab vs rosuvastatin		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	<0.0001	0.0001	0.0840	0.9076	<0.0001	0.1012
p-value alirocumab vs ezetimibe		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	0.0008	0.3223	0.0647	0.4652	<0.0001	0.0158
Week 24													
Rosuvastatin 20 mg	48	–16.3	–18.3	–6.4	–8.3	–11.3	–7.3	–4.0	–1.8	1.7	5.4	31.3%	79.4%
Ezetimibe + rosuvastatin 10 mg	47	–14.4	–20.3	–12.5	–8.7	–13.4	–9.7	–4.3	–8.3	4.0	5.0	43.1%	71.3%
Alirocumab 75/150 mg + rosuvastatin 10 mg	48	–50.6	–53.5	–44.3	–28.9	–42.7	–36.5	–27.9	–11.2	9.1	6.7	77.8%	91.4%
p-value alirocumab vs rosuvastatin		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.1454	0.0311	0.6271	<0.0001	0.1809
p-value alirocumab vs ezetimibe		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.6639	0.1491	0.5484	<0.0001	0.0047

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lipoprotein(a); NR, not recorded; Total-C, total cholesterol; TG, Triglycerides

*Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.0125 level (Bonferroni adjustment for multiple pairwise comparisons).

Table 28 Efficacy endpoints (mean percent change from baseline) in the ITT analysis; Rosuvastatin 20 mg regimen - OPTIONS II

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12													
Rosuvastatin 40 mg	52	–22.1	–22.9	NR	–13.8	–18.0	–13.7	3.5	–2.7	0.6	0.9	39.7%	73.0%
Ezetimibe + rosuvastatin 20 mg	50	–19.3	–21.8	NR	–13.9	–18.7	–14.3	7.9	–12.4	3.1	1.8	51.3%	72.8%
Alirocumab 75 mg + rosuvastatin 20 mg	53	–32.3	–35.1	NR	–19.4	–29.8	–29.0	–16.0	–10.1	8.0	9.1	44.9%	75.3%
p-value alirocumab vs rosuvastatin		0.1747	0.0980	NR	0.1563	0.0266	0.0013	0.0012	0.1908	0.0378	0.0015	0.3155	0.7223
p-value alirocumab vs ezetimibe		0.0861	0.0718	NR	0.1629	0.0342	0.0022	<0.0001	0.6854	0.1614	0.0041	0.5399	0.9888
Week 24													
Rosuvastatin 40 mg	52	–15.9	–17.0	–3.7	–8.5	–11.2	–9.8	–5.2	–9.9	1.5	2.9	29.9%	69.1%
Ezetimibe + rosuvastatin 20 mg	50	–11.0	–16.5	–4.5	–12.4	–12.9	–11.2	–5.8	–11.1	–1.8	–0.9	43.6%	64.8%
Alirocumab 75/150 mg + rosuvastatin 20 mg	53	–36.3	–41.5	–32.2	–20.6	–31.4	–28.3	–22.7	–8.7	7.2	6.7	60.1%	74.6%
p-value alirocumab vs rosuvastatin		0.0453	0.0131	0.0114	0.0193	0.0063	0.0024	0.0123	0.8088	0.0866	0.1651	0.0006	0.3736
p-value alirocumab vs ezetimibe		0.0136	0.0115	0.0169	0.1134	0.0133	0.0057	0.0131	0.7135	0.0072	0.0063	0.0657	0.3185

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lipoprotein(a); NR, not recorded; Total-C, total cholesterol; TG, Triglycerides
[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment (n=50 for rosuvastatin, n=50 for ezetimibe and n=51 for alirocumab).

Table 29 Efficacy endpoints (mean percent change from baseline) in the ITT analysis – ALTERNATIVE

Treatment (daily dose)	n	Mean percentage change from baseline (%)										Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	LDL-C (meas)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting triglycerides	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12													
Ezetimibe	122	–15.6	–18.0	NR	–11.6	–15.8	–11.6	–4.5	–9.4	7.6	3.9	0.0%	13.3%
Alirocumab (75 mg)	126	–47.0	–51.2	NR	–32.7	–41.5	–36.1	–21.7	–8.0	9.0	5.5	34.9%	63.3%
p-value		<0.0001*	<0.0001*	NR	<0.0001*	<0.0001*	<0.0001*	<0.0001	0.6855	0.4148	0.2685	<0.0001	<0.0001
Week 24													
Ezetimibe	122	–14.6	–17.1	–11.0	–10.9	–14.6	–11.2	–7.3	–3.6	6.8	2.9	0.8%	10.0%
Alirocumab 75/150 mg)	126	–45.0	–52.2	–43.9	–31.8	–40.2	–36.3	–25.9	–9.3	7.7	4.8	32.5%	61.0%
p-value		<0.0001*	<0.0001*	<0.0001	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.1426	0.6997	0.2768	<0.0001*	<0.0001

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lipoprotein(a); NR, not recorded; Total-C, total cholesterol; TG, triglycerides.
[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment (n=118 for ezetimibe and n=123 for alirocumab).
*Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level

Table 30 Efficacy endpoints (mean percent change from baseline) in the ITT analysis – MONO

Treatment (daily dose)	n	Mean percentage change from baseline (%)									Proportion of patients reaching LDL target	
		LDL-C (calc)	On treatment LDL-C[a] (calc)	Total-C	Non-HDL-C	Apo B	Lp(a)	Fasting TG	HDL-C	Apo A1	<1.81 mmol/L	<2.59 mmol/L
Week 12												
Ezetimibe	51	–19.6	–20.4	–12.0	–16.7	–11.7	–14.2	–2.3	1.6	–2.2	0.0%	30.7%
Alirocumab (75 mg)	52	–48.1	–53.2	–30.3	–42.5	–37.3	–17.2	–12.2	9.0	2.3	57.7%	88.3%
p-value		<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.5659	0.0400	0.0106	0.0320	<0.0001	<0.0001
Week 24												
Ezetimibe	51	–15.6	–17.2	–10.9	–15.1	–11.0	–12.3	–10.8	1.6	–0.6	2.4%	32.2%
Alirocumab 75/150 mg)	52	–47.2	–54.1	–29.6	–40.6	–36.7	–16.7	–11.9	6.0	4.7	59.4%	88.1%
p-value		<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.4013	0.8433	0.1116	0.0196	<0.0001*	<0.0001*

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Total-C, total cholesterol

[a]On-treatment analysis – analysis restricted to the time period during which patients actually received treatment.

*Statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

4.7.11 EQ-5D – Health Related Quality of Life

In all Phase III studies except OPTIONS I, OPTIONS II and ALTERNATIVE, quality of life (QoL) was assessed using EQ-5D-3L, a standardised and generic instrument for measuring the health status and Health Related Quality of Life for clinical and economic assessment. [101]

The EQ-5D questionnaire was completed by the patient on site and data reported onto the e-CRF by site staff. The 5 dimensional 3-level system was converted into a single index utility score, which was described by visit with the mean and the SD for each treatment group.

Hypercholesterolaemia is an asymptomatic condition, therefore, no improvement in the patient's perceived health status or QOL were anticipated with treatment. This was substantiated by the EQ-5D data captured which demonstrated little to no change in mean EQ-5D utility scores between baseline and following visit analysis time points in any of the trials.

Note: the only difference was in COMBO I where the LS mean difference at Weeks 12 (-0.062) and 52 (-0.060) were significant at the 5% level. The mean difference at Week 24 was, however, non-significant, the p-values were not adjusted for multiplicity and the LS differences were well below a clinically relevant threshold of 0.1 in utility scores.

Baseline EQ-5D was calculated via pooled analysis of the FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM clinical trials. Results were calculated for different patient sub-populations linked to the economic model (ACS 0-1 year; ACS 1-2 years; CHD; ischaemic stroke; PAD, HeFH [all]) and stratified by patients classified within the respective patient subpopulation only versus patients classified within the respective patient subpopulation that had a history of other CV events (Table 31).

Table 31 Baseline utilities as estimated by EQ-5D by patient subpopulation* pooled analysis FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM

Patient Subpopulation	Overall			No other CV event/condition		At least one other CV event/condition	
	n	Mean age (SD)	Mean EQ-5D (SD)	n	Mean EQ-5D (SD)	n	Mean EQ-5D (SD)
ACS 0–1 year	198	56.2 (10.2)	0.844 (0.197)	142	0.848 (0.201)	56	0.832 (0.189)
ACS 1–2 years	192	58.7 (9.1)	0.858 (0.187)	120	0.874 (0.185)	72	0.832 (0.190)
CHD	2731	61.4 (9.7)	0.851 (0.194)	813	0.860 (0.191)	1918	0.847 (0.195)
IS	344	63.8 (9.5)	0.797 (0.228)	164	0.804 (0.212)	180	0.791 (0.242)
PAD	188	62.8 (9.1)	0.771 (0.233)	98	0.775 (0.253)	90	0.767 (0.211)
HeFH (all)**	1254	52.7 (12.3)	0.905 (0.149)	682	0.930 (0.130)	572	0.875 (0.164)

ACS, acute coronary syndrome; CHD, coronary heart disease; CV, cardiovascular; EQ-5D, EuroQol-five dimensions; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; IS, ischaemic stroke; PAD, peripheral arterial disease; SD, standard deviation

*Includes all randomised patients regardless of treatment assignment; data includes prevalent patient groups, i.e. non-mutually exclusive

**Refers to both primary and secondary prevention

4.8 Subgroup analysis

Key Points

- Subgroup analyses of the primary efficacy endpoint showed consistent reduction of calculated LDL-C from baseline across a range of demographic and baseline characteristics
- In the economic evaluation, a range of patient subgroups will be presented in line with the Scope, covering:
  - **HeFH patients**
  - **High/very high CV risk patients (with and without statin intolerance)**
  - **Patients with recurrent CV events/ polyvascular disease**
  - **Subgroups by baseline LDL-C level**
- These groups differ only in terms of baseline risk, the relative treatment effect of alirocumab was consistent

4.8.1 Pre-Specified Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, treatment-by-subgroup factor, time point-by-subgroup factor and treatment-by time point-by subgroup factor interaction terms and a subgroup factor term were added in the primary MMRM model. LS mean difference versus control group at Week 24 was provided, as well as the corresponding 95% CI, within each subgroup. The significance level of the treatment-by subgroup factor interaction term at Week 24 was also provided for each factor for descriptive purpose. Forest plots were provided. In order to handle imbalances between randomisation stratification factors levels, population weights were used as for the primary analysis model. Subgroups of interest are study-dependent, due to specificities related to design and patient population, as shown in Table 32. Subgroup analyses were conducted when at least 10 patients were included in each treatment arm within each subgroup, except for race and ethnicity.

Table 32 Pre-specified Subgroup analyses in Phase III studies

Subgroup	Categories	Studies
BMI	<30, ≥30 kg/m^2	All
Gender	Female, Male	All
Region	North America, Eastern Europe, Western Europe, Rest of world	FH I, COMBO II, LONG TERM, ALTERNATIVE
	North America, Europe, Rest of world	HIGH FH
	North America, Western Europe	MONO
Age	<65 years, ≥65 to <75 years, ≥75 years	COMBO I, COMBO II, LONG TERM, ALTERNATIVE
	<65, ≥65 years	FH I, FH II, OPTIONS I, OPTIONS II, MONO
Race	White, Black or African American, other	All
Ethnicity	Hispanic or Latino, not Hispanic or Latino	All
Statin treatment	High dose, low/moderate dose[a]	All except OPTIONS I, OPTIONS II, ALTERNATIVE, MONO
Dose of atorvastatin at randomisation	10 mg, 20 mg, 40 mg, 80 mg	FH I, FH II, COMBO I, COMBO II, LONG TERM
Dose of rosuvastatin at randomisation	5 mg, 10 mg, 20 mg, 40 mg	FH I, FH II, COMBO I, COMBO II, LONG TERM
Dose of simvastatin at randomisation	10 mg, 20 mg, 40 mg, 80 mg	FH I, FH II, COMBO I, COMBO II, LONG TERM
LMT other than statins at randomisation	Yes, no	FH I, FH II, HIGH FH, COMBO I, LONG TERM, OPTIONS I, OPTIONS II
Prior history of MI or IS	Yes, no	All except MONO
DM	Yes, no	FH I, FH II, COMBO I, COMBO II, LONG TERM, OPTIONS I, OPTIONS II, ALTERNATIVE
Moderate CKD	Yes, no	FH II, COMBO I, COMBO II, LONG TERM, OPTIONS I, OPTIONS II, ALTERNATIVE
HeFH	Yes, no	LONG TERM
Baseline LDL-C	<100, ≥100 to <130, ≥130 to <160, ≥160 mg/dL (i.e. <2.59, ≥2.59 to <3.37, ≥3.37 to <4.14, ≥4.14 mmol/L)<	All except MONO and HIGH FH
	<190, ≥190 mg/dL (i.e. <4.91, ≥4.91 mmol/L)	HIGH FH
	130, ≥130 to <160, ≥160 mg/dL (i.e. <3.37, ≥3.37 to <4.14, ≥4.14 mmol/L)	MONO
Baseline HDL-C	<40, ≥40 mg/dL (i.e. <1.04, ≥1.04 mmol/L)	All
Baseline fasting triglycerides	<150, ≥150 mg/dL (i.e. <1.7,	All

Subgroup	Categories	Studies
	≥1.7 mmol/L)	
Baseline Lp(a)	<30, ≥30 to <50, ≥50 mg/dL (i.e. <0.3, ≥0.3 to <0.5, ≥0.5 g/L)	All except HIGH FH
	<30, ≥30 mg/dL (i.e. <0.3, ≥0.3 g/L)	HIGH FH
Baseline total PCSK9 level	<median, ≥median	FH I, COMBO II, LONG TERM, MONO
Baseline free PCSK9 level	<median, ≥median	FH I, COMBO II, LONG TERM, MONO

BMI, body-mass index; CKD, chronic kidney disease; DM, diabetes mellitus; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; Lipoprotein(a); MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9;
[a]High dose: atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily. Low/moderate dose: simvastatin whatever the daily dose, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily.

Subgroup analyses of the primary efficacy endpoint showed consistent reduction of calculated LDL-C from baseline with alirocumab versus placebo across a range of demographic and baseline characteristics including age, ethnicity, BMI, region, prior history of MI or ischaemic stroke, diabetes, baseline total and free PCSK9 levels, baseline calculated LDL-C, HDL-C, fasting TGs, Lp (a), intensity of background statin, and statins with versus without other additional LMTs at randomisation. The Forests plots for FHI can be seen in Figure 22, Figure 23, Figure 24 and Figure 25, the remaining plots can be found in Appendix 7.

Note: Least-squares (LS) mean and confidence intervals are taken from the MMRM (mixed-effect model with repeated measures) analysis. N corresponds to the number of patients with a baseline value and post-baseline value in at least one of the analysis windows used in the model.

Figure 22 Percent change from baseline in calculated LDL-C at Week 24: FH I Subgroup analyses according to demographic characteristics - Forest plot - ITT analysis

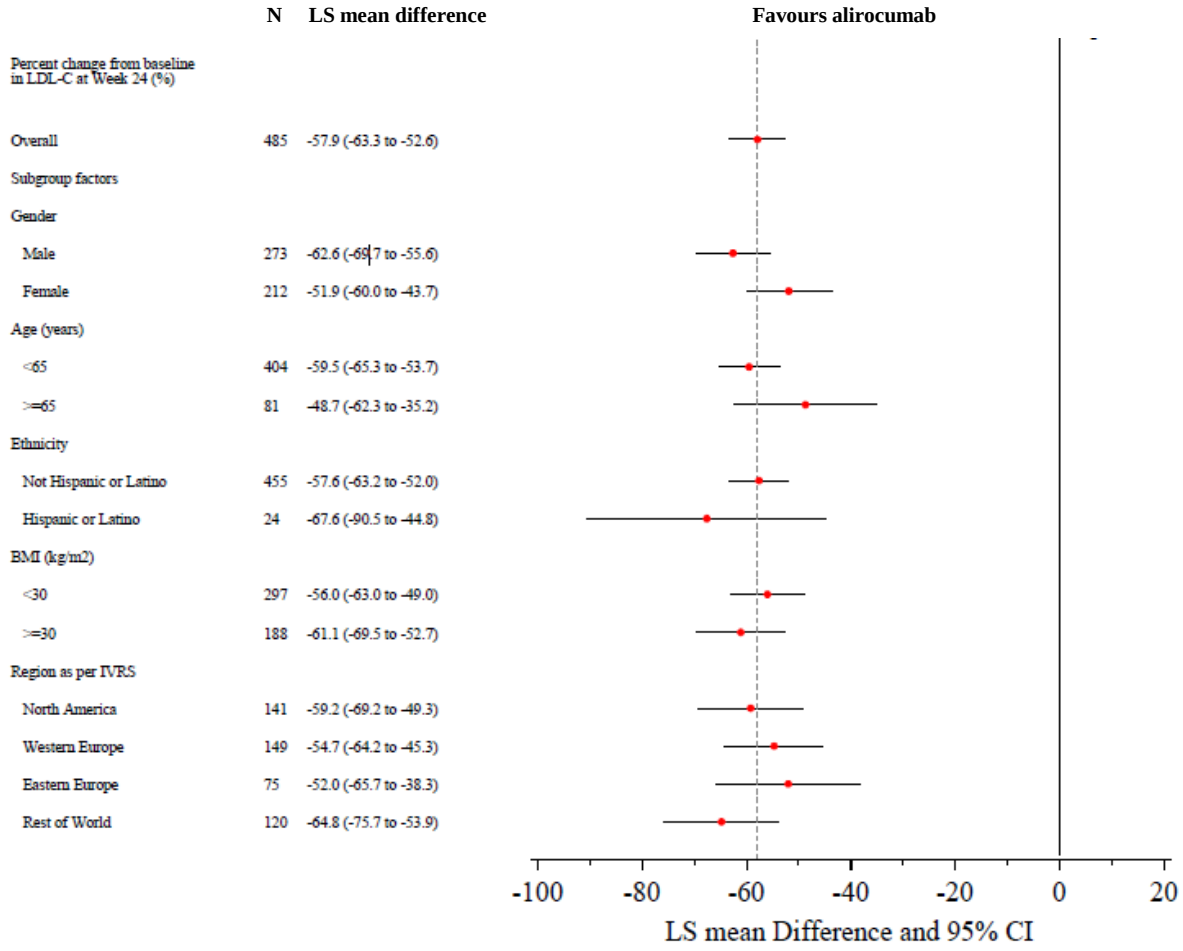


Figure 23 Percent change from baseline in calculated LDL-C at Week 24: FH I Subgroup analyses according to other baseline characteristics - Forest plot - ITT analysis

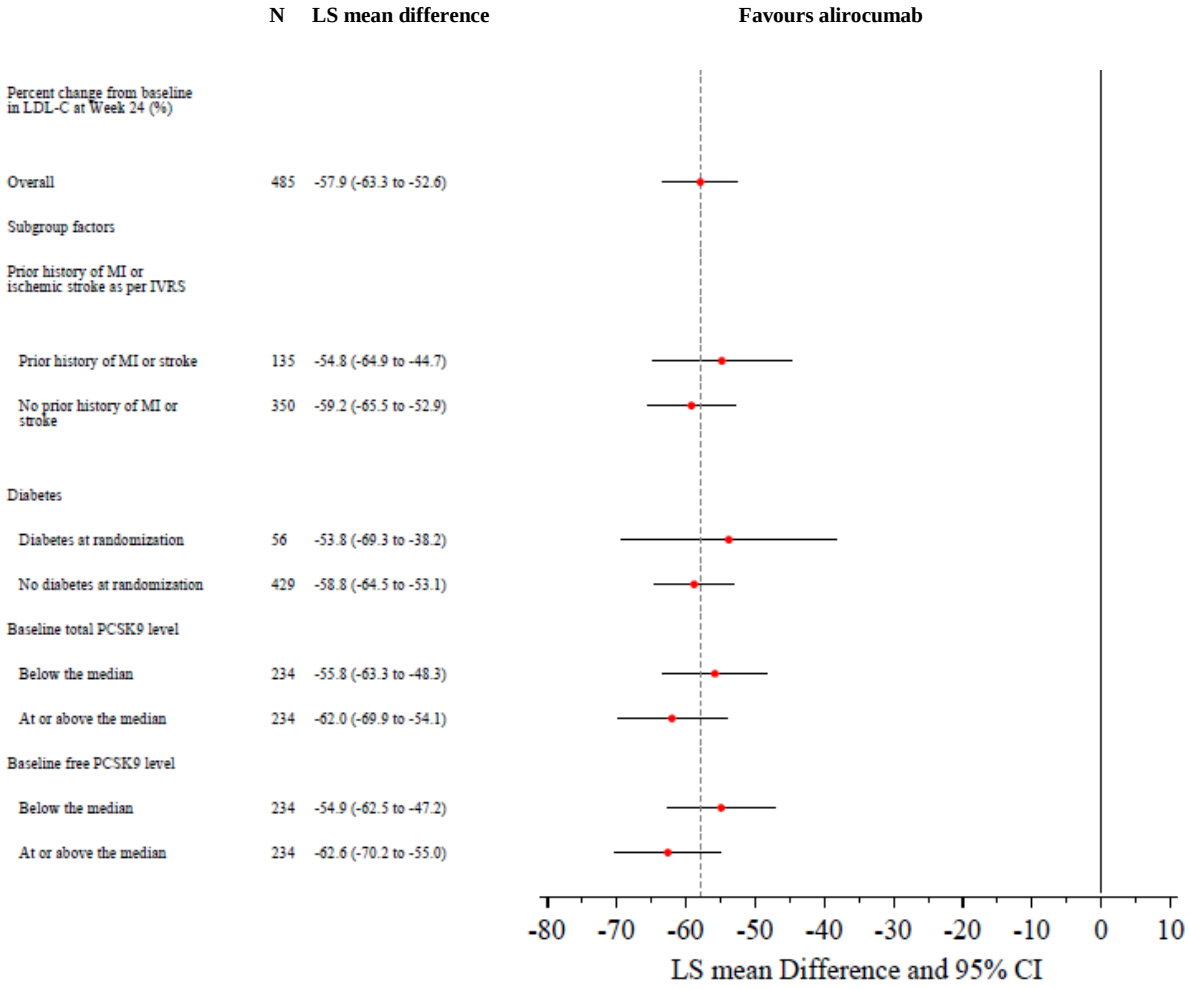


Figure 24 Percent change from baseline in calculated LDL-C at Week 24: FH I Subgroup analyses according to lipids at baseline - Forest plot - ITT analysis

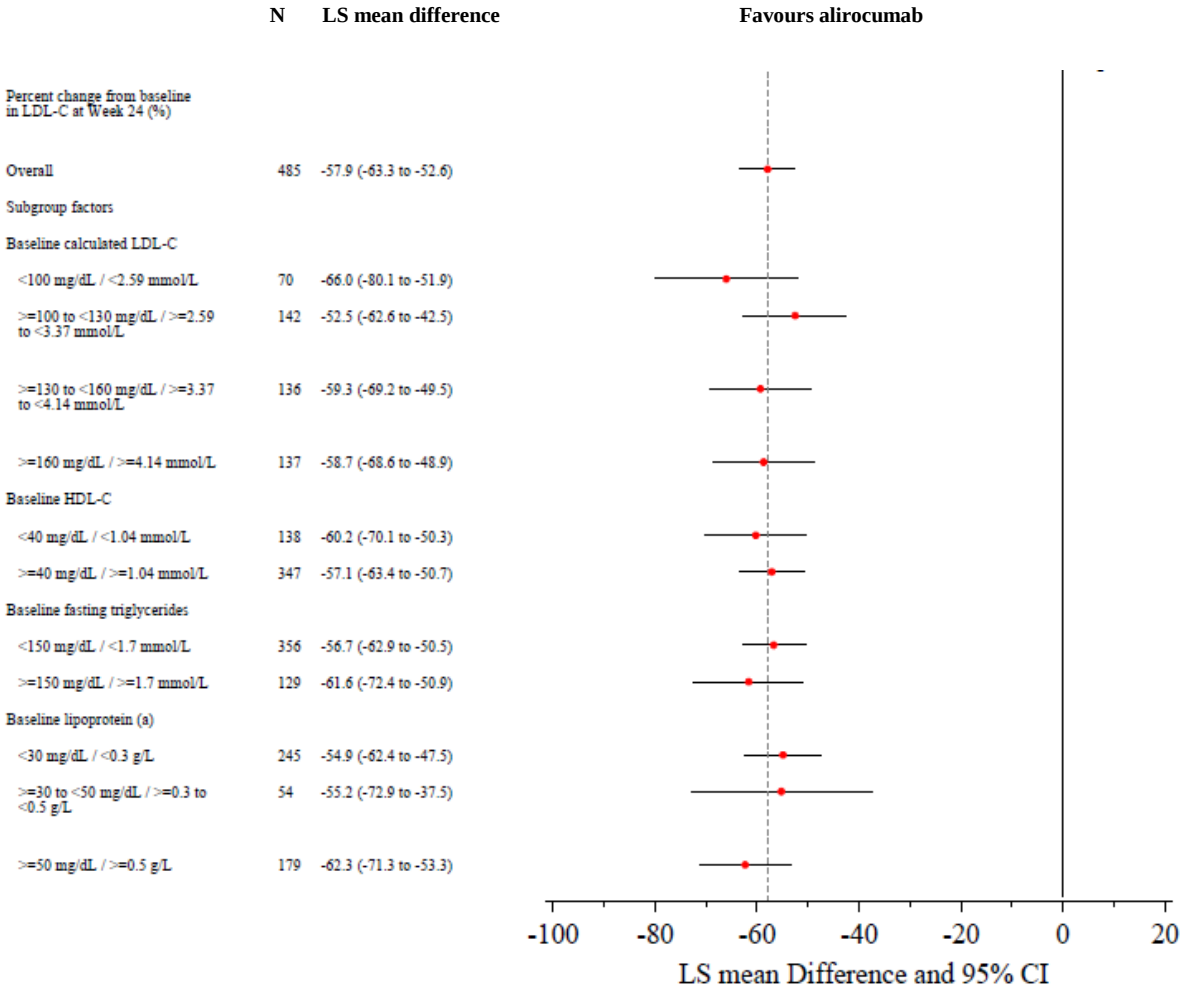
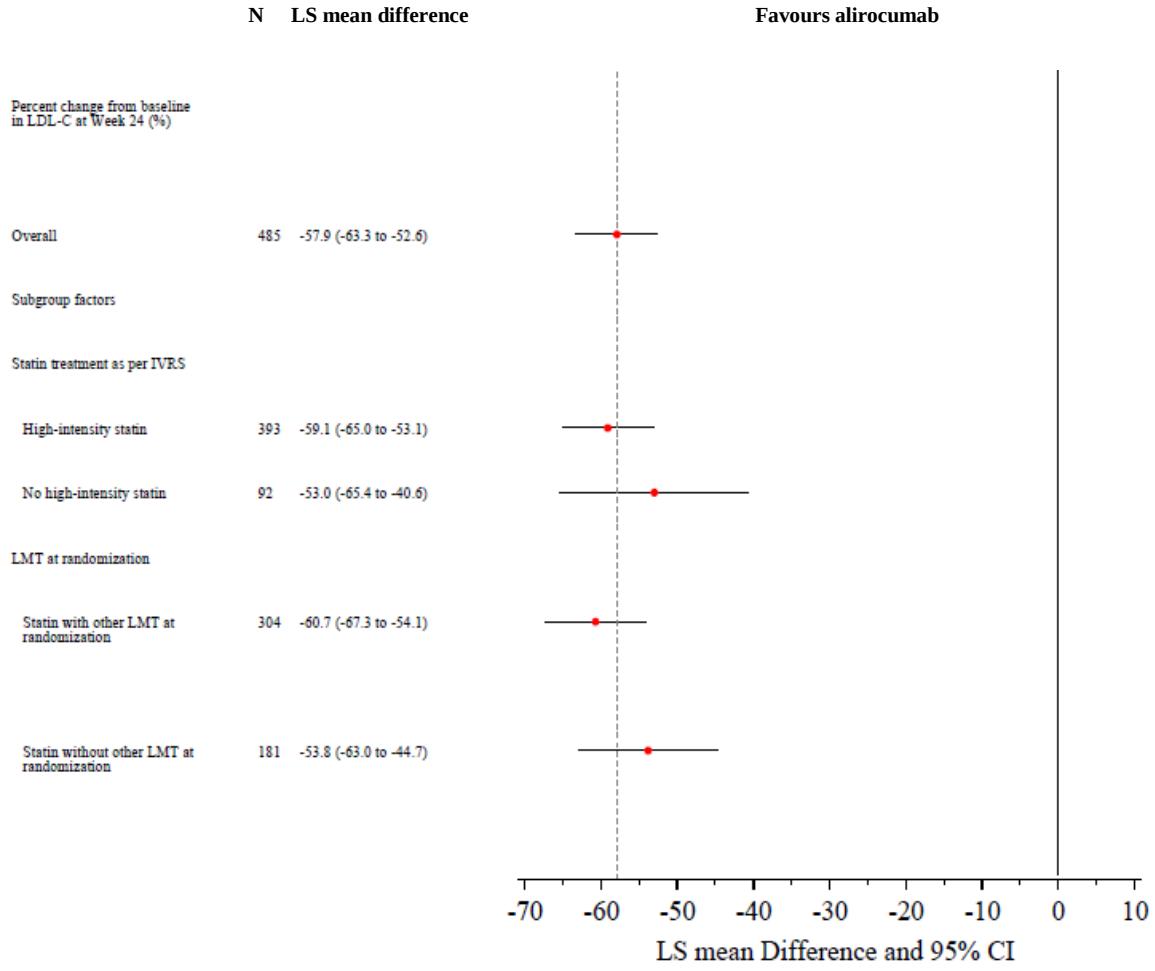


Figure 25 Percent change from baseline in calculated LDL-C at Week 24: FHI Subgroup analyses according to statins and other LMT's - Forest plot - ITT analysis



4.8.2 Patient subgroups to be presented

In order to investigate the cost-effectiveness of alirocumab in-line with the NICE scope and remit, a range of subgroups/populations will be considered.The effect of treatment on LDL-C reduction is consistent across all subgroups. However, different patient subgroups vary by baseline CV risk, and therefore in terms of economic benefit.

4.8.2.1 HeFH

The genetic condition that patients with HeFH have results in significantly raised cholesterol levels over a lifetime. Patients with HeFH are at higher risk of cardiovascular morbidity and mortality at a younger age, even despite current treatment [28] [26] As suggested in the Scope, HeFH, both primary and secondary prevention, will therefore be explored as specific patient populations.

4.8.2.2 High/very high risk CVD

This groups aligns to the subgroup “Presence or risk of CV disease” proposed in the NICE scope. For the purposes of this appraisal, patients are recognised as being at very high cardiovascular risk due to the presence of existing CVD (i.e. history of ACS [MI or unstable angina requiring hospitalisation], coronary revascularisation and other arterial revascularisation procedures, or other CHD, ischaemic stroke, PAD). With the exception of HeFH, alirocumab will only be considered for use in patients in a secondary prevention setting (i.e. those with established CV disease).

Secondary prevention subgroups with different levels of CV risk to be investigated are:

- High risk CVD patients - comprising patients with a history of CHD events and/or ischaemic stroke and/or PAD
- A subgroup of high risk CVD patients, namely patients with recurrent events/polyvascular disease whoare considered as being at even higher risk than the overall high risk CVD population.

See Section 3 for further discussion of the clinical characteristics of these groups, and 5.2.1 for further discussion of alignment in the economic model.

Within ODYSSEY, the majority of patients in non-FH trials had existing cardiovascular disease (Table 16). Patients could also be classified as “high-risk” and included in non-FH trials if they had not had prior CV events (i.e. primary prevention) but had risk factors such as DM or CKD. We have not included non-FH primary prevention patients in the economic analysis due to feedback that such patients would be unlikely to be considered for alirocumab treatment in the UK.

With regards to recurrent events/ polyvascular disease, this was not a pre-specified analysis. However, information on patients’ cardiovascular disease history was collected in the case report form. A post-hoc analysis was conducted to identify patients with recurrent coronary events (≥1 coronary event listing in CRF) or polyvascular disease (history of coronary event and history of ischaemic stroke or PAD). Between 7% - 27% of patients fitted this classification across the trials, and the treatment effect was consistent with that seen in the trial population as a whole Table 33.

Table 33: Post-hoc analysis of patients with polyvascular disease or recurrent coronary events in ODYSSEY

	Proportion of patients with polyvascular/ recurrent events		**Percentage change in LDL-C at week 24 – LS Mean (SE)**	
Study pool	**Control arm**	**Alirocumab arm**	**Control arm**	**Alirocumab arm**
Placebo-controlled studies with up-titration (FH I, FH II, COMBO I)	26 (7.4%)	48 (6.9%)	[redacted]	[redacted]
Placebo-controlled studies with 150 mg (LONG-TERM, High FH)	218 (26.7%)	392 (24.5%)	[redacted]	[redacted]
Ezetimibe controlled studies (COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE)	58 (10.4%)	105 (13.2%)	[redacted]	[redacted]

4.8.2.3 Statin Intolerance

We consider statin intolerant patients within the above high risk groups – these patients are not different in their underlying CV disease , rather they differ in terms of their existing treatment options and, therefore, their severity of hypercholesterolaemia. So we consider patients patients with high risk CVD who are completely statin intolerant, and patients with recurrent events/ polyvascular disease and statin intolerance, in the economic evaluation.

In our economic model base case, we assume that the high risk statin intolerant patients that we model will be treated with ezetimibe monotherapy and we therefore model alirocumab as an adjunct to ezetimibe monotherapy. The other key difference between patients with statin intolerance and those without is the average LDL-C level – because these patients are not receiving statins, their mean LDL-C is higher, even for similar “starting” LDL-C thresholds (see 5.2.8).

4.8.2.4 LDL-C level

In line with the NICE scope, subgroup analyses will therefore also be undertaken by severity of hypercholesterolaemia by assessment of different baseline LDL-C levels. The economic model assumes a consistent treatment effect in terms of percent change in LDL-C, in line with clinical results. However, both the baseline risk and the absolute change in LDL-C vary by baseline LDL-C

4.9 Meta-analysis

Key Points

- **Pre-specified pooled analyses were undertaken within the ODYSSEY programme and reinforce a consistency of treatment effect**
- **Several meta-analyses of PCSK9 inhibitors have been undertaken by external groups**

Pre-specified pooled analyses were undertaken within the trials of the ODYSSEY programme. These pooled analyses were based on studies for which characteristics are similar or very close in terms of population, alirocumab regimen, comparator, background therapy, and treatment duration (
Table **34**).

Table 34 Pooled analysis strategy for efficacy

Efficacy pool	Studies included	Objectives of the pool
Pool of FH studies	FH I, FH II	Summary of efficacy vs placebo in HeFH patients
Pool of studies in patients not receiving statins	ALTERNATIVE[a], MONO	Summary of efficacy vs ezetimibe in patients not receiving statins
Pool of OPTIONS studies	OPTIONS I[b], OPTIONS II	Comparison of three strategies: • Alirocumab as add-on therapy to statin • Ezetimibe as add-on therapy to statin • Statin up-titration

FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia;
[a]Excluding the atorvastatin arm.
[b]Excluding the rosuvastatin switch arm.

In addition, pooled efficacy analyses were defined in order to provide a summary of efficacy of the two following dose regimens (Table 35):

- Alirocumab 75 mg Q2W as initiation dose with potential up-titration to 150 mg Q2W
- Alirocumab 150 mg Q2W as initiation dose

Table 35 Pooled analysis strategy for efficacy of effect of individual doses and up-titration

Studies included	Objectives of the pool
FH I, FH II, COMBO I	Summary of the efficacy of alirocumab 75 mg Q2W as initiation dose with potential up-titration to 150 mg Q2W, in combination with statins, vs placebo
LONG TERM, HIGH FH	Summary of the efficacy of 150 mg Q2W as initiation dose in combination with statins, vs placebo
ALTERNATIVE, MONO[a]	Summary of the efficacy of 75 mg Q2W as initiation dose with potential up-titration to 150 mg Q2W, without statins, vs ezetimibe
COMBO II, OPTIONS I[b]**, OPTIONS II**[b]	Summary of the efficacy of 75 mg Q2W as initiation dose with potential up-titration to 150 mg Q2W, in combination with statins, vs ezetimibe

FH, familial hypercholesterolaemia; Q2W, every 2 weeks;
[a]This pool is equivalent to the Pool of monotherapy studies defined above
[b]Including only the alirocumab and ezetimibe arms

For each pooled analysis, a meta-analysis of individual patient data was performed and results presented for primary efficacy endpoint (percent change in calculated LDL-C from baseline to Week 24) and key secondary efficacy endpoints.

For the primary efficacy endpoint and secondary continuous endpoints anticipated to have a normal distribution (i.e., lipids other than TGs and Lp[a]), a fixed effect meta-analysis based on the pooled individual patient data was performed using a MMRM approach. The model included the fixed categorical effects of study, treatment group, randomisation strata (as per IVRS/IWRS), time point, study-by-time point interaction, treatment-by-time point interaction, and strata-by-time point interaction, as well as, the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. This model provided adjusted LS means estimates at Weeks 12, 24, and 52 for all treatment groups with their corresponding SEs and 95% CIs. To compare the alirocumab group to the control groups, an appropriate contrast statement was used to test the differences of these estimates, at the 2-sided 0.05 level. Further details can be found in Appendix 8.

For the continuous secondary efficacy variables anticipated to have a non-normal distribution (ie, TGs and Lp[a]), a fixed effect meta-analysis of individual patient data was performed, using a multiple imputation followed by robust regression approach.

Combined means estimates for both treatment groups, as well as the differences of these estimates, with their corresponding SEs, 95% CIs, and p-value were provided. Further details can be found in Appendix 8.

In line with the individual trial results these pooled results reinforce a consistency of treatment effect. treatment effect. Mean percentage change in LDL-C from baseline is presented in Table 36 and

Table 37.

Table 36 Mean % change from baseline in LDL-C in pooled analyses of Phase III placebo-controlled studies – On treatment analyses

Dose	Alirocumab + background statin Mean change from baseline (SE)	Placebo + background statin Mean change from baseline (SE)	Difference Mean change from baseline (SE)
Week 12			
75 mg (pooling FH I + FH II + COMBO I)	–45.1% (0.9)	+4.3% (1.3)	–49.3% (1.6)
Week 24			
75/150 mg (up-titration studies, pooling FH I + FH II + COMBO I)	–49.7% (1.0)	+4.4% (1.5)	–54.1% (1.8)
150 mg (pooling LONG TERM + HIGH FH)	–62.1% (0.7)	+0.4% (1.0)	–62.5% (1.2)
Week 12			
75 mg (pooling FH I + FH II)	–44.0% (1.1)	+5.3% (S.6)	–49.3% (1.9)
Week 24			
75/150 mg (up-titration studies, pooling FH I + FH II)	–49.3% (1.2)	+6.8% (1.7)	–56.1% (2.1)

FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; SE, standard error

Table 37 Mean % change from baseline in LDL-C in pooled analyses of Phase III ezetimibe-controlled studies – On treatment analyses

	ALTERNATIVE (monotherapy) Mean change from baseline (SE)		Pooling of COMBO II + OPTIONS I + OPTIONS II Mean change from baseline (SE)	
Dose	**Alirocumab**	**Ezetimibe**	**Alirocumab + statin**	**Ezetimibe + statin**
Week 12				
75 mg	–51.2% (1.7)	–18.0% (1.8)	–51.0% (1.1)	–23.9% (1.4)
Week 24				
75/150 mg (up-titration studies)	–52.2% (2.0)	–17.1% (2.0)	–51.6% (1.3)	–21.6% (1.6)

LDL-C, low-density lipoprotein cholesterol; SE, standard error;

4.9.1 Published Meta-Analyses

Three meta-analyses of PCSK9 inhibitors have recently been published by independent groups[39] [102] [103] the meta-analyses were all undertaken to assess the safety and efficacy of PCSK9 inhibitors. Although they all reported similar efficacy and safety endpoints (i.e. lipid fractions and adverse events) the Navarese meta-analysis investigated all-cause and cardiovascular mortality as pre-specified primary end points along with myocardial infarction and unstable angina rates as secondary endpoints. Across all analyses, significant reductions in LDL-C and other atherogenic lipid fractions were shown along with no significant difference in adverse events.

4.9.1.1 Li et al. [103]

The meta-analysis by Li et al. investigated the efficacy (in terms of lipid-lowering) and safety of PCSK9 inhibitors. RCTs of at least 8 weeks duration were included. The meta-analysis followed the PRISMA guidelines (MOOSE group) [104] Searches were run until 19th March 2015 (Cochrane Library, PUBMED and EMBASE databases).

Data extraction and quality assessment was performed by two investigators individually, with discrepancies resolved by discussion and a third person. The

quality of RCTs was qualified independently using the 5-point Jadad score [105]. 20 RCTs met the eligibility criteria and were included in the quantitative synthesis, which included 9,880 patients.

The Cochrane Q test was used to measure the heterogeneity across included trials and χ^2tests, and I^2 statistics used to assess the magnitude of heterogeneity [106 107]. If there was no unexplained statistical heterogeneity a fixed-effect model was used and a random-effect model was used if heterogeneity existed (I^2≥50%). Funnel plots and Egger's regression test were used to assess for publication bias [108] . No publication bias was identified.

PCSK9 inhibitors were shown to significantly decrease the levels of low-density lipoprotein cholesterol, total cholesterol, triglycerides, apolipoprotein-B and lipoprotein(a) and increase the levels of high-density lipoprotein cholesterol and apolipoprotein-A1. There was no significant difference in the incidence of treatment emergent adverse events, serious treatment-emergent adverse and the discontinuation of treatment between the two groups.

The results of this meta-analysis indicated that PCSK9 inhibitors were effective at lowering LDL-C and modifying other lipid parameters in patients with hypercholesterolaemia while having a satisfactory safety and tolerability profile

4.9.1.2 Navarese et al. [39]

Navarese et al. undertook a Systematic Review and Meta-analysis including Phase II or Phase III RCTs evaluating the efficacy and safety of PCSK9 antibodies in adults with hypercholesterolaemia. The meta-analysis was conducted according to Cochrane guidelines and findings reported according to the PRISMA statement [79 80] (Table 38). Results were presented pooling data for alirocumab and evolocumab. Primary clinical endpoints included

Table 38 Summary of Navarese et al. meta-analysis

Data consideration	Details	Notes
Data analysis populations	• ITT	
Primary clinical endpoints	• All-cause mortality • CV mortality	

Data consideration	Details	Notes
Secondary clinical endpoints	• MI • UA • Serum creatine level • SAEs	
Efficacy (biochemical)endpoints	• LDL-C • HDL-C • Total-C • Lp(a)	
Summary statistics	• ORs for dichotomous data • MD of percent change from baseline for continuous variables	95% CI included. If SDs were not reported they were calculated from CIs or SEs of the mean
Heterogeneity	• Cochran Q test • I^2 statistic	If no or low-to-moderate inconsistency (<50%) was found, pooled ORs were calculated by using a fixed-effects model; otherwise, a random-effects model was used

CI, confidence interval; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; Lipoprotein(a); MD, mean difference; MI, myocardial infarction; SAE, serious adverse event; SD, standard deviation; SE, standard error; Total-C, total cholesterol; UA, unstable angina

Searches were run until 4th April 2015 in MEDLINE, the Cochrane Central Register of Controlled Trials, Google Scholar, and Embase; TCTMD (www.tctmd.com), EuroPCR (www.europcr.com), ClinicalTrials.gov, Clinical Trial Results (www.clinicaltrialresults.org), the PCSK9 Education and Research Forum (www.pcsk9forum.org), and the American College of Cardiology Web site (www.cardiosource.com); and major congress proceedings. No restrictions on language, follow-up, or study size were applied.

24 studies were included in the quantitative analysis, which included 10,159 patients. Data were independently extracted by two investigators who were not involved in any of the selected studies. Any discrepancies were resolved through discussion with a third investigator. Any potential risk of bias of the RCTs was assessed by independent appraisal by two unblinded investigators using methods described in the Cochrane Collaboration guidelines[79]. No publication bias was suggested by funnel plots or Egger regression test[108].

Odds ratios (ORs) for dichotomous data and mean difference (MD) of percent change from baseline for continuous variables, with 95% CIs, were used as

summary statistics. Heterogeneity was assessed by using the Cochran *Q* test and the I^2 statistic [106,107]. If no or low to moderate inconsistency (<50%) was found, pooled ORs were calculated by using a fixed-effects model [79]; otherwise, a random-effects model was used. To account for the potential differences in follow-up between studies, a pre-specified analysis was performed with adjusted models by person-years to obtain pooled log rate ratios and CIs.

Compared with control, treatment with PCSK9 antibodies led to marked reductions in low-density lipoprotein cholesterol levels and other atherogenic lipid fractions. All cause mortality was significantly reduced, with a similar odds ratio(not statistically significant) in cardiovascular mortality. The rate of myocardial infarction was significantly reduced. Increases in the serum creatine kinase level were reduced. In addition, serious adverse events did not increase with administration of PCSK9 antibodies (Table 39).

Table 39 Summary of key findings from Navarese meta-analysis

Endpoint	Patient numbers	Result
All-cause mortality	24 RCTs; 10,159 patients	OR: 0.45 [95% CI, 0.23 to 0.86]; P=0.015; heterogeneity P=0.63; I^2=0%
CV mortality	24 RCTs; 10,159 patients	OR: 0.50 [95% CI, 0.23 to 1.10]; P=0.084; heterogeneity P=0.78; I^2=0%
MI	10 RCTs; 5195 patients	OR:0.49 [95% CI, 0.26 to 0.93]; P=0.030; heterogeneity P=0.45; I^2=0%
Serum CK level	24 RCTs; 10,159 patients	OR, 0.72 [95% CI, 0.54 to 0.96]; P=0.026; heterogeneity P=0.65; I^2=0%
SAE	24 RCTs; 10,159 patients	OR, 1.01 [95% CI, 0.87 to 1.18]; p=0.88; heterogeneity P=0.98; I^2=0%
LDL-C	24 RCTs; 10,159 patients	MD: –47.49% [95% CI, –69.64% to –25.35%]; P<0.001

CI, confidence interval; CK, creatinine kinase; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MD, mean difference; MI, myocardial infarction; OR, odds ratio; RCT, randomised controlled trial

In conclusion the meta-analysis found that PCSK9 antibodies seem to be safe and effective for adults with dyslipidaemia, producing profound reductions in LDL

cholesterol with an apparently similar level of safety and an important preliminary signal of survival benefit compared with no anti-PCSK9 treatment. The study reported several limitations, primarily that the results were derived from study-level data rather than patient-level data and that the number of CV events was small.

4.9.1.3 Zhang et al. [102]

Zhang et al. undertook a meta-analysis of 25 RCTs to assess the safety and efficacy of anti-PCSK9 antibodies. The meta-analysis was conducted in line with recommendations from the PRISMA statement [80].

Searches were run up till 6 October 2014 in PubMed, EMBASE, and the Cochrane CENTRAL database. Major conference proceedings were also searched until 20 November 2014. Eligibility assessment was carried out by two investigators. A total of 25 studies with 12,200 patients were included in the quantitative analysis. The Cochrane Collaboration tool was then used to assess the risk of bias of included trials.

For all efficacy outcomes, the mean differences following anti-PCSK9 treatment versus placebo or ezetimibe were pooled across studies using the DerSimonian-Laird random-effects models. The I^2 statistic and the χ^2-based Q tests were applied to assess heterogeneity[107,106]. Begg's test and Egger's test were performed to assess publication bias [108]. It is important to note, however, that results were reported separately for alirocumab and for evolocumab and therefore did not give a pooled effect across PCSK9 inhibitors as a whole.

The meta-analysis found that rates of common adverse events showed largely no significant difference between anti-PCSK9 antibodies and placebo (or ezetimibe). Alirocumab was, however, associated with reduced rates of death (relative risk (RR): 0.43, 95 % confidence interval (CI): 0.19 to 0.96, P = 0.04). Alirocumab was also associated with an increased rate of injection-site reactions (RR: 1.48, 95 % CI: 1.05 to 2.09, P = 0.02).

As with the other meta-analyses, it was found that both alirocumab and evolocumab substantially reduced the LDL-C level (by over 50%), increased the HDL-C level, and resulted in favourable changes in other lipids.

4.10 Indirect and mixed treatment comparisons

As direct head to head evidence from the ODYSSEY programme is available to support relevant comparisons within the Scope no indirect or mixed treatment comparisons have been made.

Evolocumab is a PCSK9 inhibitor that was approved by the EMA in July 2015. To date, no NICE guidance date, no NICE guidance has been issued on the use of evolocumab and no studies include a direct include a direct comparison of alirocumab versus. evolocumab. As such a qualitative clinical comparison clinical comparison of the ODYSSEY and PROFICIO programmes only has been made. Although made. Although alignment of trials between programmes is difficultthe tables below represent an attempt represent an attempt to summarise trials with similar patient populations (Table 40,

Table 41,

Table 42,

Table 43, Table 44, Table 45 and

Table 46).

Table 40 Study type summary

Study type	Evolocumab	Alirocumab
Combination therapy	LAPLACE-2 (n=1896) [109]	COMBO I (n=316) COMBO II (n=720) OPTIONS I (n=355) OPTIONS II (n=305) CHOICE I (n=535) **Total n=2231**
Monotherapy	MENDEL-2 (n=614) [110]	MONO (n=103)
HeFH	RUTHERFORD (n=329) [111]	FH I (n=486) FH II (n=249) HIGH FH (n=107) LONG TERM (n=415 HeFH) CHOICE I and II (n= 76 HeFH)

		Total n=1333
Statin intolerant	GAUSS-2 (n=307) [84]	ALTERNATIVE (n=314) CHOICE I (n=803; 108 confirmed SI) CHOICE II (n=233; 210 confirmed SI) **Total n=632**
Outcome studies	FOURIER (n=27,500)	CVOT (n=18,000)
Safety studies	DESCARTES (n=901) [112] OSLER (n=4465) [113]	LONG TERM (n=2341) Open-label extension (n=987)

FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; SI, statin intolerance

Table 41 PCSK9 inhibitors as monotherapy – MONO and MENDEL-2

Baseline Characteristics		**ODYSSEY**	**PROFICIO**
		MONO (N=103)	**MENDEL-2 (N=614)**
Study Design		Multicentre, randomised, double-blind, double-dummy, placebo-controlled study	Multicentre, randomised, double-blind, placebo-controlled study
Duration		24-Week	12-Week
Comparator		Placebo	Placebo
Patient Type		Hypercholesteroleamia moderate CV risk*	Hypercholesteroleamia low to moderate CV risk**
Mean Age (years)		60.2	53.2
Dosing		Alirocumab 75 mg every 2 weeks by SC injection, titrated up to 150 mg every 2 weeks at week 12 if LDL-C >70 mg/dL at week 8	140 mg every 2 weeks as a 1mL subcutaneous injection or 420 mg once a month as 3 x 1 mL subcutaneous injections
Male, n (%)		55 (53.4)	191 (31.1)
LDL-C (mg/dL (mmol/L)), Mean		138-141 (3.6)	140-144 (3.6)
Background Statin Therapy		None	None
Other background LMT		None	None
Patients with FH (%)		0	Data Unavailable
CV Risk	**10-year risk of fatal CVD (Score) (%)**	3	-
	NCEP risk categories (% of subjects)* **	-	High: 3 Moderately High: 3-8 Moderate: 26-47 Low: 49-67
Primary Endpoint		Percentage change in mean LDL-C from baseline to week 24.	Percentage change in mean LDL-C from baseline to week 12 (and also mean of weeks 10 and 12).

*SCORE risk ≥1% and <5%; **Framingham risk ≤10%; ***Risk category definitions: high, diagnosed CHD or risk equivalent; moderately high, 2 or more risk factors and Framingham risk score 10%-20%; moderate, 2 or more risk factors and Framingham risk score <10%; lower, 0 or 1 risk factor

CV = cardiovascular; CVD = cardiovascular disease; FH = familial hypercholesterolaemia; LMT = lipid-modifying therapy; NCEP = National Cholesterol Education Program

Table 42 PCSK9 mAb added onto background of statin therapy ± other LMT – COMBO I & II and PROFICIO LAPLACE-2

Baseline Characteristics	ODYSSEY		PROFICIO
	COMBO I (n=316)	COMBO II (n=720)	LAPLACE-2 (n=1896)
Study Design	Multicentre, randomised, double-blind, placebo-controlled study	Multicentre, randomised, double-blind, placebo & Ezetimibe controlled study	Multicentre, randomised, double-blind, placebo & Ezetimibe controlled study
Duration	52 Weeks	104 Weeks	12 Weeks
Comparator	Placebo	Ezetimibe	Placebo and Ezetimibe
Patient Type	Hypercholesterolaemia and established coronary heart disease or coronary heart disease risk equivalents	Hypercholesterolaemia and established coronary heart disease or coronary heart disease risk equivalents	Hypercholesterolaemia Mixed dyslipidaemia
Mean Age (years)	63.0	61.6	59.8
Dosing	Alirocumab 75 mg every 2 weeks by SC injection, titrated up to 150 mg every 2 weeks at week 12 if LDL-C >70 mg/dL at week 8	Alirocumab 75 mg every 2 weeks by SC injection, titrated up to 150 mg every 2 weeks at week 12 if LDL-C >70 mg/dL at week 8	Evolocumab 140 mg every 2 weeks or 420 mg every month as add-on therapy to atorvastatin or rosuvastatin or simvastatin (24 treatment groups).
Male, n (%)	208 (65.8)	530 (73.6)	1028 (54.2)
LDL-C (mg/dL (mmol/L)), Mean	102.2	106.9	109.1
Background Statin Therapy (%)	Maximally tolerated High-intensity**: 57.6%	Maximally tolerated High-intensity**: 66.7%	Intensive‡: 29% Non-intensive§: 41% None: 30%
Other background LMT (%)	38-50††	None	Data Unavailable
CHD History (%)	78-79	90.1	17-24
Type 2 Diabetes (%)	39-45	30-32	13-20
Primary Endpoint	Percentage change in	Percentage change in	Percentage change in

	mean LDL-C from baseline to week 24.	mean LDL-C from baseline to week 24.	mean LDL-C from baseline to week 12 (and also mean of weeks 10 and 12).

CHD = Coronary heart disease; LMT = lipid-modifying therapy

‡Atorvastatin (80 mg) and rosuvastatin (40 mg); §Atorvastatin (10 mg) and rosuvastatin (5 mg); **Patients should receive either rosuvastatin 20–40 mg, atorvastatin 40–80 mg daily, or simvastatin 80 mg daily unless not tolerated and/or appropriate other dose given according to the judgement of the investigator;

††LLT: bile acid sequestrant, ezetimibe, niacin, fenofibrate, omega 3 >1000 mg/d, stable nutraceuticals

Table 43 PCSK9 mAb add-on therapy to different statins and different doses of statins ± other LMT – OPTIONS I & II andPROFICIO LAPLACE-2

Baseline Characteristics	ODYSSEY		PROFICIO
	OPTIONS I (n=355)	OPTIONS II (n=305)	LAPLACE-2 (n=1896)
Study Design	Multicentre, randomised, double-blind, active comparator study	Multicentre, randomised, double-blind, active comparator study	Multicentre, randomised, double-blind, placebo & Ezetimibe controlled study
Duration	24 Weeks	24 Weeks	12 Weeks
Patient Type	Hypercholesterolaemia (non-FH or HeFH) High CV risk* Uncontrolled on atorvastatin	Hypercholesterolaemia (non-FH or HeFH) High CV risk* Uncontrolled on rosuvastatin	Hypercholesterolaemia Mixed dyslipidaemia
Mean Age (years)	62.9	60.9	59.8
Dosing	Alirocumab 75 mg every 2 weeks by SC injection, titrated up to 150 mg every 2 weeks at week 12 if LDL-C >70 mg/dL at week 8	Alirocumab 75 mg every 2 weeks by SC injection, titrated up to 150 mg every 2 weeks at week 12 if LDL-C >70 mg/dL at week 8	Evolocumab 140 mg every 2 weeks or 420 mg every month as add-on therapy to atorvastatin or rosuvastatin or simvastatin (24 treatment groups).
Male, n (%)	231 (65.1)	187 (61.3)	1028 (54.2)
LDL-C (mg/dL (mmol/L)), Mean	105.1	111.3	109.1
Background Statin Therapy (%)	Atorvastatin (20 mg or 40 mg)	Rosuvastatin (10 mg or 20 mg)	Intensive‡: 29% Non-intensive§: 41% None: 30%
Other background LMT (%)	± other LLT (excluding ezetimibe)	± other LLT (excluding ezetimibe)	Data Unavailable
CHD history (%)	59	63	17-24
Type 2 Diabetes (%)	50	42	13-20
Primary Endpoint	Percentage change in mean LDL-C from baseline to week 24.	Percentage change in mean LDL-C from baseline to week 24.	Percentage change in mean LDL-C from baseline to week 12 (and also mean of

			weeks 10 and 12).

*Either: a) Patients with HeFH or non-FH and with documented history of CVD or diabetes mellitus with target organ damage; or b) Patients without CVD who have HeFH, or have non-FH with a calculated 10-year fatal CVD

risk SCORE ≥5%, or have a moderate chronic kidney disease, or have diabetes mellitus but no target organ damage,

‡Atorvastatin (80 mg) and rosuvastatin (40 mg); §Atorvastatin (10 mg) and rosuvastatin (5 mg);

CHD = coronary heart disease; CV = cardiovascular; FH = familial hypercholesterolaemia; HeFH = heterozygous familial hypercholesterolaemia; LMT = lipid-modifying therapy

Table 44 PCSK9 mAb add-on therapy in patients with HeFH on background LMT – FH I, FH II and HIGH FH andRUTHERFORD-2

Baseline Characteristics	ODYSSEY			PROFICIO
	FHI (n=486)	FH II (n=249)	High FH[2](n=107)	RUTHERFORD -2 (n=329)
Study Design	Multicentre, randomised, double-blind, placebo-controlled study	Multicentre, randomised, double-blind, placebo-controlled study	Multicentre, randomised, double-blind, placebo-controlled study	Multicentre, randomised, double-blind, placebo-controlled study
Duration	78 Weeks	78 Weeks	78 Weeks	12-Week
Comparator	Placebo	Placebo	Placebo	Placebo
Patient Type	HeFH	HeFH	HeFH	HeFH
Mean Age (years)	51.9	53.2	50.6	51.2
Dosing	Alirocumab 75 mg every 2 weeks by SC injection, titrated up to 150 mg every 2 weeks at week 12 if LDL-C >70 mg/dL at week 8	Alirocumab 75 mg every 2 weeks by SC injection, titrated up to 150 mg every 2 weeks at week 12 if LDL-C >70 mg/dL at week 8	Alirocumab 150 mg every 2 weeks by SC injection	Evolocumab 140 mg every 2 weeks by SC injection OR Evolocumab 420 mg every month by SC injection
Male, n (%)	274 (56.3)	131(52.6)	57 (53.3)	190 (57.8)
LDL-C (mg/dL (mmol/L)), Mean	144.6	134.4	197.8	156.0
Background High Intensity Statin Therapy (%)	81.5†	86.3†	72.9‡	87§
Other background LMT (%)	Ezetimibe: 57.0	Ezetimibe: 66.3	Ezetimibe: 24.3	Ezetimibe: 62
CHD history (not including stroke or peripheral artery disease), n (%)	225 (46.3)	88 (35.3)	53 (49.5)	103 (31.3)
Primary Endpoint	Percentage change in mean	Percentage change in	Percentage change in	Percentage change in mean LDL-C from

	LDL-C from baseline to week 24.	mean LDL-C from baseline to week 24.	mean LDL-C from baseline to week 24.	baseline to week 12 (and also mean of weeks 10 and 12).

CHD = Coronary heart disease;; LMT = lipid-modifying therapy

†Atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily; ‡Atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg daily; §80 mg simvastatin daily, ≥40 mg atorvastatin daily, ≥20 mg rosuvastatin daily, or any dose of statin together with ezetimibe

Table 45 PCSK9 mAb in statin intolerant patients on background of other LMT – ALTERNATIVE andGAUSS-2

Baseline Characteristics	ODYSSEY	PROFICIO
	ALTERNATIVE (N=314)	GAUSS-2 (N=307)
Study Design	Multicentre, randomised, double-blind, double-dummy, active-controlled study	Multicentre, randomised, double-blind, placebo & Ezetimibe - controlled study
Duration	24 Weeks	12 Weeks
Comparator	Ezetimibe 10 mg daily Or Atorvastatin 20 mg daily (included as a re-challenge arm; comparisons in efficacy were not made	Ezetimibe 10 mg daily
Patient Type	Hypercholesterolaemia Moderate to very high CV risk Statin intolerance*	Hypercholesterolaemia Low to high CV risk Statin intolerance†
Mean Age (years)	63.4	62
Dosing	Alirocumab 75 mg every 2 weeks by SC injection, titrated up to 150 mg every 2 weeks at week 12 if LDL-C >70 mg/dL at week 8	Evolocumab 140 mg every 2 weeks by SC injection OR Evolocumab 420 mg every month by SC injection
Male, (%)	54.8	54.1
LDL-C (mg/dL), Mean	191.3	193
Background Statin Therapy	None (2-week statin washout prior to treatment)	Any: 17–20%
Other background LMT	Other than statin/ezetimibe: 37–54%	LLT other than statins: 11–19%
Patients with FH (%)	11.2-20.0	Data Unavailable
CHD History (%)	43–51	50–63‡
Primary Endpoint	Primary endpoint, percentage change in LDL-C from baseline to week 24	Percentage change in mean LDL-C from baseline to week 12 (and also mean of weeks 10 and 12).

*Unable to tolerate at least two different statins, including one at the lowest dose, due to muscle-related symptoms; †Previous intolerance to ≥2 statins, defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects; ‡Based on % subject in NCEP high risk category

CHD = coronary heart disease; CV = cardiovascular; FH = familial hypercholesterolaemia; LLT = lipid-lowering therapy;

Table 46 PCSK9 mAb added onto background of statin therapy ± other LMT – Safety Studies: LONG TERM and DESCARTES and OSLER

Baseline Characteristics	ODYSSEY	PROFICIO	
	LONG TERM (n=2341)	DESCARTES (n=901)	OSLER (n=4465)
Study Design	Double-blind, randomised, placebo controlled	Double-blind, randomised, placebo controlled	Open Label Extension
Duration (months)	18	12	11
Patient Type	Hypercholesterolaemia High CV risk* HeFH†	LDL-C ≥75 mg/dL Low to high CV risk	Hypercholesterolaemia Low to high CV risk Partial statin intolerant population
Mean Age (years)	60.5	56.2	57.9
Dosing	Alirocumab 150 mg every 2 weeks by SC injection	Evolocumab 420 mg every month by SC injection	Evolocumab 140 mg every 2 weeks by SC injection or Evolocumab 420 mg every month by SC injection
Male, n (%)	1457 (62.2)	430 (47.7%)	2255 (50.5)
LDL-C (mg/dL (mmol/L)), Mean	122–123	95–120	120–121††
Background Statin Therapy (%)	Any‡: 100% High-intensity statin§:44%	1. Diet alone 2. Low-intensity: 10 mg atorvastatin 3. High-intensity: 80 mg atorvastatin 4. Maximal: 80 mg atorvastatin + 10 mg ezetimibe**	Any: 70–71% High-intensity‡‡: 27–28%
Other background LMT (%)	Any: 28% Ezetimibe: 14.3%		Ezetimibe: 13 – 15%
CHD history (%)	68-70	0-48	20-21
Type 2 Diabetes (%)	34-35	1-25	13-15
Patients with FH (%)	18	Data Unavailable	10

*Patients with hypercholesterolaemia together with established CHD or CHD risk equivalents; †Patients with HeFH with or without established CHD or CHD risk equivalents; ‡Either rosuvastatin 20-40 mg, atorvastatin 40-80 mg daily, or simvastatin 80

mg daily unless not tolerated and/or appropriate other dose given according to the judgement of the investigator; §High intensity statin: atorvastatin 40-80 mg, rosuvastatin 20-40 mg, or simvastatin 80 mg daily; **Patients were started on various forms of background LLT depending on CV risk (ATPIII NCEP) for a run-in period of 4–12 weeks prior to treatment period;

††Range of median values, as opposed to mean values;
‡‡Intensity of statin therapy was defined according to the 2013 ACC/AHA cholesterol treatment guidelines

CHD = coronary heart disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolaemia; FH = familial hypercholesterolaemia; LMT = lipid-modifying therapy

In summary, the ODYSSEY and PROFICIO trial programmes have broadly looked to investigated broadly similar patient populations. Differences, however, are present. The principal differences are:

- Primary Endpoint – In general primary endpoint analyses occur at Week 24 for alirocumab vs. Week 12 or 10/12 for evolocumab
- Patient cohort - more studies have been conducted in high CV risk patients in ODYSSEY (Table 8 Section 4.6) than in PROFICIO, with several PROFICIO studies including low risk patients (MENDEL-2, GAUSS-2, LAPLACE-2 and DESCARTES)
- The majority of ODYSSEY trials allow for dose titration based on pre-defined treatment goals which is not factored into the PROFICIO phase III programme
- The principal ODYSSEY trials focus on 2 weekly dosing as opposed to the PROFICIO trial programme which focusses on 4 weekly dosing

4.11 Non-randomised and non-controlled evidence

N/A

4.12 Adverse reactions

Key Points

- **The Phase II/ and Phase III studies submitted as part of the EMA filing included 3340 patients randomised to alirocumab, and provided more than 5000 patient years double blind exposure and 3451 years of alirocumab exposure**
- **No difference in the safety profile was observed between the two doses**
- **There were no drug-drug interactions observed in the programme which may have safety implication**
- **Signals were only identified for local injection site reactions and general allergic reactions**
    - **Incidence rates were low and the events were typically mild and transient**
- **No specific safety signals were identified relating to patients with two consecutive LDL-C levels <25mg/dL (0.65 mmol/L)**
- **A global pool of Phase III studies indicated a trend towards decrease of CV events in the alirocumab arm**
    - **The large safety study LONG TERM indicated a decrease in MACE events with an HR of 0.52 (95% CI: 0.31 to 0.90)**

The safety profile of alirocumab has been assessed in different populations of patients with hypercholesterolaemia, i.e., HeFH patients, non-FH patients, including patients with mixed dyslipidaemia. The majority of the patients studied were treated with a maximally tolerated dose of statins with or without other LMT. In addition, alirocumab was also studied in patients who are not on statin therapy, including patients with statin intolerance, either as monotherapy or as add-on to their existing, non-statin LMT.

In summary, a total of 5234 patients with hypercholesterolaemia were included in the safety pool (submitted to the EMA), among whom 3340 patients were treated with alirocumab at a dose of 75 or 150 mg administered SC once every 2 weeks.

Treatment duration was up to 18 months (including 2856 patients exposed to alirocumab for at least 24 weeks, 2408 patients exposed for at least 52 weeks, and 639 patients exposed for at least 76 weeks), leading to an overall exposure of 3451 patient-years in the alirocumab group. Following regulatory filing, the number of patients treated for at least 76 weeks has increased up to 1717 as of December 2014. This large safety database, with long-term exposure in the target patient population, allows a comprehensive assessment of the alirocumab safety profile.

All patients in the placebo-controlled pool [Phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I), Phase II (DFI11565, DFI11566, CL-1003, DFI12361)] and the majority of patients in the ezetimibe-controlled pool [Phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)] were at high or very high CV risk, with the majority of patients in both pools having a history of CHD (60 to 70% of patients). In addition, approximately 30% of patients reported a history of diabetes mellitus.

The Phase II/III programme included a significant number of elderly patients: 1799 patients were ≥65 years of age and 375 patients were ≥75 years of age. Almost all patients in the placebo-controlled pool and 75–80% patients in the ezetimibe-controlled pool took the IMP on top of maximally tolerated concomitant statin usage.

The approach to the safety analysis considered 3 tiers of TEAEs. Tier 1 consisted of TEAEs for which hypotheses and a comprehensive analytical approach were prospectively defined. Hypotheses were based on literature review, suggestions by regulatory authorities, or ADRs identified in product labeling of other products that

treat hypersholesterolaemia. These included local injection site reactions, allergic events, neurologic events including neurocognitive events, skeletal muscle-related AEs, diabetes mellitus, ALT increase, and ophthalmologic events. Tier 2 represented common TEAEs (not pre-specified). “Common” adverse events were defined as those for which there were at least 9 patients with an event overall in the placebo-controlled pool and at least 6 patients with an event in the ezetimibe-controlled pool. Tier 3 represented infrequent TEAEs which are assessed clinically.

A summary of the pooled adverse event data can be seen in Table 47, Table 48, Table 49. Pooled common TEAEs reported at ≥1% incidence can be found in Appendix 9.

Table 47 Overview of adverse event profile: TEAEs (Safety population) - Pool of placebo-controlled studies and Pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
n (%)*	**Placebo (n=1276)**	**Alirocumab (n=2476)**	**Ezetimibe (n=618)**	**Alirocumab (n=864)**
Patients with any TEAE	975 (76.4%)	1876 (75.8%)	421 (68.1%)	607 (70.3%)
Patients with any treatment-emergent SAE	182 (14.3%)	340 (13.7%)	69 (11.2%)	113 (13.1%)
Patients with any TEAE leading to death	11 (0.9%)	13 (0.5%)	7 (1.1%)	2 (0.2%)
Patients with any TEAE leading to permanent treatment discontinuation	65 (5.1%)	131 (5.3%)	60 (9.7%)	76 (8.8%)

Placebo-controlled studies: phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I), phase II (DFI11565, DFI11566, CL-1003, DFI12361). Ezetimibe-controlled studies: phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE).
AE, adverse event; FH, familial hypercholesterolaemia; SAE, serious adverse event; TEAE, treatment-emergent adverse event
*Number and percentage of patients with at least one TEAE.

Table 48 Number (%) of patients with Local injection site reaction TEAE(s) (Safety population) - Global pool

	Control (n=1894)	Alirocumab (n=3340)
Any local injection site reaction TEAE		
n (%)*	78 (4.1%)	205 (6.1%)
95% mid-p CI	3.3% to 5.1%	5.4% to 7.0%

Number of patients with an event per 100 patient-years[a]	4.2	6.0
95% CI	3.3 to 5.2	5.2 to 6.9
HR vs control (95% CI)[b]		1.50 (1.15 to 1.95)

Placebo-controlled studies: phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I), phase II (DFI11565, DFI11566, CL-1003, DFI12361). Ezetimibe-controlled studies: phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). MedDRA 17.0: the selection of PTs is based on pre-specified category on AE e-CRF form or HLT "injection site reaction", depending on the study.
AE, adverse event; CI, confidence interval; e-CRF, electronic case report form; FH, familial hypercholesterolaemia; HLT, high-level term; HR, hazard ratio; PT, preferred term; TEAE, treatment-emergent adverse event
*Number and percentage of patients with at least one event.
[a]Calculated as the number of patients with an event divided by total patient-years. For patients with an event, the number of patient-years is calculated up to the date of the first event; for patients without an event, it corresponds to the length of the TEAE period.
[b]Calculated using a Cox model stratified on the study.

Table 49 Number (%) of patients with TEAE(s) of special interest by PT (Safety population) - Pool of placebo-controlled studies and Pool of ezetimibe controlled studies adverse events reported in ≥1% of patients

TEAE n (%)	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (n=1276)	**Alirocumab (n=2476)**	**Ezetimibe (n=618)**	**Alirocumab (n=864)**
General allergic TEAE	99 (7.8%)	213 (8.6%)	33 (5.3%)	59 (6.8%)
HR vs control (95% CI)		1.10 (0.87 to 1.40)		1.31 (0.85 to 2.02)
Hypersensitivity (SMQ)	99 (7.8%)	213 (8.6%)	33 (5.3%)	59 (6.8%)
Rash	17 (1.3%)	30 (1.2%)	6 (1.0%)	12 (1.4%)
Pruritus	5 (0.4%)	28 (1.1%)	3 (0.5%)	7 (0.8%)
Any neurological TEAE	45 (3.5%)	86 (3.5%)	15 (2.4%)	29 (3.4%)
HR vs control (95% CI)		0.98 (0.68 to 1.41)		1.43 (0.76 to 2.69)
Guillain-Barre syndrome (SMQ)	39 (3.1%)	78 (3.2%)	14 (2.3%)	24 (2.8%)
Paraesthesia	9 (0.7%)	25 (1.0%)	2 (0.3%)	6 (0.7%)
Peripheral neuropathy (SMQ)	42 (3.3%)	70 (2.8%)	13 (2.1%)	20 (2.3%)
Paraesthesia	9 (0.7%)	25 (1.0%)	2 (0.3%)	6 (0.7%)
Any neurocognitive disorders	9 (0.7%)	21 (0.8%)	6 (1.0%)	8 (0.9%)
HR vs control (95% CI)		1.18 (0.54 to 2.58)		0.94 (0.32 to 2.74)
Any diabetic complications	40 (3.1%)	83 (3.4%)	17 (2.8%)	17 (2.0%)
HR vs control (95% CI)		1.05 (0.72 to 1.53)		0.60 (0.31 to 1.19)
DM or diabetic complications (CMQ)	40 (3.1%)	83 (3.4%)	17 (2.8%)	17 (2.0%)
DM	14 (1.1%)	32 (1.3%)	10 (1.6%)	7 (0.8%)

Type 2 DM	12 (0.9%)	31 (1.3%)	2 (0.3%)	5 (0.6%)
Any related to hepatic disorders	23 (1.8%)	61 (2.5%)	14 (2.3%)	16 (1.9%)
HR vs control (95% CI)		1.36 (0,84 to 2.20)		0.69 (0.34 to 1.43)
Hepatic disorders	23 (1.8%)	61 (2.5%)	14 (2.3%)	16 (1.9%)
ALT increased	9 (0.7%)	28 (1.1%)	5 (0.8%)	5 (0.6%)
Any ophthalmological	18 (1.4%)	44 (1.8%)	3 (0.5%)	7 (0.8%)
HR vs control (95% CI)		1.24 (0.72 to 2.15)		1.36 (0.35 to 5.31)
Retinal disorders (SMQ)	13 (1.0%)	35 (1.4%)	3 (0.5%)	6 (0.7%)

AE, adverse event; ALT, alanine aminotransferase; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; PT, preferred term; SMQ, standardised MedDRA queries; TEAE, treatment-emergent adverse event

The percentages of patients who experienced at least 1 TEAE, at least 1 treatment-emergent SAE and any TEAEs leading to permanent treatment discontinuation were similar between the alirocumab and control groups. The most common adverse reactions leading to treatment discontinuation in patients treated with alirocumab were local injection site reactions (0.2% patients in the alirocumab group versus 0.3% in control groups).

The analysis revealed no differences between alirocumab and controls, and as such no ADRs were identified, in regard to the following: neurologic events, neurocognitive events, musculoskeletal-related events, diabetes mellitus, hepatic disorders, ophthalmological events, and haemolytic anaemia. The data suggest that alirocumab is therefore not associated with hepatic effects or muscle-related AEs, common safety concerns associated with statins.

The incidence of the skeletal muscle-related TEAEs was similar between treatment groups, however, in ALTERNATIVE, there were fewer patients with skeletal muscle-related TEAEs in the alirocumab group than the atorvastatin (HR 0.61 [0.38 to 0.99]) or ezetimibe (HR 0.70 [0.47 to 1.06]) groups.

Differences between alirocumab and controls were noted for local injection reactions and general allergic events. The occurrence of local injection site reactions was higher in the alirocumab group compared to the pooled control group. The incidence rate of local injection site reactions was low and the events were typically mild and

transient. Injection site reactions were more common in patients with treatment-emergent ADA. Injection site reactions are identified as ADRs.

General allergic events were more frequently reported in patients treated with alirocumab compared to the pooled control group. The primary event responsible for this difference was pruritus, and as such pruritus is considered an ADR. The incidence rate of pruritus was low and the events were typically mild and transient. In addition, rare and sometimes serious allergic reactions (eg, hypersensitivity, eczema nummular, urticaria, and hypersensitivity vasculitis) were reported.

Signals were therefore only identified for local injection site reactions and general allergic reactions, ADRs that would be expected for a therapeutic monoclonal antibody.

No difference in the safety profile was observed between the 2 doses (75 mg and 150 mg administered every 2 weeks) used in the Phase III program. There were no drug-drug interactions observed in the programme which may have safety implication.

The consequences of LDL-C levels <25 mg/dL were also evaluated in an analysis of the pooled data. None of the potential risks considered to be associated with low LDL-C levels were confirmed. The analysis of overall TEAEs in patients with 2 consecutive LDL-C values <25 mg/dL (<0.65 mmol/L) or <15 mg/dL (<0.39 mmol/L) did not reveal any specific safety signal. Neurologic and neurocognitive events were reported overall at a low and comparable incidence rate in patients in the alirocumab and the placebo or ezetimibe control groups with no safety signal identified. There were no clinically meaningful changes with regard to cortisol, gonadal hormones or fat soluble vitamins associated with administration of alirocumab and no cases of haemolytic anaemia were reported.

In patients who were treated with alirocumab in the global pool of Phase III studies, a treatment emergent anti-alirocumab antibody (ADA) positive response was measured in 4.8% of patients (compared with 0.6% in the control groups). In most patients treated with alirocumab, the ADA response was considered to be transient and in all but 21 (0.7%) patients, ADA titers were low (≤240). The presence of a treatment-emergent ADA positive response was not associated with any safety

concern apart from an increased incidence of injection site reactions (PT) (incidence rate in 100 patient-years of 9.9 in patients with treatment-emergent ADA positive response versus 5.4 in patients with ADA negative response).

In a pooled analysis of Phase III studies, all-cause mortality was 0.6% (20 of 3182) of patients in the alirocumab group and 0.9% (17 of 1792) of patients in the control group. The primary cause of death (as per adjudication) in the majority of these patients was CV events (Table 50). There were no deaths in Phase I or II studies.

Table 50 Summary of deaths adjudication results (Safety population) - Global pool of Phase III studies

Primary cause of death as per adjudication, n (%)	Control (n=1792)	Alirocumab (n=3182)
Death on study	17 (0.9%)	20 (0.6%)
CHD death	9 (0.5%)	12 (0.4%)
Any CV	11 (0.6%)	15 (0.5%)
Acute MI	0	4 (0.1%)
CV haemorrhage	1 (<0.1%)	2 (<0.1%)
CV procedure	1 (<0.1%)	1 (<0.1%)
Heart failure or cardiogenic shock	1 (<0.1%)	1 (<0.1%)
Stroke – haemorrhagic	0	1 (<0.1%)
Sudden cardiac death	8 (0.4%)	6 (0.2%)
Any non-CV	6 (0.3%)	4 (0.1%)
Accidental	1 (<0.1%)	1 (<0.1%)
Pancreatic	1 (<0.1%)	1 (<0.1%)
Pulmonary	2 (0.1%)	2 (<0.1%)
Suicide	1 (<0.1%)	0
Other non-CV	1 (<0.1%)	0
Non-CV: infection	1 (<0.1%)	0
Non-CV: malignant	2 (0.1%)	2 (<0.1%)
New malignancy	1 (<0.1%)	1 (<0.1%)
Worsening prior malignancy	1 (<0.1%)	1 (<0.1%)
Not adjudicated	0	1 (<0.1%)

CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction

In Phase III studies, suspected CV events and all deaths that occurred from time of randomisation until the follow-up visit were adjudicated. Analyses of the adjudicated events were performed on the global pool, placebo-controlled pool, and ezetimibe-controlled pool. The data from the adjudication are presented below with primary

focus on MACE events (CHD death, nonfatal MI, fatal or nonfatal ischaemic stroke, and unstable angina requiring hospitalisation) (Table 51, Table 52, Figure 26, Figure 27 and Figure 28). The MACE composite endpoint is generally considered the most appropriate and rigorous one to assess cardiovascular outcome and it is the primary endpoint of the CVOT.

Table 51 Positively adjudicated cardiovascular TEAEs: MACE EVENT - Summary table according to adjudication (Safety population) - Global pool of Phase III studies

Category of adjudication n (%)*	Control (n=1792)	Alirocumab (n=3182)
Any patients with a treatment-emergent MACE		
n (%)*	33 (1.8%)	52 (1.6%)
95% mid-p CI	1.3% to 2.5%	1.2% to 2.1%
Number of patients with an event per 100 patient-years[a]	1.8	1.5
95% CI	1.2 to 2.5	1.1 to 1.9
HR vs control (95% CI)[b]		0.81 (0.52 to 1.25)
CHD death (including undetermined cause)	9 (0.5%)	8 (0.3%)
NF MI	23 (1.3%)	30 (0.9%)
Fatal and NF IS (including stroke not otherwise specified)	3 (0.2%)	12 (0.4%)
Unstable angina requiring hospitalisation	1 (<0.1%)	2 (<0.1%)

Placebo-controlled studies: phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I). Ezetimibe-controlled studies: phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE).

CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; FH, familial hypercholesterolaemia; HR, hazard ratio; IS, ischaemic stroke; MACE, major adverse cardiac event; MI, myocardial infarction; NF, non-fatal; TEAE, treatment-emergent adverse event; UA, unstable angina

*Number and percentage of patients with at least one event.

[a]Calculated as the number of patients with an event divided by total patient-years. For patients with an event, the number of patient-years is calculated up to the date of the first event; for patients without an event, it corresponds to the length of the TEAE period.

[b]Calculated using a Cox model stratified on the study.

Figure 26 Positively adjudicated cardiovascular TEAEs: MACE EVENT - Kaplan-Meier Curve - Global pool of Phase III studies

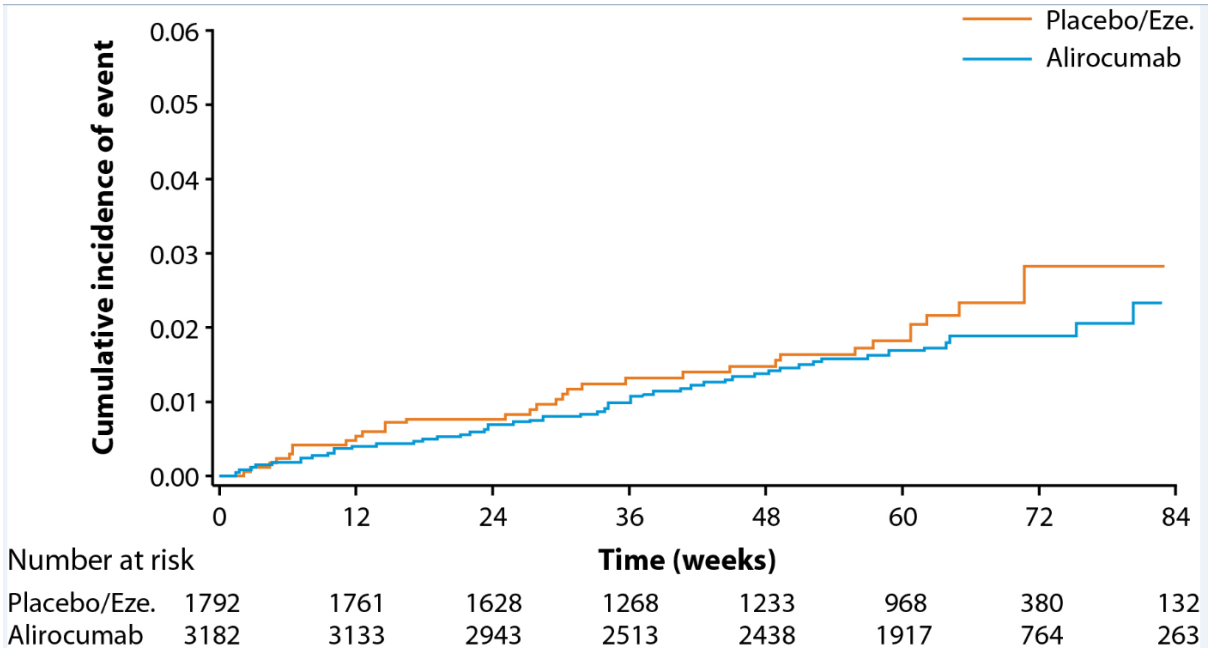


Table 52 Positively adjudicated cardiovascular TEAEs: MACE EVENT - Summary table according to adjudication (Safety population) - Pool of Phase III placebo-controlled studies and Pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
Category of adjudication n (%)*	**Placebo (n=1174)**	**Alirocumab (n=2318)**	**Ezetimibe (n=618)**	**Alirocumab (n=864)**
Any patients with treatment-emergent MACE				
n (%)*	27 (2.3%)	35 (1.5%)	6 (1.0%)	17 (2.0%)
95% mid-p CI	1.6% to 3.3%	1.1% to 2.1%	0.4% to 2.0%	1.2% to 3.1%
Number of patients with an event per 100 patient-years[a]	1.9	1.3	1.3	2.3
95% CI	1.3 to 2.8	0.9 to 1.7	0.5 to 2.8	1.4 to 3.7
HR vs control (95% CI)[b]		0.65 (0.40 to 1.08)		1.51 (0.59 to 3.85)
CHD death (including undetermined cause)	7 (0.6%)	6 (0.3%)	2 (0.3%)	2 (0.2%)
NF MI	19 (1.6%)	17 (0.7%)	4 (0.6%)	13 (1.5%)
Fatal and NF IS (including stroke not otherwise specified)	2 (0.2%)	11 (0.5%)	1 (0.2%)	1 (0.1%)
UA requiring hospitalisation	1 (<0.1%)	1 (<0.1%)	0	1 (0.1%)

Placebo-controlled studies: phase III (LTS11717, FH I, FH II, HIGH FH, COMBO I). Ezetimibe-controlled studies: phase III (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE).

CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; FH, familial hypercholesterolaemia; HR, hazard ratio; IS, ischaemic stroke; MACE, major adverse cardiac event; MI, myocardial infarction; NF, non-fatal; TEAE, treatment-emergent adverse event; UA, unstable angina
*Number and percentage of patients with at least one event.
[a]Calculated as the number of patients with an event divided by total patient-years. For patients with an event, the number of patient-years is calculated up to the date of the first event; for patients without an event, it corresponds to the length of the TEAE period.
[b]Calculated using a Cox model stratified on the study.

Figure 27 Positively adjudicated cardiovascular TEAEs: MACE EVENT – Kaplan-Meier Curve - Pool of Phase III placebo-controlled studies

Figure 28 Positively adjudicated cardiovascular TEAEs: MACE EVENT – Kaplan-Meier Curve - Pool of Phase III ezetimibe-controlled studies

As noted (Section 4.7), in the largest placebo-controlled study, LONG TERM (LTS11717), a post-hoc analysis of MACE was undertaken. This analyses wasperformed on the safety population and included only those CV events that occurred in the TEAE period. The rate of MACE was 48% lower with alirocumab than with placebo (27 (1.7%) vs. 26 (3.3%); hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal P = 0.02). (Section 4.7, Table 18, Figure 15).

Note: across the other smaller placebo-controlled studies, a low number of MACE events was observed, leading to variable estimates of HR seen above.

Overall, in the placebo-controlled pool of Phase III studies, a clear trend towards decrease of MACE events in the alirocumab arm when compared to placebo was observed, with an HR of 0.65 (95% CI: 0.40 to 1.08. Greater variability in estimating the HR was observed in the pool of ezetimibe-controlled studies likely due to the fact that this pool is much smaller and consequently there are relatively few events (HR = 1.51; 95% CI: 0.59 to 3.85). When pooled together in the global pool of Phase III studies, the trend towards decrease of CV events in the alirocumab arm observed in

the placebo-controlled pool is still evident, with an HR of 0.81 (95% CI : 0.52 to 1.25).

It should be noted that in addition to events included in the MACE endpoint, revascularisations and CHF hospitalisations are not included in the MACE endpoint. Clinical standards for revascularisation vary across the globe and it is likely that many of these cases reflect the greater attention to previous disease in the context of a clinical study. Overall, in the global pool, when CHF hospitalisation and revascularisation were also considered alongside MACE endpoints, confirmed CV events were reported in 110 (3.5%) patients in the alirocumab group and 53 (3.0%) patients in the control group. The incidence rate (per 100 patient years) was 3.2 and 2.8 in the alirocumab and control groups, respectively, with an HR of 1.08 (95% CI: 0.78 to 1.50).

The effect on cardiovascular morbidity and mortality is being fully evaluated in the ongoing CVOT study where the primary endpoint is adjudicated MACE events.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Summary of clinical benefits and harms

Across the ODYSSEY programme of 10 Phase III trials (Table 8) in more than 5000 patients alirocumab demonstrated substantial (39–62% versus placebo on top of existing therapy) and consistent reductions in LDL-C in the target patient populations. A rapid onset of efficacy and persistence of treatment effect was observed up to 78 weeks and about 80% of patients were followed for at least 1 year. The treatment effect was highly consistent across a range of different patient subgroups and demographics and on top of ongoing LMTs (including maximal tolerated dose of statins with or without other LMTs), with no heterogeneity observed.

Alirocumab also had a positive impact across a spectrum of lipid parameters that would be expected to be associated with a reduction in CV risk. Non-HDL-C, which is the main target parameter referred to in CG181, was reduced by −37 to −52%

across trials. Mean reductions of -32 to -53% were demonstrated in ApoB, and Lp(a), a similar but distinct atherogenic lipoprotein from LDL-C, and which statin therapy does not affect, had mean reductions in the range −17 to −30%. Alirocumab also was associated with favorable changes in fasting triglycerides, HDL-C, and Apo A-1.

The combined Phase II/III safety database had a pool of 5234 patients of whom 3340 patients were treated with alirocumab, with an overall exposure of 3451 patient-years in the alirocumab group. Overall, the rate of TEAEs and serious TEAEs was similar between the alirocumab and control arms. Local injection site reactions were more commonly observed in alirocumab-treated patients, 6% in the alirocumab groups and 4% in the pooled control groups. However only one was reported as severe, and none was reported as a serious adverse event and injection site reactions only rarely led to discontinuation of treatment. Discontinuations due to general allergic adverse events were also infrequent, but occurred in a higher percentage of alirocumab-treated patients compared to control (a total of 0.6% and 0.2% of patients in the alirocumab and placebo groups, respectively). There was no difference in ADRs between alirocumab and controls regarding neurologic events, neurocognitive events, musculoskeletal-related events, ophthalmological events, and haemolytic anaemia (pre-specified as adverse events of special interest and therefore monitored very closely), or in rates of diabetes mellitus or hepatic disorders.

The analysis of overall TEAEs in patients with very low LDL-C values (two consecutive LDL-C values <0.65 mmol/L or <0.39 mmol/L) did not reveal any specific safety signal. No difference in the safety profile was observed between the two alirocumab doses (75 mg and 150 mg administered every 2 weeks). There were no drug-drug interactions observed in the programme which may have safety implications.

In a pre-specified pooled analysis of the Phase III studies, major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischaemic stroke, or unstable angina requiring hospitalisation, MACE) were reported in 52 of 3182 patients (1.5 per 100 patient-years) in the alirocumab group and 33 of 1792 patients (1.8 per 100 patient-years) in the control group (placebo or active control); HR=0.81 (95% CI, 0.52 to 1.25). In a

post hoc analysis of the largest and longest trial (LONG TERM), the rate of MACE was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal P = 0.02). A cardiovascular outcomes trial, CVOT, is ongoing and due to report in 2018.

4.13.2 Internal validity

The ODYSSEY trials were randomised, double-blind, international, and multi-centre. There was adequate randomisation, including first concealment, comparable groups including attrition and no significant differential loss to follow-up, with clear definition of interventions and relevant primary and broad secondary outcomes measured. Analyses were conducted both as ITT and on-treatment and there was a good degree of consistency between these. The studies are expected therefore to have a high degree of internal validity. The primary endpoint, LDL-C reduction, is an objective endpoint, unlikely to be subject to assessor bias. One potential limitation was that LDL-C was calculated according to the Friedewald formula. However, measured LDL-C (a secondary endpoint) was also collected and showed a high degree of consistency with calculated LDL-C. LDL-C is the biochemical parameter most closely and most extensively linked to CV risk and is therefore the strongest surrogate marker to have as the primary endpoint in trials; other biochemical parameters evaluated as secondary endpoints showed changes consistent with LDL-C.

4.13.3 External validity

The use of statins over the past two decades to reduce LDL-C has successfully decreased the risk of CV events, reinforcing the role of lowering LDL-C as a major means for diminishing cardiovascular morbidity and mortality. For patients who are unable to achieve sufficient LDL lowering despite the best treatment with maximal tolerated current therapies, there is a clear unmet need for additional lipid-lowering therapies. ODYSSEY evaluated alirocumab in this setting – in high risk populations such as patients with HeFH and high risk CVD, as an adjunct to maximal dose current therapy.

Trials evaluating alirocumab as an adjunct to statins used maximal tolerated dose of statin therapy. One consideration or limitation is that in LONG TERM, only 44% of

study patients were receiving high-dose statins. Previous muscle symptoms or creatine kinase elevations during receipt of a high-dose statin accounted for 17% of study patients and regional practices or local labelling accounted for 28% of study patients that did not receive high-dose statins. Approximately 50% of patients in the FH trials were also on statins plus ezetimibe, as were approximately 14% of patients in the LONG-TERM study and 8% in COMBO I. COMBO II,OPTIONS I and II, and ALTERNATIVE also include a direct head-to-head comparisons with ezetimibe. UK guidelines recommend high dose, high intensity statins for all high risk patients (patients with existing CVD, and patients with FH, as well as other categories) and NICE guidance also recommends ezetimibe for patients unable to reach targets on current therapy or who are intolerant to statins. The position in therapy evaluated in ODYSSEY is therefore consistent with current UK treatment and guidelines and the anticipated usage of alirocumab in the UK.

The type of patients included in ODYSSEY are reflective of the patients in whom it is anticipated alirocumab will be used in the UK. 36 UK NHS centres participated in the ODYSSEY programme and a number of sites are involved in the CV outcomes trial. Demographic characteristics were broadly consistent with those of UK patients. As is generally the case, trial patients tend to be somewhat younger, with fewer comorbidities than the general population. Nevertheless ODYSSEY included a high percentage of patients at high CV risk (97.1%), with 78.5% at very high CV risk . 1377 (26%) of patients in ODYSSEY had confirmed FH. Around 25% of patients in LONG-TERM and high FH, with smaller proportions in other trials, had recurrent coronary events and/or polyvascular disease in their previous CV history. One potential limitation is that the latest NICE guideline quotes non-HDL-C targets whereas ODYSSEY measured LDL-C. However, ODYSSEY also reports non-HDL-C, and reductions observed in this parameter were consistent with those observed in LDL-C. Moreover, it is anticipated that alirocumab will mainly be prescribed in specialised, secondary care lipid centres and the types of patients being treated here will also be assessed for LDL-C.

In summary, ODYSSEY is an extensive trial programme which included patients with HeFH and patients at high cardiovascular risk who have elevated LDL-C on current maximal existing therapy. In these patients alirocumab has shown a substantial

reduction in LDL-C, a well-established risk factor for cardiovascular events. A full outcomes trial is ongoing.

4.14 Ongoing studies

Table 53 Ongoing Clinical Studies

Trial no. (acronym)	Intervention	Comparator	Population	Expected completion
CL-1216 (ESCAPE)	Alirocumab	Placebo	Patients with HeFH undergoing lipid apheresis therapy	Feb 2016
EFC13786 (CHOICE II) open-label extension	Alirocumab	Placebo	Patients with primary hypercholesterolaemia not treated with a statin and who are at moderate, high or very high CVD risk	May 2016
LTS13463 open-label extension	Alirocumab	N/A	Patients with HeFH who have completed one of the four parent studies (EFC12492, CL-1112, EFC12732 and LTS11717)	Jun 2016
CL-1018 open-label extension	Alirocumab	N/A	Patients having completed the double-blind period of the study (CL-1018)	Sep 2016
CL-1032 open-label extension CL-1003	Alirocumab	N/A	Patients with HeFH (enrolled in the parent study CL-1003) receiving concomitant treatment with statins ± other LMTs	Sep 2016
EFC11570 (CVOT – ODYSSEY OUTCOMES)	Alirocumab	Placebo	Patients with LDL-C ≥70 mg/dL (≥1.81 mmol/L) who have recently (within the last 12 months) experienced an acute coronary event and who are not adequately controlled with statin ± other LMTs	Jan 2018

The majority of studies in the ODYSSEY programme assess the impact of alirocumab on LDL-C and other liprotein levels. The objective of the CVOT study, however, is to evaluate the ability of alirocumab to reduce CV events in patients who recently experienced an ACS event [114]. It is estimated that approximately 18,000 patients will be enrolled with a minimum follow-up of approximately 24 months and a total duration of approximately 5 years. The proposed primary efficacy endpoint is the effect of alirocumab, compared to placebo on top of background therapy, on the occurrence of the following composite endpoint: coronary heart disease (CHD) death, non-fatal myocardial infarction, non-fatal and fatal ischaemic stroke, and unstable angina requiring hospitalisation (adjudicated major adverse cardiovascular events – MACE). This trial is ongoing an expected to report in 2018.

In addition the following are also underway:

- ODYSSEY APPRISE - LPS14245 (Europe and Canada)
    - Programme in patients at high risk for cardiovascular events
    - A multi-country, single-arm, open-label study to document the safety, tolerability and effect of alirocumab on atherogenic lipoproteins in High CV Risk Patients with severe hypercholesterolaemia not adequately controlled with conventional medication
- Compassionate Use Programme (United States)
    - Alirocumab for the treatment of patients with severe hypercholesterolaemia not controlled with maximally tolerated doses of stable lipid-lowering therapies administered according to the standard of care (CUP14366)
    - The primary objective of this study is to provide access to alirocumab prior to its commercial availability in patients with severe hypercholesterolaemia not controlled with maximal tolerated dose of lipid-lowering therapy administered according to standard of care and in adjunct to diet.
    - The secondary objective is to document alirocumab safety and efficacy
- “Named Patient Programmes” (UK, Ireland, Netherlands, Australia and Canada)
    - Note in the UK this takes the form of an “Unlicensed Supply of Alirocumab Programme”.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

A systematic literature review was undertaken to retrieve relevant cost-effectiveness studies. It was designed to identify economic evaluations of alirocumab or ezetimibe, used alone or in combination with statins or other lipid- lowering therapies, among individuals with hypercholesterolaemia at high-risk of cardiovascular events – including those with familial hypercholesterolaemia. Economic evaluations reporting measures of cost-effectiveness, cost-utility, costs, or resource utilisation were considered eligible for inclusion.

Searches were run in Medline, Medline in process, EMBASE, NHS Economic evaluation database (NHS EED) and EconLit. In addition, conference proceedings from the International Society For Pharmacoeconomics and Outcomes Research (ISPOR), AHA, ADA, EASD) were handsearched.

A total of eight economic evaluations were included. None of these included alirocumab or any other PCSK9 inhibitor.

Full details of the searches, methodology and included studies are provided in Appendix 8. The results of this literature review provided insight and guidance on model development and structure. However as no studies evaluated alirocumab, they are not considered directly relevant to the decision problem and therefore the results are provided in the Appendix.

5.2 De novo analysis

Key points:

- **A Markov model was developed to assess the incremental cost-effectiveness of alirocumab**
- **Patient populations included in the model are:**
    - **HeFH (both primary and secondary prevention)**
    - **Patients at high CV risk due to existing CV disease (history of MI, unstable angina, revascularisation or other evidence of CHD, ischaemic stroke, peripheral arterial disease)**
    - **A subgroup of patients with existing CV disease at even higher risk, namely patients with recurrent CV events/ polyvascular disease**
- **The model allows evaluation by different "starting" LDL-C thresholds. In the base case for HeFH and recurrent events/ polyvascular we model patients with an LDL-C of at least 2.59 mmol/L (on existing therapy); for patients with high risk CVD we model an LDL-C of at least 3.36 mmol/L**
- **Alirocumab was modelled as an adjunct to existing maximal therapy – maximal dose statins, with or without ezetimibe, and on top of ezetimibe in high risk statin intolerant patients. Base case comparisons are:**
    - **Alirocumab + maximal tolerated dose statins + ezetimibe versus maximal tolerated dose statins + ezetimibe (HeFH patients)**
    - **Alirocumab + maximal tolerated dose statins versus maximal tolerated dose statins (patients with high risk CVD and patients with recurrent CV events/ polyvascular disease)**
    - **Alirocumab + ezetimibe versus ezetimibe monotherapy (in the**

above high risk patient groups, in patients who are completely intolerant to statins)

- **Baseline risk of cardiovascular events and transition probabilities were derived from real-world data from the UK THIN database. One of the key challenges was accurately quantifying the baseline risk for HeFH patients in the post-statin era**
- **Data on LDL-C lowering efficacy came from the ODYSSEY pivotal trial programme. The relationship between LDL-C lowering and CV risk reduction came a meta-analysis of PCSK9 inhibitor outcomes data (Navarese et al). Utility data came from ODYSSEY as well as from published sources**
- **The incremental cost-effectiveness of alirocumab varies depending on the CV risk of the population. The uncertainty has been explored using deterministic and probabilistic analyses.**

5.2.1 Patient population

The de novo model was developed to assess the incremental cost-effectiveness of alirocumab in adults with primary hypercholesterolaemia. The cost-effectiveness analysis considers a number of different patient populations/ subgroups, in line with the Scope and reflecting the ODYSSEY trial populations. The treatment effect of alirocumab observed in ODYSSEY was consistent across different patient subgroups. However, the patient groups considered in the model differ in terms of demographics and disease characteristics and in particular the baseline risk of cardiovascular events, which is a key driver of cost-effectiveness.

5.2.1.1 Patient groups considered

The populations that are modelled are:

- Patients with HeFH (both primary and secondary prevention)

- Patients with existing high risk CVD (i.e. history of ACS [MI or unstable angina requiring hospitalisation], coronary revascularisation and other arterial revascularisation procedures or other CHD, ischaemic stroke, PAD). This group is considered as at very high risk of further CV events in clinical guidelines (see Section 3 for further discussion).

- Patients with recurrent CV events - we also consider a subgroup of the above CVD patients with recurrent incidence of CV events or evidence of disease in multiple vascular beds (i.e. polyvascular disease). This is a group which is clinically considered to be at even higher risk than the group of patients with existing CV disease as a whole. This subgroup includes patients with polyvascular disease, who have been shown to be at higher risk compared to patients with disease in only one vascular bed [33 35] i.e. patients who have had an ACS event and a stroke event or existence of PAD. This group also includes patients with multiple coronary events, who are also at higher risk compared to patients with only one previous coronary event [31 32]. Currently, in the model baseline risk data are only available for patients with polyvascular manifestations of disease.

All of these patient groups were included in ODYSSEY (see also Section 4.8). ODYSSEY also included primary prevention patients with risk equivalents such as diabetes or CKD; we have not included such patients in the economic analysis due to feedback that such patients would be unlikely to be considered for alirocumab treatment in the UK.

5.2.1.2 Statin intolerance

We model alirocumab as an adjunct to statin-based therapy, and we also model alirocumab in patients who are completely intolerant to statins. We consider statin intolerant patients within the above high risk groups – these patients are not different in their underlying CV disease , rather they differ in terms of their existing treatment options and, therefore, their severity of hypercholesterolaemia. So we consider patients with HeFH who are completely statin intolerant, patients with high risk CVD and statin intolerance, and patients with recurrent events/ polyvascular disease and statin intolerance.

As a base case, we assume that the high risk statin intolerant patients that we model will be treated with ezetimibe monotherapy and we therefore model alirocumab as an adjunct to ezetimibe. The other key difference between patients with statin intolerance and those without is the average LDL-C level – because these patients are not receiving statins, their mean LDL-C is higher, even for similar "starting" LDL-C thresholds (see 5.2.8).

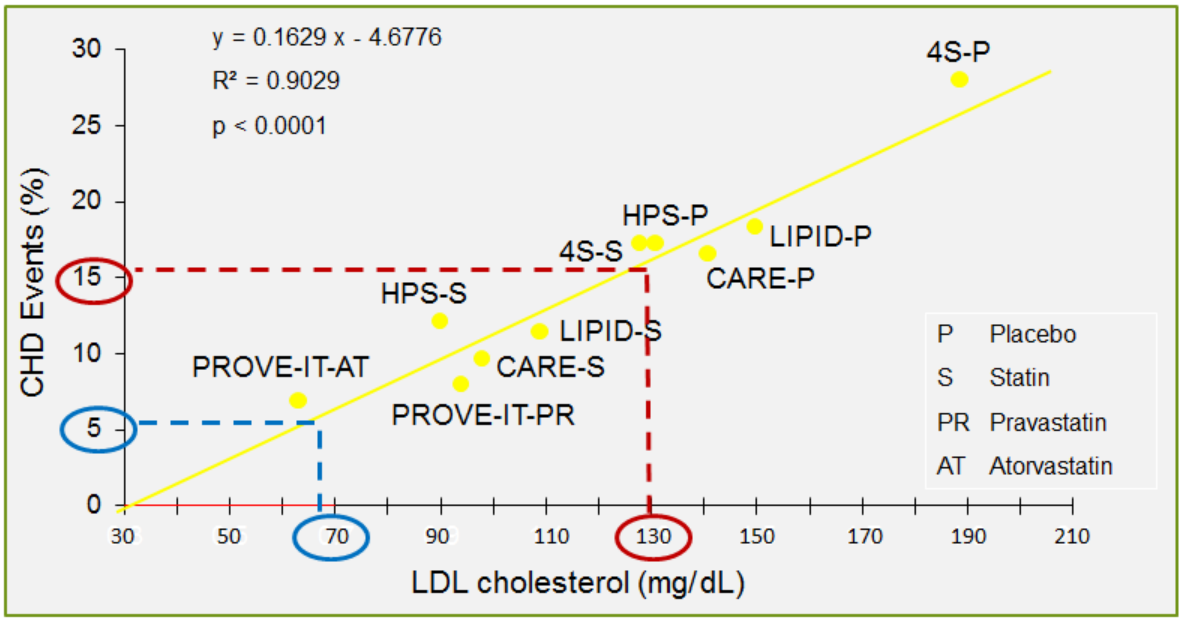
5.2.1.3 – LDL-C levels modelled

Patient populations are modelled according to the severity of hypercholesterolaemia – i.e. according to their baseline LDL-C level before starting alirocumab.

In the base case for HeFH and for patients with recurrent events/ polyvascular disease, we consider patients whose LDL-C is at least 2.59 mmol/L on existing therapy (a level recognised in guidelines and ODYSSEY as indicating elevated LDL-C that should be reduced).

In the group of patients with high risk CVD, we consider in the base case patients whose LDL-C is at least 3.36 mmol/L (i.e. far from recommended targets). This reflects the fact that, clinically and economically, in this large population it is reasonable to focus on patients with a higher LDL-C where their disease and further event risk is strongly driven by LDL-C. This is illustrated in the figure below which shows that in these patients the risk of coronary events is 3 times greater than for patients with LDL-C levels of 1.81 mmol/L [115].

Figure 29: Higher event risk in patients with baseline LDL-C ≥3.36 mmol/L



Adapted from O'Keefe et al. JACC 2004; 43: 2142-6

These are "starting thresholds" – an average LDL-C for the cohort is applied in the model based on the starting threshold (see 5.2.8).

We show in sensitivity analyses in Section 5.9 the impact of different "starting" LDL-C levels.

It is important to note that we refer to absolute LDL-C targets, because from an economic modelling perspective it is necessary to specify a mean starting LDL-C level. By structuring the model in this way we are considering patients who have high LDL-C either because they have not achieved the percentage reductions recommended by NICE, or because their LDL-C level is such that it would still be considered clinically as high despite having achieved a substantial percentage reduction with existing therapy.

5.2.1.4 Position in therapy

In line with current guidelines the high risk groups described above should be appropriately managed with LMT [25,23]. The indication for alirocumab is for patients who are unable to reach LDL-C goals on the maximum tolerated dose of a statin, or in patients who are statin intolerant or for whom a statin is contraindicated. In line with the licence and with clinical guidelines, we model alirocumab as an adjunctive

therapy in patients who are not at target LDL-C levels on existing maximal therapy (see 5.2.8).

5.2.2 Model structure

Key features of the de novo analysis are summarised in Table 54.

Table 54: Features of the *de novo* analysis

Factor	Chosen values	Justification
Time horizon	Lifetime	Reference case
Were health effects measured in QALYs; if not, what was used?	QALYs	Reference case
Discount of 3.5% for utilities and costs	3.5% for both utilities and costs	Reference case
Perspective (NHS/PSS)	NHS/PSS	Reference case

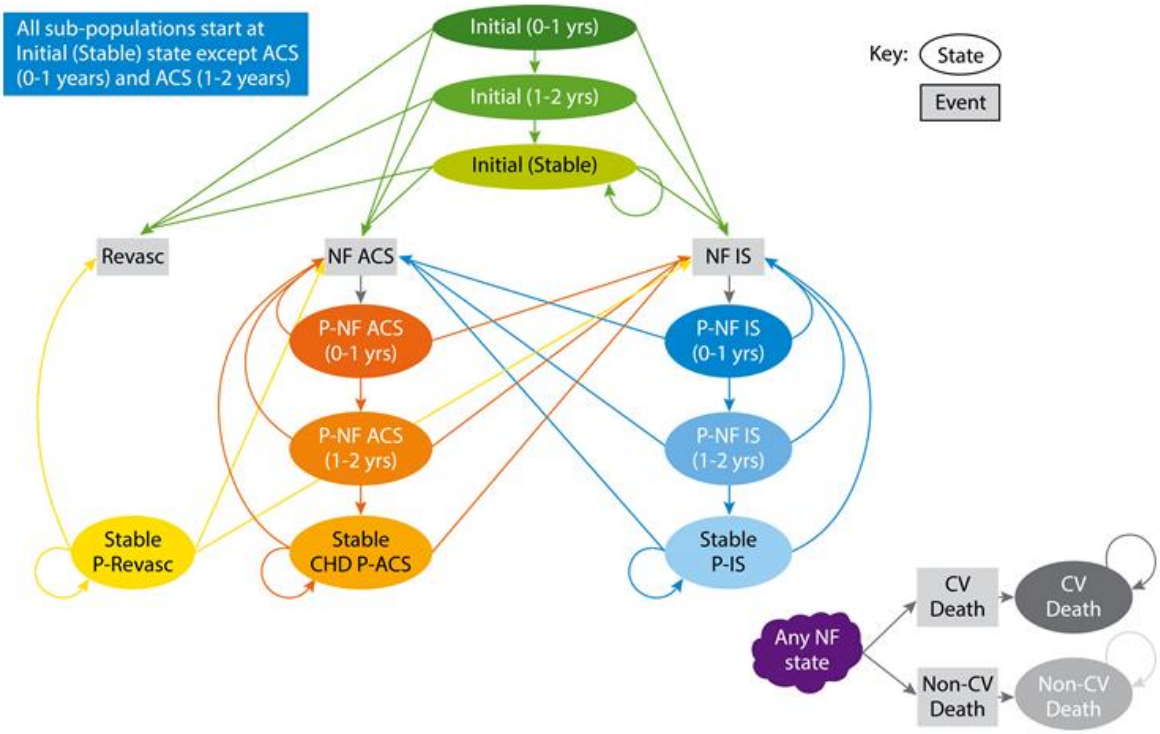
NHS, National Health Service; PSS, personal social services; QALY, quality-adjusted life-year

A Markov model structure with one-year cycles was developed (Figure 30). A review of NICE HTA submissions and Guidelines [24,116,117,25,23], associated with modelling CV conditions, along with the output of the economic evaluation systematic literature review (Appendix 10) indicated that this was an appropriate model structure to adequately address the decision problem.

The model structure allows utilities and costs for multiple events to be modelled with sufficient flexibility to allow variation in these parameters from time since an event, in order to adequately reflect clinical practice.

The model development incorporated feedback from individual experts and health economic and HTA Advisory Boards. The Advisory Boards provided recommendations on the model structure, inclusion and sources of inputs, and major assumptions from clinical and health economic perspectives.

Figure 30: Structure of the cost-effectiveness model



ACS=acute coronary syndrome; IS=ischaemic stroke; NF=non-fatal; P=post-; Revasc=elective revascularizaton

Events in the model are treated as instantaneous and patients remain in states for the entire model cycle.

Patients enter the model in one of the initial states. There are three initial states in the model (0-1 years; 1-2 years and stable) in order to model patients entering the model following a recent ACS event, or with established CV disease (stable). It is well-recognised that the risk of a further event is substantially elevated in the first year [118, 119] following an ACS event – this risk is dynamic and declines over time and so the three initial states were developed in order to appropriately reflect this. This is also reflected in the post-NF ACS health states later in the model. In the model CV events are chosen as a "gateway" to post-event health states. They occur instantaneously at the beginning of the cycle. ACS patients starting in the initial 0 -1 or 1 -2 years states can either experience events and transition to post-event health states, or can transition through to the "initial" stable state. Patients starting in the initial stable state (or transitioning to this from the 0 – 1 or 1 -2 years post-ACS states) can experience events and transition to post-event health states, or can stay

in the initial stable state. In terms of events, patients can experience a NF ACS event (defined as an MI or an episode of unstable angina requiring hospitalisation), or a NF ischaemic stroke event, or an elective revascularisation (ie a revascularisation undertaken that is not undertaken as part of treatment for an event).

Post-event health states include a 0-1 year post-CV event state, a 1-2 year post-CV event state, and a >2 years post-event state (equivalent to a stable post-CV event state). The risk of a further event is substantially elevated in the first year post-ACS. The decision to split out the 1 -2 year post-CV event state from the >2 years state was based on evidence from the CV risk analysis conducted to inform the model, which showed that while the event rate 1 -2 years post-ACS was lower than in the first year, it was still higher than that observed for stable CHD (>2 years post-ACS event). Therefore, it was considered appropriate to model this as a separate state in order to more accurately reflect the risks over time. In any of the post-NF ACS or post-NF stroke event states, patients can transition to have another event of the same type or to have a different type of event (i.e. they can have an ACS following a stroke or a stroke following an ACS), or they can remain in the “stable” post-event states. Patients can transition from any state to death, either due to CV death or non-CV death.

The model assumes that transitions between health states occur between two cycles and patients are constant for that fixed time in a particular health state. However, in order to avoid over/under estimation of results, due to the fact that in reality patients will move continuously between different health states and just not at discrete time point, a half-cycle correction has been applied.

Transitions from post-NF ACS events to NF IS events are allowed, and vice versa. In theory, transitions from the NF-IS to NF-ACS health states could be problematic due to the fact that post-stroke health states are usually associated with lower utilities, leading to the paradoxical situation of an ACS event which occurs after a stroke event resulting in an increase in a patients quality of life. However, the blocking of such transitions was investigated and had little impact on the ICER calculations. As such, in order to ensure all events are accrued correctly and thereby all events are captured, no transitions are blocked in the model.

The instantaneous events in the cost-effectiveness model are defined in Table 55

Table 55: Event Definitions

Event	Definition
NF ACS	Composite of NF MI or NF UA with hospitalisation
Revascularisation	An elective revascularisation that did not occur as a result of an ACS event; revascularisations are considered elective if they did not occur within 30 days of the ACS event
NF IS	NF IS; excludes TIA
CV death	Death due to any CV event (inclusive of ischaemic and non-ischaemic CV events)
Non-CV death	Death due to any non-CV cause

ACS, acute coronary syndrome; CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; NF, non-fatal; TIA, transient ischaemic attack; UA, unstable angina

The NF-ACS health states are a composite of MI and UA with hospitalisation. It was considered appropriate to do this as these are often grouped together in definitions of clinical trial populations or endpoints, and treatment approaches are often similar. Weighted averages are used to derive the risks, costs and utilities for this health state.

Elective revascularisation was identified and included as a discrete health state based on feedback from clinical experts as it has a different pattern of risk, and of costs and utilities, to urgent revascularisation occurring as part of an episode of care for an ACS event. The model does not allow transition from NF-ACS and NF-IS events to elective revascularisation as the impact of these health states effectively dominate revascularisation in terms of their cost and quality of life effects. However, a proportion of patients in the stable post-ACS health state would experience elective revascularisations. To account for this cost, the model will include the cost of the elective revascularisation event in the stable post-ACS and post IS health state without moving the patients to the post-revascularisation health state.

The model simulates identical entry cohorts for comparator and alirocumab patients over a specified time horizon (lifetime horizon as base case), and compares the costs and outcomes between two groups. The cohort is defined based on a number of criteria, including starting age, proportion of males, prevalence of diabetes,

baseline LDL-C and CV risk category. The background therapy is identical between the arms (see discussion below in 5.2.6).

The model can simulate either a single cohort, or a mixed cohort. For example, the high CVD risk population is comprised of a mixed cohort of patients with a recent ACS event (0 – 1 years ago, 1 – 2 years ago), a history of previous ACS events (> 2 years ago) or other manifestations of CHD, a history of ischaemic stroke, or a history of PAD. The mixed cohort takes into account different risks and different baseline utilities for the different patient types included in the high CVD risk population.

5.2.3 Specification of baseline CV risk

Annual CV event probabilities are assigned to health states based on the characteristics of patients in that health state. For example, a CHD cohort will start the model in the initial (stable) health state with a baseline CV risk corresponding to the CHD subpopulation and to its age and LDL-C level. Based on this CV risk, a proportion of patients will experience an ACS and will move to the P-NF ACS (0-1 year) health state. Their CV risk will be updated with the CV risk of patients with an ACS (0-1 year) to reflect the higher CV risk in the first year after an ACS event.

A proportion of patients will experience an ischaemic stroke and move to the P-NF IS health state. Their CV risk will be updated with the CV risk of patients with a history of ischaemic stroke. The model takes into account the initial starting cohort in determining the probability of subsequent CV events in the model. For example, if the user models an ischaemic stroke cohort and some of those patients go on to have an ACS event, the probabilities of subsequent CV events post-ACS are derived from a prevalent sub-population that has experienced both an ACS event and an ischaemic stroke event. This is shown in more detail in Table 56.

To inform CV event probabilities we used real-world UK data from The Health Improvement Network [120]. Risk estimators such as QRISK2 are not validated for and are not suitable for high-risk groups such as those with existing CVD or with HeFH [23]. Therefore, we used real-world data specific to the patient populations included in the model, derived from THIN, a general practice electronic record healthcare database. THIN data has been used previously in CV research [121] and has the

advantages of being real-world UK data, and also of being a single coherent database, rather than using registries that focus on single event types. This is discussed further in 5.3.2.

Table 56: Mapping Prevalent Sub-Populations Based on Health States and Initial Sub-Populations

		Living health states									
		Initial (0–1 year post-event)	Initial (1–2 years post-event)	Initial (stable)	Stable post-revascularisation	P-NF ACS (0–1 year)	P-NF ACS (1–2 years)	Stable CHD	P-NF IS (0–1 year)	P-NF IS (1–2 years)	Stable P-IS
Possible Initial Starting Cohorts	HeFH (primary prevention)	N/A	N/A	HeFH (primary prevention)	Patients with elective revascularisation who had no prior ACS	ACS (0-1 years)	ACS (1-2 years)	ACS (>2 years, i.e. old MI)	IS	IS	IS
	HeFH (secondary prevention)	N/A	N/A	HeFH (secondary prevention)	CHD due to elective revascularisation	ACS (0–1 years)	ACS (1–2 years)	ACS (>2 years, i.e. old MI)	IS	IS	IS
	ACS 0–1 years	ACS 0–1 years	ACS (1–2 years)	ACS (>2 years, i.e. old MI)	Patients with elective revascularisation who had prior ACS	ACS (0–1 years)	ACS (1–2 years)	ACS (>2 years, i.e. old MI)	IS and old MI	IS and old MI	IS and old MI
	ACS 1–2 years	N/A	ACS 1–2 years	ACS (>2 years, i.e. old MI)	Patients with elective revascularisation who had prior ACS	ACS (0–1 years)	ACS (1–2 years)	ACS (>2 years, i.e. old MI)	IS and old MI	IS and old MI	IS and old MI
	Ischaemic Stroke	N/A	N/A	IS	CHD due to elective revascularisation	IS and any ACS (0–1 years)	IS and any ACS (1–2 years)	IS and old MI	IS	IS	IS
	Other CHD	N/A	N/A	Other CHD	CHD due to elective revascularisation	ACS (0–1 years)	ACS (1–2 years)	ACS (>2 years, i.e. old MI)	IS	IS	IS
	Peripheral Arterial	N/A	N/A	PAD	Patients with elective revascularisation who	ACS (0–1	ACS (1–2	ACS (>2 years,	IS	IS	IS

		Living health states									
		Initial (0–1 year post-event)	Initial (1–2 years post-event)	Initial (stable)	Stable post-revascularisation	P-NF ACS (0–1 year)	P-NF ACS (1–2 years)	Stable CHD	P-NF IS (0–1 year)	P-NF IS (1–2 years)	Stable P-IS
	Disease				had no prior ACS	years)	years)	i.e. old MI)			

ACS, acute coronary syndrome; CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolaemia; IS, ischaemic stroke; MI, myocardial infarction; N/A, not available; PAD, peripheral arterial disease; P-IS, post-ischaemic stroke; P-NF, post-non-fatal

5.2.3.1 CV risk adjustment

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

For age, an age adjustment of 3% each year is used as the base case for non-fatal CV events and 5% for CV death [34].

For gender the only difference is in non-CV death rates. Although gender is known to have an influence on CV risk, the split (percentage of males) by CV risk category is taken from UK THIN data and this is assumed to be representative of the UK population of a whole, therefore the results from the cohort should be generalizable without any adjustment of CV risk by gender (unless the decision problem were to be considered separately by gender, which we do not consider to be appropriate).

CV event rates were generated for patients with and without diabetes, however we apply the prevalence of diabetes by CV risk category from the UK THIN data and therefore the results generated are generalizable to the total population.

In order to explore the cost-effectiveness of alirocumab by severity of hypercholesterolaemia, as specified in the Scope, it is important to take account of the influence of baseline LDL-C on CV risk. In order to do this, the model takes account of the average LDL-C value found for the different CV risk categories in the THIN data. If a higher LDL-C value is applied for the cohort, the model adjusts the CV risk upwards. For example, if a cohort of patients with an average LDL-C of 2 mmol/L has an annual CV risk of x%, if we consider a cohort of patients with an average LDL-C of 3 mmol/L, a higher CV risk (eg $x + 2\%$) is applied, based on what is known about the relationship between LDL-C and CV risk. There are different options in the model for performing this risk adjustment.

The CTT meta-analysis is probably the best known source for estimating the relationship between LDL-C and CV risk. This analysis estimates the rate ratio (RR) per unit reduction in LDL-C (denoted as α) for various CV events. The relative risk reduction (RRR) per unit reduction in LDL-C is thus $(1 - \alpha)$. The CTT papers report a

log-linear relationship. Based on this information, the relationship between event probability and LDL-C change can be represented as follows:

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

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

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

Where:

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

These equations are used to adjust the CV risk based on the baseline LDL-C – i.e. if the THIN cohort overall had a baseline LDL-C of L_0, and an event rate of E_{01}, when considering a cohort with a baseline LDL-C of L_i, Equation 2 is used to estimate the event rate E_1. The CTT analysis estimates the relationship between LDL-C reduction and CV event reduction. However, the 2012 CTT publication also includes a Cox model that estimates the relationship between *baseline* LDL-C and *baseline* CV risk – this is applied in a scenario analysis and the two provide very similar results [17] .

Average LDL-C levels by different "starting" thresholds

The model allows the user to set a minimum starting threshold for LDL-C (i.e. models patients with an LDL of at least x or above). The model then applies the average LDL-C value for patients with an LDL-C above this cut-off value, as found in the THIN data.

The average values found corresponding to different LDL-C cut-offs are shown in Table 57. For most populations these are derived from THIN data for patients on statin-based treatment. To model patients with complete statin intolerance, and not receiving any statins, data from the ALTERNATIVE trial were used. Due to the washout period the mean LDL-C at baseline (191.3 mg/dL [~4.95 mmol/L])

corresponds to LDL-C levels of non-treated patients. To estimate LDL-C for statin intolerant patients receiving ezetimibe monotherapy, we applied the mean LDL-C at Week 4 in the ezetimibe arm. To model a direct comparison with ezetimibe, the mean LDL-C values at baseline in ALTERNATIVE (with washout) can be used.

Table 57 Average LDL-C values by LDL-C cut-off

Cut-off threshold	≥1.81 mmol/L	≥2.59 mmol/L	≥3.36 mmol/L	≥4.14 mmol/L
HeFH (primary prevention)	4.50	4.82	5.28	5.59
HeFH (secondary prevention)	4.40	4.56	4.80	5.23
ACS (0-12 months)	2.60	3.31	4.11	4.83
ACS (13-24 months)	2.62	3.31	4.07	4.93
Ischaemic Stroke	2.65	3.27	4.00	4.67
Other CHD	2.67	3.30	4.02	4.73
PAD	2.79	3.36	4.03	4.73
Polyvascular	2.66	3.31	4.05	4.78
Statin intolerant patients on Ezetimibe monotherapy	3.74	4.00	4.55	5.07

ACS, acute coronary syndrome; CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral arterial disease

5.2.4 Non-CV death

The probabilities of non-CV death for various age ranges and gender are based on UK Life Tables [122] [123]. By default, the model analyses a cohort over its remaining lifetime, which is assumed to be to a maximum of 99 years of age.

5.2.5 Cohort baseline characteristics

The model allows specification of key baseline characteristics that have an impact on CV risk and other parameters: age, gender, prevalence of diabetes, starting LDL-C threshold and average LDL-C.

In addition, when modelling the high risk CVD group, because this consists of different patient types (patients with a history of MI, patients with a history of stroke),

it is modelled as a mixed cohort and it is therefore necessary to specify the proportion of different patient histories that make up the mixed cohort. It is important to note that the relative clinical effect of alirocumab is homogeneous, and is independent of the baseline patient characteristics.

In the base case, we use the prevalence of diabetes and proportion of males by CV risk category from the THIN data. The average age in THIN was higher than in the ODYSSEY trials, and potentially in clinical practice alirocumab may be initiated in patients who are younger than average. The average age in THIN was approximately 70 years, while in ODYSSEY it was approximately 60 years; in the interests of simplicity, a starting age of 65 years was selected and the impact of this investigated in sensitivity analyses. For HeFH patients, a starting age of 50 years was selected for primary prevention, which corresponds both to average ages in ODYSSEY trials and the median age of FH patients in the UK National FH audit [30] and 60 years for secondary prevention. The base case assumptions and justifications are tabulated below (Table 58).

Table 58: Baseline cohort assumptions

Population	HeFH (primary prevention)	HeFH (secondary prevention)	High-risk CVD	Recurrent events/ polyvascular disease
Age (years) (justification)	50 (in line with ODYSSEY trial data and with UK National FH audit)	60 (assumed older than primary prevention but younger than secondary prevention as a whole)	65 (UK THIN data shows an average age of ~70 years; ODYSSEY had an average age of 60 years – see discussion above)	65 (see discussion of high-risk CVD)
% males (justification)	50% (in line with ODYSSEY and UK National FH audit – no gender difference)		60% (based on UK THIN data)	60% (based on UK THIN data)
% with diabetes (justification)	7% (observed in UK THIN data), in line with estimates of prevalence of diabetes in FH patients		23% (based on prevalence observed in UK THIN data)	30% (based on prevalence observed in UK THIN data)
Baseline LDL-C (minimum)	2.59 mmol/L (represents patients above currently recommended targets despite current therapy)		3.36 mmol/L (represents patients far from currently recommended targets)	2.59 mmol/L (represents patients above currently recommended targets despite current therapy)

CVD, cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol

The split of different patient types (by CV event history) included in the high risk CVD cohort is shown in Table 59. This is based on the split of different patient types observed in the THIN database. Patients with an ACS in the last 2 years have been categorised separately to patients with other CHD (ACS >2 years ago or other evidence of CHD) due to the dynamic evolution of risk over time that the model accounts for.

Table 59: High risk CVD cohort proportions by patient types

ACS ≤12 months prior to index	3.28%
ACS 12–24 months prior to index	2.83%
Ischaemic Stroke	11.05%
Other CHD	68.55%
PAD	14.29%

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; IS, ischaemic stroke; PAD, peripheral arterial disease

5.2.6 Assumptions on Treatment and Dosing

In the base case we model alirocumab treatment as it was applied in the majority of ODYSSEY trials i.e. initiation with alirocumab 75 mg Q2W with an up-titration to 150 mg Q2W in patients with insufficient LDL-C lowering (i.e. not at target at Week 8 as per in clinical trials). The proportion of patients requiring up-titration is based on the initial LDL-C level and assuming a normal distribution for treatment effect at Week 12 to estimate the proportion of patients not reaching the specific target. In UK practice we assume up-titrations will be based on an LDL-C measurement by Week 8 which will occur as part of routine monitoring and follow-up.

Once an up-titration option is selected, the treatment effect and cost of alirocumab for the cohort are calculated as a weighted average of the 75 mg and 150 mg alirocumab dosing based on the estimated proportion of patients who would be up-titrated. Since up-titration decisions are made at Week 8, the weighting treatment effect and weighting costs are used starting in the first cycle.

The model also allows consideration of initiation and treatment continuation with alirocumab 75 mg SC Q2W and of alirocumab 150 mg SC Q2W. In addition, up-titration can be modelled with a user-specific input.

The base case assumption is that treatment duration is lifetime, in line with the treatment intention of LDL-C lowering therapy. In ODYSSEY, there are very high continuation rates in patients up until the end of follow-up (78 weeks). The model allows the evaluation of different alirocumab treatment durations (1 year, 2 years etc.). It is assumed that at the end of the treatment duration, both the alirocumab and comparator cohorts no longer receive the benefits of treatment and instead have the baseline LDL-C and baseline CV risk associated with only background therapy.

5.2.6.1 Discontinuation and Compliance

Treatment is assumed to be given indefinitely without interruption within the treatment duration defined in the model. The model assumes 100% compliance and applies costs and efficacy (on treatment analyses) in line with this. In ODYSSEY, compliance rates were high (~98%). It is assumed that in clinical practice compliance rates will be slightly lower but still high, as alirocumab will only be prescribed in high risk, high unmet need patients, and will be supported by a homecare delivery service and patient support programme. Existing LMTs are all oral daily therapies, and are not suitable analogues for considering likely adherence with alirocumab, which is a fortnightly injectable monoclonal antibody that is likely to be only prescribed in specific high risk patients.

Sensitivity analyses assume that a certain percentage (3% and 8%) of patients discontinue alirocumab and comparator treatment each year. When patients discontinue alirocumab or comparator treatment, it is assumed that they no longer receive the benefits of treatment nor incur the costs of treatment. After patients discontinue alirocumab or comparator treatment, it is assumed that they return to the baseline CV risk associated with that cohort. It is worth noting that patients who discontinue alirocumab or comparator treatment are still on background therapy. Including discontinuation in the model lowers the efficacy and therefore increases the LDL-C of the alirocumab and comparator cohorts as well as lowering the cost of treatment with alirocumab and comparator (Section 5.8)

5.2.7 Efficacy

5.2.7.1 LDL-C lowering efficacy

Pooled estimates from the ODYSSEY trials (for each dose) were used to estimate the efficacy of alirocumab on LDL-C lowering by patient population and by dosing strategy. The efficacy of the alirocumab 75 mg strategy is estimated using the percent change in calculated LDL-C from baseline to week 12 (before up-titration). The efficacy of the alirocumab 150 mg strategy is estimated using the percent change in calculated LDL-C from baseline to week 24 using pooling with 150mg Q2W trials.

Table 60 summarises the mean percent change from the baseline in LDL-C applied in the model based on the pooled analyses.

Results from mITT analyses (on-treatment analyses) were used with assumption of 100% adherence to treatment. Sensitity analyses were performed assuming different continuation rates.

Table 60 Mean % change in LDL-C in pooled analyses of Phase III placebo-controlled studies

			Percent Reduction in LDL-C		Standard Error	
			As Monotherapy	As Add-On To Statin	As Monotherapy	As Add-On To Statin
Comparison vs Placebo [1]	**FH**	Alirocumab (75 mg)	49.3%	49.3%	1.9%	1.9%
		Alirocumab (150 mg)	59.6%	59.6%	2.3%	2.3%
	High CV Risk	Alirocumab (75 mg)	49.3%	49.3%	1.6%	3.2%
		Alirocumab (150 mg)	62.5%	62.5%	1.2%	1.2%
Comparison vs Ezetimibe [2]	**FH**	Alirocumab (75 mg)	51.2%	51.0%	1.7%	1.1%
		Alirocumab (150 mg)	59.6%	59.6%	2.3%	2.3%
	High CV Risk	Alirocumab (75 mg)	51.2%	51.0%	1.7%	1.1%
		Alirocumab (150 mg)	62.5%	62.5%	1.2%	1.2%
Vs. Placebo	**FH**	Alirocumab Up-	56.5%	56.5%	1.9%	1.9%
	High CV Risk		58.5%	58.5%	1.6%	3.2%

			Percent Reduction in LDL-C		Standard Error	
			As Monotherapy	As Add-On To Statin	As Monotherapy	As Add-On To Statin
		Titration				
Ezetimibe (10 mg)			18.0%	23.9%	1.8%	1.4%

[1] Difference vs placebo; [2] Reduction relative to baseline

The mean percent change in LDL-C is multiplied by the initial LDL-C level to get the absolute reduction in LDL-C obtained with the treatment.

5.2.7.2 Modelling the relationship between LDL-C lowering and CV risk reduction

The effect of alirocumab on LDL-C was translated into a reduction in CV event risk based on the Navarese meta-analysis [39]. In the absence of final data from the ODYSSEY Outcomes trial (CVOT), this was considered the best available data-source to inform the relationship between LDL-C reduction with alirocumab and CV event reduction as it is a meta-analysis of 24 randomised controlled trials of PCSK9 inhibitors (see Section 4.9 [39]). When the model compares alirocumab with ezetimibe, data from the IMPROVE-IT trial is used. When the model compares alirocumab with no active comparator (placebo), the question of the most appropriate way of informing CV event reduction for the comparator arm is essentially irrelevant, as no reduction in LDL-C and thus no reduction in CV events is expected. This is discussed further below in Section 5.3.

5.2.8 Intervention technology and comparators

Ezetimibe is implemented in the model as per its marketing authorisation and alirocumab as per its marketing authorisation.

Alirocumab is licensed for adults with primary hypercholesterolaemia in combination with a statin or a statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated.

In the base case we model alirocumab as an adjunctive therapy to existing maximally tolerated current therapy. For those patients able to tolerate statins, this can be either maximal tolerated dose of statins or maximal tolerated dose of statins plus ezetimibe.

NICE recommends ezetimibe and some patients, particularly FH patients, will already be receiving ezetimibe in combination with maximally tolerated dose of statins. This reflects usage in ODYSSEY where ~50% of HeFH patients were receiving statins plus ezetimibe as background therapy. Therefore, for the base case for HeFH, we model alirocumab + statins + ezetimibe versus statins + ezetimibe.

However, ezetimibe usage is not universal, with wide variation in regional formulary access and in uptake [124]. IMS Sales data indicates a reduction in units of ezetimibe prescribed in the UK from approximately 2.9M in 2011 to 2.46M in 2014 [77], although sales rose in FH patients. The Health and Social Care Information Centre prescribing comparator indicated that for the quarter April to June 2014 there was a 5.9 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.91% to 5.38% of the total population (NICE 2015, Key therapeutic topics: Lipid-modifying drugs). Because ezetimibe usage in the NHS is highly varied we also model alirocumab as an add-on therapy to maximal tolerated dose statins (alone, not in combination with ezetimibe). Based on the trends observed in UK usage of ezetimibe, we model alirocumab + statins versus statins as the base case for high CV risk patients.

We also consider alirocumab in high CV risk patients who are completely intolerant to statins. We assume that in the main such patients would be receiving ezetimibe and therefore in this situation we model alirocumab as an add-on to ezetimibe therapy.

5.3 Clinical parameters and variables

5.3.1 CV Outcomes

The ODYSSEY Outcomes trial (CVOT) is ongoing at this time and is not due to report until 2018 (Section 4.14). Therefore, there is a need to rely on preliminary or surrogate data to model the benefit of alirocumab on CV outcomes.

As discussed in Section 3 there is strong evidence that reducing LDL cholesterol levels reduces cardiovascular events and therefore we model a CV benefit, as has been done for previous LMTs considered by NICE prior to results from CV outcomes trials [24] .

There are several different data sources to inform modelling the potential CV benefit of alirocumab. There have been three published meta-analyses of PCSK9 inhibitors. Of these, the meta-analysis by [39] specifically focussed on estimating the effect of PCSK9 inhibitors, as a class, on CV outcomes (see 4.9.1.2).

The meta-analysis was based on 24 RCTs comprising 10,159 patients and found a significant reduction in MI (OR 0.49 [CI, 0.26 to 0.93]) and in all-cause mortality and a trend for lower CV mortality (OR 0.50 [CI, 0.23 to 1.10]) relative to control. Very similar results were found in the analyses that adjusted for duration of follow-up: for MI the OR and CI was identical, and for CV mortality the OR from the adjusted analysis was 0.49 [CI 0.23 – 1.07]. Based on these results the risk reduction (confidence interval) per 1 mmol/L reduction in LDL-C for CV mortality was estimated as 0.64 (0.40-1.04) and for MI as 0.64 (0.43-0.96). The advantage of this study is that it is an independent peer-reviewed meta-analysis based on PCSK9 outcomes data. The limitations are that the analysis was done using study-level data rather than patient-level data, the data were derived from a small number of events, and the duration of follow-up in the studies was relatively short.

The most well-known data source to estimate the relationship between LDL-C reduction and reduction in CV events is that derived from the CTT database [15 16-18]. These results are based on a meta-analysis of data from 22 trials of statin therapy versus control (n=134 537) and five trials of more-intensive versus less-intensive statin therapy (n=39 612). This provides estimates of the risk reduction per 1 mmol/L reduction in LDL cholesterol for major coronary events and vascular death. The strength of the CTT data is its large sample size, resulting in estimates with relatively small confidence intervals. The most obvious limitation of these data is that they are derived exclusively from trials of statin therapy. Further, the population in these trials differed from those of alirocumab, as alirocumab was primarily studied as an adjunct in patients who had hypercholesterolaemia despite treatment with maximal tolerated dose statin therapy.

Although as with any data source there are limitations of the Navarese meta-analysis we use the risk reduction estimates derived from this analysis in the basecase of our cost-effectiveness model for two main reasons. We believe that it is appropriate to use estimates derived from PCSK9 inhibitor studies in the basecase rather than estimates derived from statin studies. Further we believe that the patient populations included in the Navarese et al. meta-analysis more closely reflect the population (those who have hypercholesterolaemia despite maximum tolerated statin treatment) that will be treated with alirocumab. We present results using estimates derived from the CTT relationship in the sensitivity analysis. We also present results using outcomes data from the LONG-TERM trial of alirocumab, and from the pooled placebo-controlled phase III trials, in sensitivity analyses. In scenario analyses when ezetimibe is considered as a comparator, we use data from the recently reported IMPROVE-IT trial for ezetimibe [14] .

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

- RR per 1 mmol/l reduction in LDL-C = EXP(LN(HR)/absolute reduction).

A difference of 1.6 mmol/L in LDL-C was calculated from the trials included in the Navarese meta-analysis. The meta-analysis reports HR values for different CV events adjusted by follow-up. The rate ratios for individual events are reported in Table 61.

Table 61: Results based on Navarese et al – RR per 1 mmol/L reduction in LDL-C for different event types

Event type	Mean value (95% CI)
Non-fatal MI	RR per 1 mmol/L reduction in LDL-C = EXP(LN(0.49)/1.6) = **0.64**
Coronary revascularisation	No results presented – assumed to be the same as other non-fatal CV events
IS	No results presented in IS – assumed to be the same as other non-fatal CV events
Vascular death	RR per 1 mmol/L reduction in LDL-C = EXP(LN(0.49)/1.6) = **0.64**

For IMPROVE-IT: A HR of 0.928 was reported on major vascular events which resulted in a RR per 1 mmol/l reduction in LDL-C = EXP(LN(0.928)/0.334)=0.80 [14].

For the LONG-TERM study: HR per 1 mmol/L reduction in LDL-C = EXP(LN(0.52)/1.83)=0.70 [38]. The HR is provided for the composite CV events (CHD death, Non-fatal MI, Fatal and non-fatal IS, Unstable Angina requiring hospitalisation). The same HR per 1 mmol/L reduction is applied to all CV events in the model.

For the pooled Phase III vs placebo: RR per 1 mmol/L reduction in LDL-C = EXP(LN(0.65)/1.82)=0.79. The same HR per 1 mmol/L reduction is applied to all CV events in the model

For the CTT meta-analysis, values for risk reduction per 1 mmol reduction in LDL-C are reported per event type (Table 62).

Table 62: CTT analysis – RR per 1 mmol/L reduction in LDL-C for different event types

Event type	Mean value (95% CI)
Non-fatal MI	0.74 (0.71–0.77)
Coronary revascularisation	0.76 (0.73–0.78)
IS	0.79 (0.74–0.85)
Vascular death	0.88 (0.84–0.91)

CI, confidence interval; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction

For the base case analysis using Navarese et al 2015 the rate ratio per 1 mmol/l reduction ($\propto_i$) is therefore set to 0.64 for all CV events to adjust the CV risk during alirocumab treatment.

5.3.2 Transition Probabilities

Event probabilities are a key component of the model. Event probabilities vary based on each subpopulation, baseline LDL-C, age, and health state. They are based on descriptive Kaplan-Meier analyses from the THIN database in the UK which are used to calculate CV risk in the model [120].

5.3.2.1 CV risk analysis in THIN database

An observational retrospective cohort analysis was conducted. The objective was to describe the one year cardiovascular (CV) risk associated with a cross Sectional cohort of people in the THIN database with established CVD, diabetes, familial hypercholesterolaemia (HeFH), or chronic kidney disease (CKD).

The index date for the analysis was chosen as 1st January 2010. The study period comprised a baseline period, an index date and a follow-up period. Each patient's baseline period was a minimum of 24 months immediately prior to the index date. Patients were followed forward for 12 months, until a subsequent event or death occurred, the patient transferred out of the database, or until 31st December 2010, whichever was the soonest.

Patients were classified into different CV risk categories according to their CV history, and were followed up for the occurrence of major adverse cardiovascular events including MI, Unstable Angina, Coronary Revascularisation, Ischaemic Stroke, and CV death. All the coding for the different CVD risk categories and events was undertaken by a team which included a clinician, specialist cardiologist, and epidemiologist. The search strategy for READ codes was undertaken by the clinician and the extracted codes reviewed by the whole team.

Full details of the study methodology are provided in Appendix 11, with codes in Appendix 12.

THIN is a representative, large, well-validated electronic record database, however one of the limitations is that primary care recording does inevitably miss some events. A BMJ publication evaluated this using the CALIBER linked records system and found that primary care recording missed 25% of all recorded non-fatal MIs (that were recorded in any source) [125]. Therefore, an adjustment was applied to the raw data from THIN for non-fatal events in line with the data reported in Herrett et al.

5.3.2.2 – HeFH data

A literature review was undertaken on the risk of cardiovascular events in HeFH. Keywords for HeFH and cardiovascular risk, together with handsearching of

reference lists, were undertaken. This identified seven key publications. However, all of them have some limitations from an economic modelling perspective. Two publications were from the UK, based on the Simon Broome Register. These report data on excess mortality in HeFH in the pre and post-statin era, but are relatively old and focus on mortality rather than CHD incidence [126] [26]. A report from the Copenhagen General Population study [27] describes a cohort of ~500 FH patients in Denmark and reports the odds ratio for CHD incidence in FH versus non-FH patients. The odds ratio for coronary artery disease off cholesterol-lowering medication was 13.2 (10.0 –17.4) in definite/probable FH compared with non-FH subjects; the corresponding odds ratio for FH subjects on cholesterol-lowering medication was 10.3 (7.8 –13.8) [27]. Mundal [28] describes the increased mortality risk in HeFH as standardised mortality ratios relative to the general population based on a registry of over 4000 patients in Norway, but does not report CHD incidence [28]. A publication from the Netherlands describes the risk of cardiovascular events and cardiovascular death in patients on statins [63] Two other publications identified are also based in the Netherlands [127, 128] – one describes the impact of statins in reducing the risk of CHD in FH patients and a second describes the increased risk in severe versus non-severe HeFH, but neither report data in a format conducive to economic modelling.

Initial analyses identifying patients according to the specific READ codes in THIN for HeFH (“Familial Hypercholesterolaemia” and “Familial Hypercholesterolaemia according to Simon Broome criteria”), identified puzzling characteristics, with LDL-C levels that were not higher than the other populations, and a prevalence rate of diabetes of over 70%, which is clinically implausible given FH patients are known to have a lower rate of diabetes compared to the general population. This raised questions over the quality of coding using these READ codes. Therefore, further research was undertaken using an algorithm to identify patients according to Dutch Lipid criteria (described in the THIN study methods in Appendix 11). This algorithm has its limitations as clearly it is not possible to identify patients as being definitively HeFH patients, however it was considered as a rational approach in the absence of better data.

Identification of primary prevention HeFH patients through Dutch Lipid criteria identified data that had reasonably good face validity, with low percentage rates of diabetes, and a younger mean age than other patient groups.

For secondary prevention HeFH patients, the patient characteristics of the cohort identified through Dutch Lipid Criteria still raises some questions. The rate of diabetes was higher than expected (26%) and the mean age relatively high (66). Given the known low prevalence of diabetes in HeFH patients, this raises further questions. Additional analyses were therefore run using data from the Morschladt 2004 publication which provided data on rates of CV events and CV death in secondary prevention FH patients. The advantage of this study is that it included patients with a confirmed diagnosis of HeFH. The limitations of this study are its age and the relatively small sample size (131 secondary prevention patients, with 1105 years of follow-up). The study quotes the rate of all CV events (143 per 1000 patient years) and the rate of fatal CV events (12 per 1000 patient years), and also the distribution by type of CV events. PAD manifestations were included as events – these were subtracted from the rate of all CV events on the grounds that our model does not include PAD. The mean age of the secondary prevention cohort in Morschladt et al was 54. The mean LDL-C post-statin treatment was estimated as 4.51 (the paper reported the mean LDL-C for the secondary prevention group was 7.27 mmol/L, and that 1 year of statin treatment reduced LDL-C levels by 38%).

The analysis based on Morschladt was used in the base case as this is definitively based on HeFH patients. We present results from THIN in scenario analyses and results show good agreement.

5.3.2.3 Variance in transition probabilities over time

As described in Section 5.2.3 and 5.2.4, transition probabilities vary over time in the model due to the influence of age. Non-CV death probabilities increase in accordance with UK Life Tables. Probability of CV events increase with age according to published data [34].

5.3.2.4 Increased risk with multiple events

Recurrent events are associated with higher risk of future events [35] [31] [32]. Consistent with this, an increase in event probabilities is modelled as further events are experienced in the model. This assumption in the model is informed by a publication by Smolina et al. This study of over 387,000 MIs in England found that the risk of death in survivors of recurrent AMI 1.5 times higher than that for survivors of first MI. Thus, the model increases the baseline probability of CV death in all post-ACS health states for the ACS sub-populations (ACS 0-1 year, ACS 1-2 year, CHD, polyvascular and HeFH secondary prevention sub-populations) by 1.5 times. This increase was also applied to the probability of ACS in all post-ACS health states for the ACS sub-populations. This same logic was applied to the probability of CV death and ischaemic stroke in the post-IS health states for the subpopulation with prior history of ischaemic stroke.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

In all Phase III studies except OPTIONS I, OPTIONS II and ALTERNATIVE, quality of life was assessed using EQ-5D, a standardised and generic instrument for measuring the health status and health related quality of life for clinical and economic assessment [101].

The EQ-5D questionnaire was completed by the patient on site and data reported onto the e-CRF by site staff. The analysis of quality of life data was performed on the mITT population. Baseline is defined as the Visit 3 (Week 0) evaluation and only patients with baseline and a post baseline assessment were considered in the analysis. The 5 dimensional 3-level system was converted into a single index utility score, which was described by visit with the mean and the SD for each treatment group. The change from baseline to following visits was analysed using the same MMRM model as for the primary endpoint, with treatment group and randomisation strata as fixed effects, and baseline value as covariate.

Hypercholesterolaemia is an asymptomatic condition, therefore, no improvements in the patient's perceived health status or QOL were anticipated with treatment. This was substantiated by the EQ-5D data captured which demonstrated little to no change in mean EQ-5D utility scores between baseline and following visit analysis time points in any of the trials.

Note: the only difference was in COMBO I where the LS mean difference at Weeks 12 (-0.062) and 52 (-0.060) were significant at the 5% level. The mean difference at Week 24 was, however, non-significant, the p-values were not adjusted for multiplicity and the LS differences were well below a clinically relevant threshold of 0.1 in utility scores.

Baseline EQ-5D was calculated via pooled analysis of the FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM clinical trials. Results were calculated for each patient subpopulation (ACS 0-1 year; ACS 1-2 years; CHD; ischaemic stroke; PAD, HeFH [all]) and stratified by patients classified within the respective patient

subpopulation only versus patients classified within the respective patient subpopulation that had a history of other CV events.

Table 63 Baseline utilities as estimated by EQ-5D by patient subpopulation* pooled analysis FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM

Patient subpopulation	Overall			No other CV event/condition		At least one other CV event/condition	
	n	Mean age (SD)	Mean EQ-5D (SD)	n	Mean EQ-5D (SD)	n	Mean EQ-5D (SD)
ACS 0–1 year	198	56.2 (10.2)	0.844 (0.197)	142	0.848 (0.201)	56	0.832 (0.189)
ACS 1–2 years	192	58.7 (9.1)	0.858 (0.187)	120	0.874 (0.185)	72	0.832 (0.190)
CHD	2731	61.4 (9.7)	0.851 (0.194)	813	0.860 (0.191)	1918	0.847 (0.195)
IS	344	63.8 (9.5)	0.797 (0.228)	164	0.804 (0.212)	180	0.791 (0.242)
PAD	188	62.8 (9.1)	0.771 (0.233)	98	0.775 (0.253)	90	0.767 (0.211)
HeFH (all)**	1254	52.7 (12.3)	0.905 (0.149)	682	0.930 (0.130)	572	0.875 (0.164)

ACS, acute coronary syndrome; CHD, coronary heart disease; CV, cardiovascular; EQ-5D, EuroQol-five dimensions; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; IS, ischaemic stroke; PAD, peripheral arterial disease; SD, standard deviation
*Includes all randomised patients regardless of treatment assignment; data include prevalent patient groups, i.e. non-mutually exclusive.
**Refers to both primary and secondary prevention.

Due to the clinical trials design, where there was no collection of EQ-5D data at the time of CV event, as well as the small number of CV events captured, an assessment of utility associated with CV outcomes could not be estimated from the ODYSSEY program. Estimates from published literature (see below) are therefore being used to inform the cost-effectiveness model

5.4.2 Mapping

No mapping was conducted.

5.4.3 Health-related quality-of-life studies

Identification of Studies

A systematic literature review was undertaken to retrieve relevant health state utility values (HSUVs). The objective of this study was to identify and summarize studies that have reported HSUVs for CV events associated with hypercholesterolaemia, or

for standardised health states describing CV events associated with hypercholesterolaemia.

The systematic literature review was designed to identify studies reporting HSUVs of CV events associated with hypercholesterolaemia, including: non-fatal MI, unstable angina, revascularisations, ischaemic stroke, non-specific stroke (including transient ischaemic attack (TIA) if part of the non-specific stroke population), peripheral vascular disease, and heart failure. Studies reporting HSUVs that were either directly elicited from the general population (using the time trade off (TTO) or standard gamble (SG) methods) or indirectly elicited from individuals with a CV event (using the EuroQol-5 dimensions (EQ-5D), Short-form (SF)-6D, SF-12, SF-36 or health utility index 3 (HUI3)) were eligible for inclusion.

Full details of the methodology and results are provided in Appendix 13.

5.4.4 Adverse reactions

As noted (Section 4.12) the percentages of patients who experienced at least 1 TEAE, at least 1 treatment-emergent SAE and any TEAEs leading to permanent treatment discontinuation were similar between the alirocumab and control groups, including placebo. Signals were only identified for local injection site reactions and general allergic reactions. Most injection site reactions were transient and of mild intensity. As such it was assumed there was no impact on HRQoL due to adverse events associated with usage of the technology. This is supported by EQ-5D data from trials.

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

5.4.5.1 Impact of disease on patients' quality of life

Hypercholesterolaemia itself is an asymptomatic condition. The impact on patients quality of life is rather due to the impact of experiencing CV events. The impact of CV events on patient quality of life comprises an acute impact and a chronic impact. Acute symptoms of an ACS include central chest pain, which may spread to the arms, neck or jaw, feeling sick or sweat or short of breath. Patients suffering an ST-elevation MI (STEMI) are recommended to receive percutaneous coronary intervention. Patients suffering a non-ST-segment elevation MI (STEMI) are

recommended to have early coronary angiography and revascularisation (NSTEMI). Treatment and hospitalisation for treatment have an acute impact on quality of life. However, this is likely to be a short-term decrement and a patient's HRQL is likely to improve then over the course of the year following the event, and over following years. Longer-term impacts can include reduced fitness/ capacity to maintain activities of daily living, and anxiety about future events. Repeated events can have a cumulative impact on patients overall health and quality of life. The impact of stroke on quality of life is highly dependent on the severity of the stroke. Stroke can be severely debilitating and result in long term impact on quality of life and ability to perform usual activities.

5.4.5.2 – Utility data in model

HRQL is not constant over time but varies according to CV events experienced in the model. We model utility in two main ways, firstly applying an age-adjusted baseline with multiplicative disutilities based on Health Survey for England data, and secondly applying data from ODYSSEY for baseline, with multiplicative disutilities for CV events.

5.4.5.3 – HSE data

Acute and chronic disutilities are applied to reflect the greater disutility immediately after an event (i.e. during the first year after the CV event) and the stabilisation afterward (>1 year after the CV event). Utilities are applied in a multiplicative manner. This is in line with the Technical Support Document (TSD) produced by NICE's Decision Support Unit (DSU) which states that when HSUVs from cohorts with combined health conditions are not available, based on the current evidence, the multiplicative method should be used to combine the data derived from subgroups with the single health conditions. The multiplier used to combine these data should be estimated using age-adjusted data, rather than an assumption of perfect health, to increase accuracy in the estimated values [129]

To follow this methodology we utilised a study by Ara & Brazier [130]. We selected this study as, based on the SLR, it was the most complete and coherent source of utility values for all the health states in the model. This study used data from the 2003 and 2006 Health Survey for England (HSE), which included questions about history of

CVD and where a random sample were asked to complete the EQ-5D questionnaire [42 43]. Preference-based HSUVs for a range of CVD health states were estimated using the weights obtained using time trade off valuations from the UK general public. The study included a regression by age for both patients without a history of a CV event, and for the general population, which allowed estimation of multipliers based on age-adjusted data, in line with DSU guidance.

Primary prevention

We only model alirocumab in primary prevention in HeFH patients. For primary prevention patients, for baseline, we have applied the regression equation for individuals reporting no history of CVD derived from the analysis of Health Survey for England (HSE) data [130]:

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

We then calculated multipliers for the various disutilities associated with CV events. These are then applied in the model to the age-adjusted baseline. Acute disutilities applied to the 0 -1 years post-event state are based on the values in Ara et al for patients with an event <12 months ago. Chronic disutilities are based on the values in Ara et al for patients with an event >12 months ago.

For example, in the HSE data the utility for patients with angina less than 12 months ago and a history of just angina is 0.615. This average utility corresponds to an average age of 68.8 years old. A population of people without a history of CVD who are 68.8 years and 50% male would have a baseline utility of 0.804 based on the above equation. Assuming that the average patient aged 68.8 years old with no CV history would have had a utility of 0.807, the utility multiplier due to angina is 0.615/0.804 = 0.765. The HSE utility data and the multipliers calculated for different events are shown in Table 64. The multipliers as they are applied in the model corresponding to different health states are shown in Table 65. In the model, elective revascularisation is assumed to not incur any disutility.

Table 64 Age-Adjusted Multipliers calculated from Ara et al

	Baseline utility in HSE data	Mean Age	Calculated multiplier*
Angina <12 months, history of just angina**	0.615	68.8	0.765
No event <12 months, history of just angina	0.775	68.0	0.960
Heart attack <12 months, history of just heart attack***	0.615	68.8	0.765
No event <12 months, history of just heart attack	0.742	65.1	0.906
Stroke <12 months, history of just stroke	0.626	67.9	0.775
No event <12 months, history of just stroke	0.668	66.8	0.822
No event <12 months, history of heart attack + other CV condition	0.685	69.2	0.854

* Note: The values above correspond to an assumption of 50% male
**Angina is assumed to apply to unstable angina in the model
*** Note: The sample size for the acute post-MI utility in Ara et al [17] was very small (N=31). Thus, the acute post-MI utility was assumed to be the same as the acute post-unstable angina utility.

Table 65 Summary of utility values for cost-effectiveness analysis – CV event disutility multipliers

CV event based utilities	Mean			SE		
	First year	Second year	Stable beyond 2 years	First year	Second year	Stable beyond 2 years
NF MI	0.765	0.906	0.906	0.019	0.020	0.020
UA	0.765	0.960	0.960	0.019	0.015	0.015
ACS	0.765	0.924	0.924	0.019	0.018	0.018
Revascularisation	N/A	N/A	1.000	N/A	N/A	N/A
IS	0.775	0.822	0.822	0.038	0.018	0.018

ACS, acute coronary syndrome; CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; N/A, not available; NF, non-fatal; SE, standard error; UA, unstable angina

Secondary prevention

For secondary prevention patients (i.e. high risk CVD, recurrent events/ polyvascular disease, and secondary prevention HeFH), for baseline, age-adjusted utility is estimated multiplying the age-adjusted utility for patients with no history of CVD (the same equation as above) by the age-adjusted multiplier of the event observed in the

past. So, for example for the high risk CVD cohort, the baseline utility for patients with a previous history of a heart attack is obtained by multiplying the age-adjusted utility for people with no history of CVD by the “chronic” multiplier for patients with a previous heart attack i.e. 0.906. These are summarised in

Table 66.

Table 66 Multipliers for secondary prevention baseline

Baseline utility multipliers	Multiplier	SE
HeFH (secondary prevention)	0.924	0.018
ACS (0–12 months)	0.765	0.019
History of IS	0.822	0.018
ACS (13–24 months)	0.924	0.018
CHD	0.924	0.018
PAD	0.924	0.018
HeFH (primary prevention)	N/ A (1.000)	N/A
Polyvascular	0.854	0.024

ACS, acute coronary syndrome; CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolaemia; IS, ischaemic stroke; N/A, not available; PAD, peripheral arterial disease; SE, standard error

Disutilities for further CV events occurring in the model are then applied using the appropriate acute and chronic multipliers, calculated as described above and summarised in Table 65.

5.4.5.4 Utility data from ODYSSEY

EQ-5D data were also collected in ODYSSEY (see Section 4.7). We applied these in sensitivity analyses. When these are applied they are constant throughout the model with no decline due to age. Further analyses of these data are ongoing with regards to the relationship between age and utility. Baseline utility data from ODYSSEY as implemented in the model are shown in Table 67.

Table 67 Baseline utility data from ODYSSEY applied in the model

Baseline Utilities	Mean	Standard Error Values
HeFH (Secondary Prevention)	0.875	0.007
ACS (0-12 months)	0.844	0.014
History of Ischaemic Stroke	0.797	0.014
ACS (13-24 months)	0.858	0.013
CHD	0.860	0.007

PAD	0.775	0.026
HeFH (Primary Prevention)	0.930	0.005
Diabetes	0.814	0.006
Polyvascular	0.771	0.018

In this situation we apply multiplicative disutilities from the CG181 guideline [23].

The model also allows application directly of the utilities from CG181.

5.5 Cost and healthcare resource use identification, measurement and valuation

Costs included in the analysis cover direct CV event costs and background therapy and comparators costs.

The model includes the costs for up to the first three years post-CV event, assuming the patient survives until that point. Additionally, if the patient has two CV events within three years of each other, the model will stop incurring costs for the first event once the second event occurs. For example, if a patient has an ischaemic stroke a year after an ACS, the patient only incurs the event and first year costs of the ACS and then starts to incur the costs of the ischaemic stroke, without ever incurring the second or third year costs of the ACS.

The model sets the cost of an ACS event equal to a weighted average of non-fatal MI and unstable angina requiring hospitalisation. The proportions were based on the average one-year event probability for the target population as derived from the THIN analyses. The cost of urgent revascularisation (i.e. occurring within 30 days after an ACS) is included in the event cost of the MI/unstable angina requiring hospitalisation. The cost of elective revascularisation is not part of the cost associated with ACS or IS, neither as the event cost or as follow-up cost. As shown in Figure 30, the model restricts patients from transitioning from the post-ACS and post-IS health states to an elective revascularisation due to the unrealistic positive impact on utility and CV risk. However, a proportion of patients in the stable post-ACS health state would experience elective revascularisations. To account for these costs, the model will include the cost of the elective revascularisation event in the stable post-ACS and post IS health state without moving the patients to the post-revascularisation health state.

Note: In addition this analysis does not include non-CV costs. Thus, the cost of a non-cardiovascular death is assumed to be zero. Additionally, non-CV background costs are not included in the model (See Section 5.5).

5.5.1 Resource identification, measurement and valuation studies

The primary costs in the model are the costs of treatment for hypercholesterolaemia, and costs of CV events. These costs are based on the cost of hospitalisation, follow-up care, medication, etc. Direct CV event costs are broken down into the cost of the event and the incremental follow-up costs.

Costs are based on CG181 [23 100]. In 2014 NICE published clinical guideline CG181 - Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. The clinical guideline development group (GDG) developed a Markov model and undertook a detailed assessment of costings to support the analysis of the impact of lipid modification via its impact on CV events. It was noted this analysis and the health states incorporated into the model were well aligned to our modelling approach and as such it was deemed that adoption of the approach taken by NICE in the development of CG181 was appropriate.

When assessing CG181 we noticed that there were significant differences between the costs applied in the draft and final guidelines. This appeared to be due a change in methodology for estimating health state costs. In discussion with the GDG, the following response was provided:

> *"In the draft version, the estimates used in the previous models were inflated. However, the GDG were unhappy with that method as most of the values in those models were based on assumptions on the resource use of people with cardiovascular disease, and many aspects of treatment for CVD have changed over the years since those models were composed. Despite looking through more recent literature we could not find any better recent costs for people with CV conditions, so we decided it would be preferable to construct our own estimates."*

Based on the work done for CG181 we considered it appropriate to use their final costs within the model.

The health state costs were estimated by the GDG by:

"*Resource use was based on GDG expert opinion, drawing on the advice of NICE cardiovascular guidelines where available.*
Unit costs were taken from the references given following Table 84:[100]

- *BNF & NHS Drug Tariff: drug prices*
- *NHS Reference costs: hospital procedures (including revascularisation, hospitalisation and bed days, consultations with specialists)*
- *PSSRU unit costs of H&SC: primary care consultations*
- *In addition the cost of a stroke rehabilitation programme was taken from NICE CG162*

Drug costs were calculated separately *"The costs of statins and the routine primary care monitoring (consultation and blood tests) are added on to all patients (except in the control arm) on top of the health state costs and are not included within them."*

A number of different costings have been reported in the UK and comparable countries for CV events and these vary considerably. The costings applied in the model are relatively low and may underestimate the total cost impact of CV events on the NHS. We investiage this in sensitivity analyses by applying a standard increase of 20% and then by doubling the CV event costings.

5.5.2 Intervention and comparators' costs and resource use

The model includes the costs of background treatment including statins and non-statin LMT. Due to the anticipated positioning of alirocumab on top of maximally tolerated current therapy it is expected that resource usage (in terms of monitoring etc) will be identical between arms.

When background therapy includes statins, it is based on high dose, high intensity statins namely atorvastatin and rosuvastatin. The model has the capacity to include other costs and intensities but we focus on high dose, high intensity statins.

Drug costs were taken from the BNF and are shown in Table 68.

Table 68: Drug costs

Treatment	Dose	Annual cost* (£)
Ezetimibe	10 mg	342.97
Atorvastatin (Lipitor)	10 mg	15.51
	20 mg	18.90
	40 mg	21.77
	80 mg	34.94
Rosuvastatin (Crestor)	5 mg	235.03
	10 mg	235.03
	20 mg	339.19
	40 mg	386.51

5.5.3 Health-state unit costs and resource use

A summary of the costs associated with each health state in the *de novo* model can be found in Table 69.

Table 69: CV event costs

	Event cost (£)	Incremental second year costs (£)	Incremental third year costs (£)
NF MI	3337.00	788.00	788.00
UA	3313.00	385.00	385.00
ACS	3329.00	653.67	653.67
Revascularisation	3802.32	N/A	N/A
IS	4092.00	155.00	155.00
CV death	1174.00	N/A	N/A
Non-CV death	0.00	N/A	N/A

ACS, acute coronary syndrome; CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; N/A, not available; NF, non-fatal; UA, unstable angina

5.5.4 Adverse reaction unit costs and resource use

As with the effect of adverse events on HRQoL (see above), as adverse events were similar between the alirocumab and control groups, including placebo, adverse event costs were not modelled.

5.5.5 Miscellaneous unit costs and resource use

N/A

5.6 Summary of base case de novo analysis inputs and assumptions

5.6.1 Summary of base case de novo analysis inputs

The variables applied in the economic model are summarised in Table 70. The key assumptions are tabulated in

Table **71**.

Table 70: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to Section in submission
High CVD risk cohort (mixed cohort)	Composed of patients with prior ACS, CHD, Ischaemic stroke and PAD	Description of patient types – not associated with uncertainty	Table 59
Age	65 (for high risk CVD), 50 for primary prevention HeFH, 60 for secondary prevention HeFH	Varied in PSA according to distribution around age	See Table **58**, link to baseline characteristics table also
Gender	60% males for high risk CVD, 50% for HeFH	Varied in PSA according to distribution around gender split and diabetes prevalence	See Table **58**, link to baseline characteristics table also
Diabetes prevalence	23% diabetes for high risk CVD, 30% for recurrent events, 7% for HeFH (based on UK THIN data)	Varied in PSA according to distribution around gender split and diabetes prevalence	See Table **58**, link to baseline characteristics table also
Baseline LDL-C	Mean LDL-C from THIN epidemiological data, corresponding to different LDL-C cut-offs	Varied in PSA according to distribution around mean level	Table 57
Baseline CV risk	From THIN data		See Section 5.3 and Appendix11
Baseline utility	Age-adjusted, ODYSSEY used as sensitivity analyses	Varied according to distribution around the mean chronic utility (past event), with recalculation of multipliers	See Table 66
Disutilities due to CV events	Based on HSE data	Varied according to variation in original sample, with recalculation of	See Table 65

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to Section in submission
		multipliers (same ones as for the baseline utility)	
Costs of CV events	Taken from CG181	Varied according to arbitrary assumption around CI	Table 69

ACS, acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HSE, Healthy and Safety Executive; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral arterial disease; PSA, probabilistic sensitivity analysis; THIN, The Health Improvement Network

Table 71: Table of assumptions in the economic model

Assumption	Justification (reference to relevant part of submission)
THIN data is representative of UK general population CV risk	THIN is a general practice medical records database containing medical records from over 12 million patients, of which over 3.6 million are actively registered. It has been used previously in UK research, for example in development of the QRISK score.
Alirocumab relative LDL-C reduction is constant across subgroups	ODYSSEY evidence shows a homogeneous treatment effect across a range of different subgroups and therefore it is reasonable to assume the same treatment effect can be consistently applied across different patient subgroups.
LDL-C lowering and CV benefit stops immediately on treatment cessation	Data from ODYSSEY shows LDL-C levels return fairly quickly to baseline following treatment cessation. The assumption is that CV benefit stops immediately on treatment cessation is the most conservative and appropriate.
Alirocumab dosing will reflect ODYSSEY treatment	Up-titration is applied in the model in line with the approach applied in ODYSSEY and the flexibility provided by the two different doses. It is not certain that UK practice will follow exactly the same approach. Different treatment rules are applied in scenario analyses.

CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; THIN, The Health Improvement Network

5.7 Base case results

We present results below separately for HeFH patients, and for high CV risk patients.

5.7.1 Base case incremental cost effectiveness analysis results

5.7.1.1. Base case results for HeFH

Table 72 presents the cost-effectiveness results for alirocumab used as an add-on to current maximal therapy (maximal dose of statins combined with ezetimibe), in primary prevention and secondary prevention HeFH patients, with a baseline LDL-C of at least 2.59 mmol/L. Results for HeFH are shown based on the input data from THIN, and that from Morschladt et al (as described in section 5.3.2). There is good agreement between the results obtained using the two sources.

Table 72: Base case results in HeFH

Patient population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs baseline (QALYs)
HeFH – primary prevention (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	1.62	1.42	[redacted]
	Statins + ezetimibe	[redacted]	[redacted]	[redacted]				
HeFH –secondary prevention (baseline LDL-C ≥2.59 mmol/L) ***Baseline risk data from Morschladt et al***	Alirocumab + statins + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	3.04	2.33	[redacted]
	Statins + ezetimibe	[redacted]	[redacted]	[redacted]				
HeFH –secondary prevention (baseline LDL-C ≥2.59 mmol/L) ***Baseline risk data from THIN***	Alirocumab + statins + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	2.85	2.14	[redacted]
	Statins + ezetimibe	[redacted]	[redacted]	[redacted]				

HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; LYG, life-years gained; QALY, quality-adjusted life-year

5.7.1.2. Base case results for high risk CVD and recurrent events/ polyvascular

Table 73 presents the cost-effectiveness results for alirocumab used in addition to current maximal therapy (maximal dose statins) compared with maximal dose statin therapy alone, in high risk CVD patients and patients with recurrent events/ polyvascular disease.

Table 74 presents the cost-effectiveness results for alirocumab used in addition to ezetimibe versus ezetimibe alone in in high risk CVD patients and patients with recurrent events/ polyvascular disease who are completely intolerant to statins.

Alirocumab was cost-effective in both patient populations and setting. There is a lower ICER in statin intolerant patients because of the higher average baseline LDL-C in this group.

Table 73 Base case results for High Risk CVD and Recurrent events/ Polyvascular Disease

Patient population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs baseline (QALYs)
High-risk CVD (baseline LDL-C ≥3.36mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	[redacted]	2.38	1.76	[redacted]
	Statins	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	[redacted]	2.42	1.64	[redacted]
	Statins	[redacted]	[redacted]	[redacted]				

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

Table 74 Base case results for High Risk CVD and Recurrent events/ Polyvascular Disease – *Statin intolerant patients*

Patient population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs baseline (QALYs)
High-risk CVD (baseline LDL-C ≥3.36mmol/L)	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	2.76	2.04	[redacted]
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	3.52	2.40	[redacted]
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; LYG, life-years gained; QALY, quality-adjusted life-year; SI, statin intolerance

5.7.2 Results – additional comparisons

The most relevant evaluation of alirocumab is in addition to maximally tolerated existing therapy, as presented above. In line with the scope, we present below comparisons directly versus ezetimibe, however these are presented as a summary only and will not be considered further in the more detailed results presentations below this is not considered to be the most relevant way of evaluating alirocumab. Results are shown in

Table **75**, Table 76 and Table 77.

Table 75 Comparison with Ezetimibe in HeFH patients

Patient population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)vs baseline (QALYs)
HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	[redacted]	1.07	0.95	[redacted]
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	[redacted]	2.21	1.70	[redacted]
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				

HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; LYG, life-years gained; QALY, quality-adjusted life-year

Table 76 Comparison with Ezetimibe in patients with High Risk CVD and Recurrent events/ Polyvascular Disease

Patient population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)vs baseline (QALYs)
High-risk CVD (baseline LDL-C ≥3.36 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	[redacted]	1.75	1.29	[redacted]
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	[redacted]	1.83	1.25	[redacted]
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				

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

Table 77 Comparison with Ezetimibe in High Risk CVD and Recurrent events/ Polyvascular Disease – *Statin intolerant patients*

Patient population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs baseline (QALYs)
High-risk CVD (baseline LDL-C ≥3.36 mmol/L)	Alirocumab	[redacted]	[redacted]	[redacted]	[redacted]	2.40	1.78	[redacted]
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab	[redacted]	[redacted]	[redacted]	[redacted]	3.12	2.14	[redacted]
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; LYG, life-years gained; QALY, quality-adjusted life-year; SI, statin intolerance

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis methods

Probabilistic sensitivity analysis (PSA) was undertaken for the key parameters in the mode, including cohort characteristics, treatment effect on LDL-C, link between LDL-C reduction and CV events, costs and utilities. Table 78 below reports the distributions used and source of variations in the PSA. 500 iterations were run.

Table 78: PSA key parameters

	Distribution	Variation
Cohort characteristics		
Proportion with diabetes	Normal	SE from proportion of population with diabetes in THIN (1%)
Proportion of males	Normal	Standard error calculated as +/- 25% / 6
Baseline LDL-C	Log-Normal	Standard error calculated as +/- 25% / 6
Initial age	Normal	Standard error calculated as +/- 25% / 6
LDL-C lowering efficacy for alirocumab and comparators	Normal	ODYSSEY trial programme
CV costs	Gamma	Standard error calculated as +/- 25% / 6
Utilities	Beta	According to uncertainty in original estimates in Ara paper (multipliers recalculated each time)
Relative risk reduction	Log-Normal	According to CIs reported in Navarese 2015
Annual increase in CV risk due to age	Normal	According to CIs reported in Wilson 2012 [34]

CI, confidence interval; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; N/A, not available

5.8.2 PSA Results

Figure 31 to Figure 34 show the scatter plots and cost-effectiveness acceptability curves (CEAC) for the key patient populations.

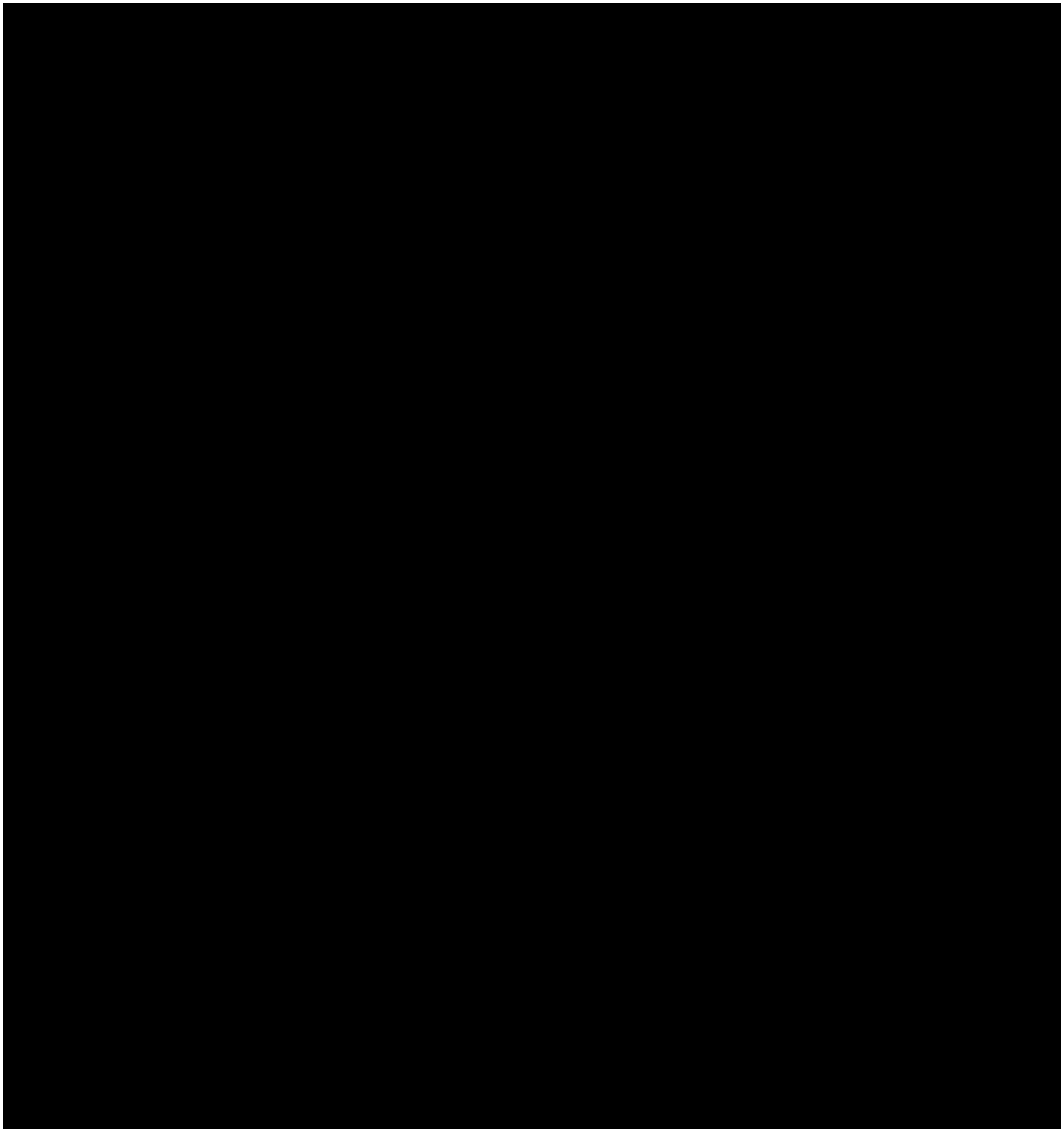


Table 79 shows the probability of cost-effectiveness at different willingness to pay thresholds.

There is considerable uncertainty in the results as illustrated in the PSA. This reflects the wide confidence intervals deriving from preliminary PCSK9 inhibitor outcomes data.

5.8.2.1 HeFH primary prevention, Alirocumab + statins + ezetimibe versus statins + ezetimibe

Figure 31: HeFH primary prevention, Scatter plot and CEAC

[redacted]

5.8.2.2 HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe

Figure 32: HeFH secondary prevention, Scatter plot and CEAC

[redacted]

[redacted]

5.8.2.3 High risk CVD, alirocumab + statins versus statins

Figure 33: High Risk CVD, scatter plot and CEAC

[redacted]

[redacted]

5.8.2.4 Recurrent events/ Polyvascular disease, alirocumab + statins versus statins

Figure 34: Polyvascular, scatter plot and CEAC

[redacted]

[redacted]

Table 79 Probability of cost-effectiveness by Willingness to Pay for key patient groups

	HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	High-risk CVD (baseline LDL-C ≥3.36 mmol/L) – alirocumab + statins versus statins	Recurrent events/ polyvascular disease (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins versus statins
Willingness to pay	**Probability of cost-effectiveness**			
20,000/QALY	0%	21%	0%	4%
30,000/QALY	7%	53%	39	40%

40,000/QALY	23%	72%	66%	67%

CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; QALY, quality-adjusted life-year

5.8.3 Deterministic sensitivity analysis methods

Deterministic sensitivity analysis was undertaken. The key parameters and the extent to which they were varied is reported in Table 80 below.

Table 80: Deterministic sensitivity analysis key parameters

Parameter	Variation
Annual CV risk	+/- 20%
Adjustment of CV risk by age	+/- 20%
CV costs	+/- 20%
CV event costs	Doubled
Alirocumab efficacy (LDL-C lowering)	Upper/lower CI from ODYSSEY
Rate ratio per 1 mmol/L reduction for calculation of baseline CV risk	Upper/lower CI
Rate ratio per 1 mmol/L reduction for the treatment effects	Upper/lower CI
Acute disutilities	Upper/lower CI
Baseline utilities	Upper/lower CI
Chronic disutilities	Upper/lower CI

CI, confidence interval; CV, cardiovascular; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol

5.8.4 Deterministic sensitivity analysis results

Results for the key patient populations are tabulated in Table 81 to Table 84. The parameter with by far the biggest impact is the relationship between LDL-C reduction and CV event reduction. This is because of the wide CI observed in the Navarese meta-analysis, in particular for CV mortality (reflecting the relatively small amount of data currently available). The other parameter that has a significant impact is the baseline CV risk, when varied by an arbitrary +/- 20%,

The model is relatively stable to adjustments in the other parameters. Of note, there is limited sensitivity to CV event costs, even when these were doubled.

5.8.4.1 HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe

Table 81 HeFH primary prevention, deterministic sensitivity analysis

Parameter	Variation	ICER (£/QALY)
Base case		[redacted]
Annual CV risk	–20%	[redacted]
Annual CV risk	+20%	[redacted]
Adjustment of CV risk by age	–20%	[redacted]
Adjustment of CV risk by age	+20%	[redacted]
CV costs	–20%	[redacted]
CV costs	+20%	[redacted]
CV event costs	Doubled	[redacted]
Alirocumab efficacy (LDL-C lowering)	Lower CI	[redacted]
Alirocumab efficacy (LDL-C lowering)	Upper CI	[redacted]
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	[redacted]
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	[redacted]
Rate ratio per 1 mmol/L for treatment effect	Lower CI	[redacted]
Rate ratio per 1 mmol/L for treatment effect	Upper CI	[redacted]
Acute CV disutilities	Lower CI	[redacted]
Acute CV disutilities	Upper CI	[redacted]
Baseline utilities	Lower CI	[redacted]
Baseline utilities	Upper CI	[redacted]
Chronic CV disutilities	Lower CI	[redacted]
Chronic CV disutilities	Upper CI	[redacted]

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio

5.8.4.2 HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe

Table 82 HeFH secondary prevention, deterministic sensitivity analysis

Parameter	Variation	ICER (£/QALY)
Base case		[redacted]

Parameter	Variation	ICER (£/QALY)
Base case		[redacted]
Annual CV risk	–20%	[redacted]
Annual CV risk	+20%	[redacted]
Adjustment of CV risk by age	–20%	[redacted]
Adjustment of CV risk by age	+20%	[redacted]
CV costs	–20%	[redacted]
CV costs	+20%	[redacted]
CV event costs	Doubled	[redacted]
Alirocumab efficacy (LDL-C lowering)	Lower CI	[redacted]
Alirocumab efficacy (LDL-C lowering)	Upper CI	[redacted]
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	[redacted]
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	[redacted]
Rate ratio per 1 mmol/L for treatment effect	Lower CI	[redacted]
Rate ratio per 1 mmol/L for treatment effect	Upper CI	[redacted]
Acute CV disutilities	Lower CI	[redacted]
Acute CV disutilities	Upper CI	[redacted]
Baseline utilities	Lower CI	[redacted]
Baseline utilities	Upper CI	[redacted]
Chronic CV disutilities	Lower CI	[redacted]
Chronic CV disutilities	Upper CI	[redacted]

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio;

5.8.4.3 High Risk CVD - alirocumab + statins versus statins

Table 83 High risk CVD, deterministic sensitivity analysis

Parameter	Variation	ICER (£/QALY)
Base case		[redacted]
Annual CV risk	–20%	[redacted]
Annual CV risk	+20%	[redacted]

Parameter	Variation	ICER (£/QALY)
Base case		[redacted]
Adjustment of CV risk by age	–20%	[redacted]
Adjustment of CV risk by age	+20%	[redacted]
CV costs	–20%	[redacted]
CV costs	+20%	[redacted]
CV event costs	Doubled	[redacted]
Alirocumab efficacy (LDL-C lowering)	Lower CI	[redacted]
Alirocumab efficacy (LDL-C lowering)	Upper CI	[redacted]
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	[redacted]
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	[redacted]
Rate ratio per 1 mmol/L for treatment effect	Lower CI	[redacted]
Rate ratio per 1 mmol/L for treatment effect	Upper CI	[redacted]
Acute CV disutilities	Lower CI	[redacted]
Acute CV disutilities	Upper CI	[redacted]
Baseline utilities	Lower CI	[redacted]
Baseline utilities	Upper CI	[redacted]
Chronic CV disutilities	Lower CI	[redacted]
Chronic CV disutilities	Upper CI	[redacted]

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio

5.8.4.4 Recurrent events/ Polyvascular Disease - alirocumab + statins versus statins

Table 84 Recurrent events/ polyvascular, deterministic sensitivity analysis

Parameter	Variation	ICER (£/QALY)
Base case		[redacted]

Parameter	Variation	ICER (£/QALY)
Base case		[redacted]
Annual CV risk	–20%	[redacted]
Annual CV risk	+20%	[redacted]
Adjustment of CV risk by age	–20%	[redacted]
Adjustment of CV risk by age	+20%	[redacted]
CV costs	–20%	[redacted]
CV costs	+20%	[redacted]
CV event costs	Doubled	[redacted]
Alirocumab efficacy (LDL-C lowering)	Lower CI	[redacted]
Alirocumab efficacy (LDL-C lowering)	Upper CI	[redacted]
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	[redacted]
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	[redacted]
Rate ratio per 1 mmol/L for treatment effect	Lower CI	[redacted]
Rate ratio per 1 mmol/L for treatment effect	Upper CI	[redacted]
Acute CV disutilities	Lower CI	[redacted]
Acute CV disutilities	Upper CI	[redacted]
Baseline utilities	Lower CI	[redacted]
Baseline utilities	Upper CI	[redacted]
Chronic CV disutilities	Lower CI	[redacted]
Chronic CV disutilities	Upper CI	[redacted]

CI, confidence interval; CV, cardiovascular; ICER, incremental cost-effectiveness ratio

5.8.5 Scenario analysis methods

A number of key assumptions were varied in scenario analyses. These are outlined in Table 85 below.

Table 85: Scenario analyses conducted

Assumption	Base case	Scenarios
Discontinuation rate	0%	3%
		8%
Cost and benefit discount rates	3.5%	0%
		5%
Treatment duration	Lifetime	1 year
		5 years
Model time horizon	Lifetime	5 years
		10 years
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis
		LONG TERM study
		Pooled Phase III vs placebo
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P-NF, post-non-fatal

5.8.6 Scenario analysis results

Scenario analysis results are shown below.

The model was sensitive to different sources (CTT, LONG-TERM trial, Placebo-controlled phase III trials) to inform the relationship between LDL-C reduction and CV event reduction, with substantially higher ICERs found using the CTT relationship.

Using baseline utility data from ODYSSEY with disutilities from the literature decreases the ICER considerably. Accounting for age-related declines in utility over time is in accordance with best practice which is why we have used this in the base case. Nevertheless we consider that using EQ-5D data from the ODYSSEY trials should be considered as a plausible alternative scenario. Ongoing analysis of EQ-5D data from ODYSSEY may better inform this.

A discount rate of 0% resulted in a substantial reduction in the ICER, reflecting that many of the benefits of LDL-C lowering are accrued many years in the future. A shorter time horizon also had a dramatic impact on the ICER by removing the potential benefits that accrue relative to the cost.

As discussed two different ways of modelling baseline risk in secondary prevention HeFH were utilised. There was relatively good agreement between the ICERs (Table 87).

The model was relatively stable to other important assumptions including different data on the relationship between baseline LDL-C and baseline CV risk, discontinuation rates, and different structural assumptions.

5.8.6.1 HeFH primary prevention - alirocumab plus statins plus ezetimibe versus statins plus ezetimibe

Table 86 HeFH primary prevention, Scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case			[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.5%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non fatal; QALY, quality-adjusted life-year

5.8.6.2 HeFH secondary prevention- alirocumab plus statins plus ezetimibe versus statins plus ezetimibe

Table 87 HeFH secondary prevention – Scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case			[redacted]
Baseline risk data	As per Morschladt	As per THIN	[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]

Cost and benefit discount rates	3.5%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; HSE; Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non-fatal

5.8.6.3: High risk CVD - alirocumab plus statins versus statins

Table 88: High Risk CVD – Scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case			[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.5%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]

Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; CVD, cardiovascular disease; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P-NF, post-non-fatal

5.8.6.1 Recurrent events/ Polyvascular Disease - alirocumab plus statins versus statins

Table 89 Recurrent events/ polyvascular disease – Scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case			[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.5%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P-NF, post-non-fatal

5.9 Clinical outcomes from the model

Table 90 summarises the clinical outcomes in the model for HeFH patients, and Table 91 for high risk CVD patients. Because CVOT will not report until 2018, it is not possible to compare the modelled results with actual trial data. The modelled results demonstrate reductions in both non-fatal and fatal events with alirocumab compared to control therapy.

Table 90: Clinical outcomes from the model - HeFH patients

Patient population	Technologies	Total number of events (lifetime)	Total number of NF events (lifetime)	ACS	Stroke	Revascularisation	Total number of fatal events (lifetime)
HeFH primary prevention (baseline LDL-C ≥ 2.59 mmol/L)	Alirocumab + statins + ezetimibe	0.47	0.36	0.26	0.05	0.05	0.11
	Statins + ezetimibe	1.62	1.19	0.88	0.20	0.12	0.42
HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins + ezetimibe	1.30	1.00	0.73	0.07	0.20	0.30
	Statins + ezetimibe	2.54	1.89	1.43	0.18	0.27	0.65

ACS, acute coronary syndrome; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal

Table 91: Clinical outcomes from the model - high risk CVD patients and Recurrent events/ Polyvascular Disease patients

	Technologies	Total number of events (lifetime)	Total number of NF events (lifetime)	ACS	Stroke	Revascularisation	Total number of fatal events (lifetime)
High-risk CVD (baseline LDL-C ≥3.36mmol/L)	Alirocumab + statins	0.69	0.42	0.26	0.10	0.07	0.27
	Statins	1.55	0.97	0.64	0.21	0.12	0.58
Recurrent events /polyvascular (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins	1.02	0.59	0.35	0.17	0.07	0.43
	Statins	1.68	1.00	0.63	0.28	0.09	0.68

ACS, acute coronary syndrome; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal

5.9.1 – Markov traces from the model

Figure 35 - Figure 36 show the Markov traces for alirocumab used as an add-on to maximal current therapy (statins + ezetimibe) for HeFH primary prevention.

Traces for HeFH secondary prevention, high risk CVD, and recurrent events/ polyvascular disease are shown in Appendix 14 in the interests of space. Traces are not shown for alirocumab used as an add-on to ezetimibe in statin intolerant patients, or versus ezetimibe, because the patterns observed are very similar. In all populations, patients spend the majority of time in the initial stable state, transitioning through individual events but spending a relatively small proportion of total time in post-event states, and then transitioning through to the death states.

Figure 35: Markov trace - HeFH primary prevention, alirocumab plus statins plus ezetimibe

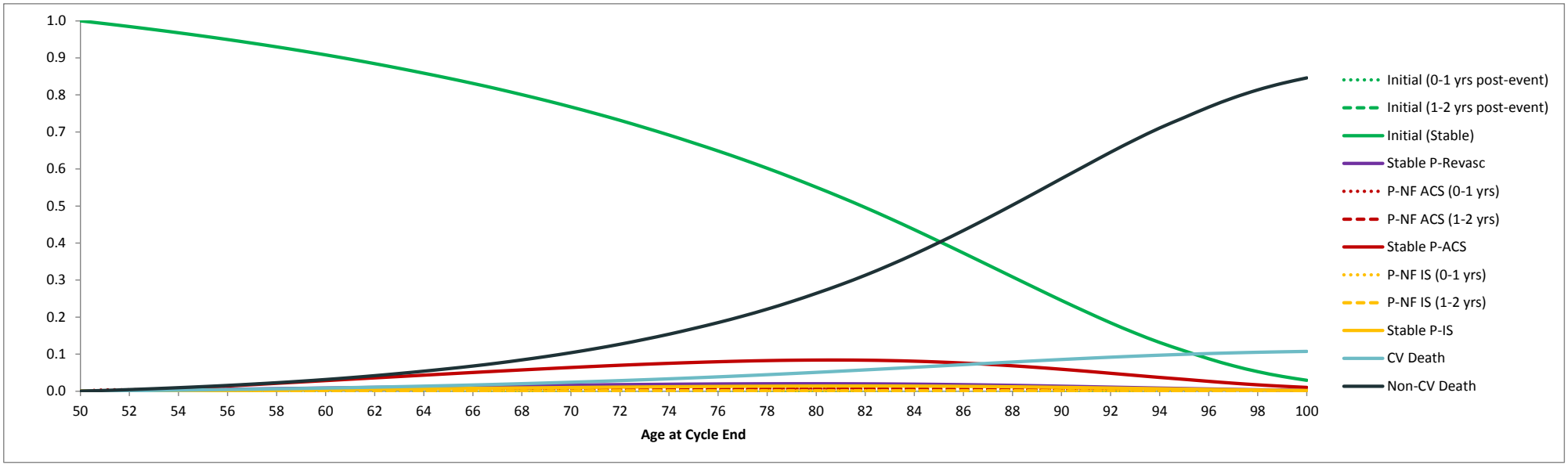
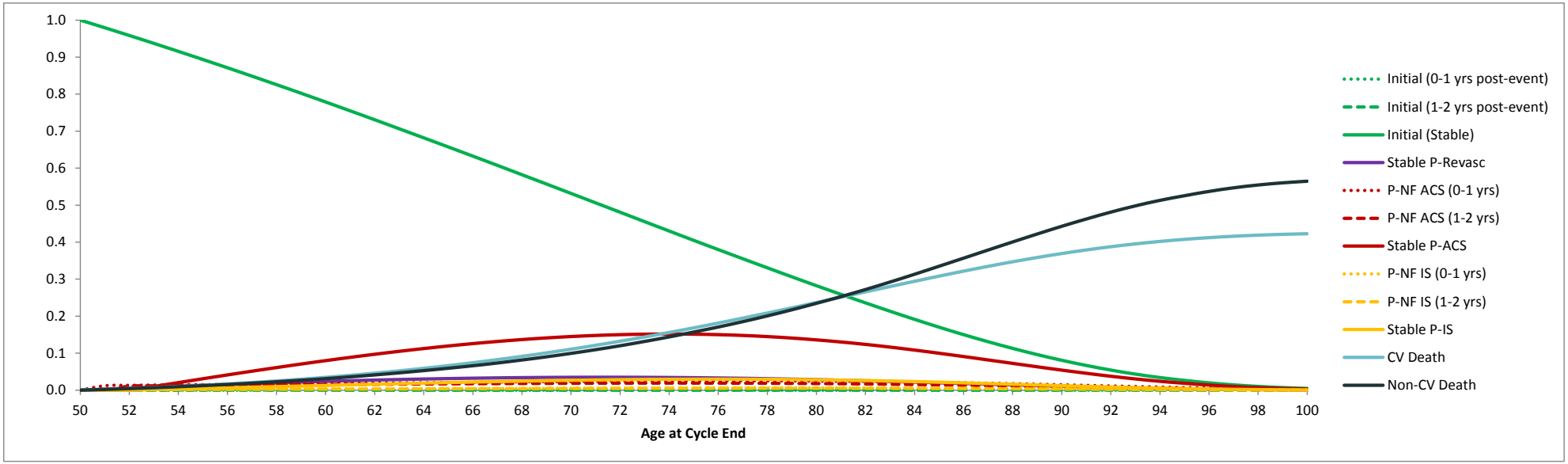


Figure 36: Markov trace - HeFH primary prevention, statins plus ezetimibe



5.9.2 Accrual of QALYs over time

Reflecting the patterns observed in the Markov traces, the vast majority of QALYs are accrued in the initial stable health state. This reflects the relatively short proportion of total time spent in post-event states and of course the fact that no QALYs are accrued in death states. Traces are shown in Figure 37 to Figure 38 for HeFH primary prevention, with figures for the other populations in Appendix 14.

Figure 37: Accrual of QALYs - HeFH primary prevention, alirocumab + statins + ezetimibe

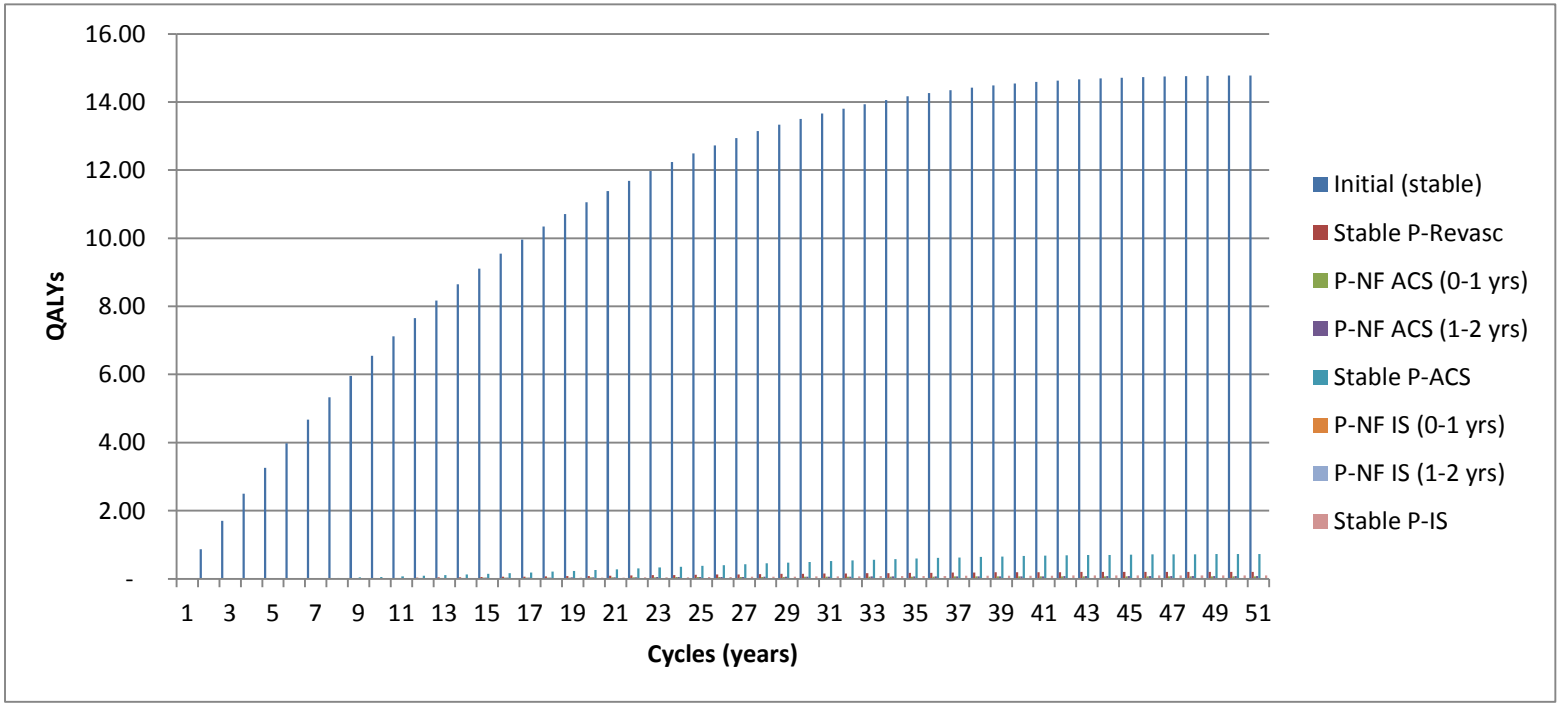
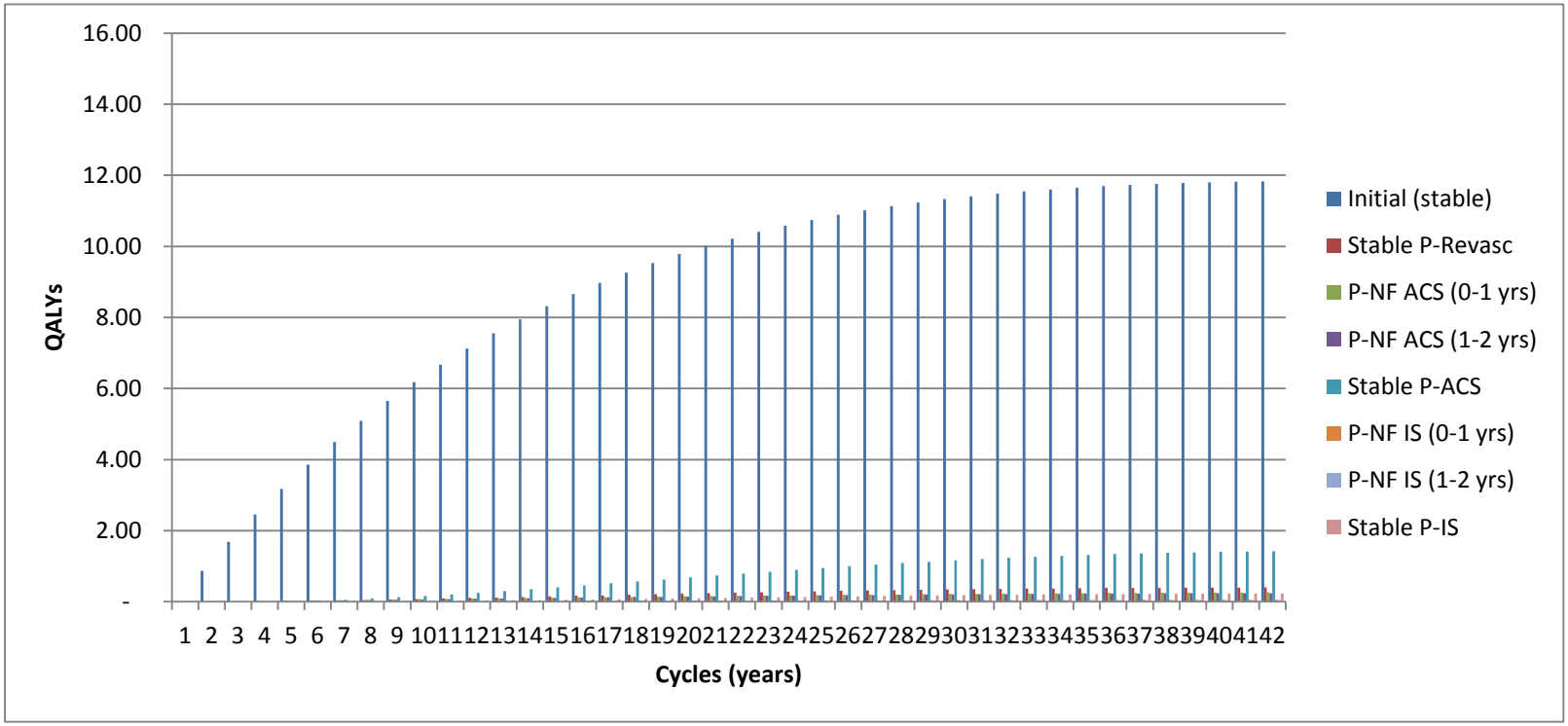


Figure 38 Accrual of QALYs - HeFH primary prevention, statins + ezetimibe



5.9.3 Disaggregated results of the base case incremental cost effectiveness analysis

Table 92 to Table 95 summarise the QALY gain by health state. The incremental QALYs for alirocumab derive from longer time spent in the baseline state without experiencing events. Alirocumab is associated with fewer QALYs in the event states due to fewer events experienced in the alirocumab arm. This is consistent across different patient groups.

Table 92: Summary of QALY gain by health state – HeFH primary prevention

Health state	QALY intervention (alirocumab plus statins plus ezetimibe)	QALY comparator (statins plus ezetimibe)	Increment
Baseline	14.78	11.87	2.91
Stable post-revascularisation	0.21	0.41	-0.20
P-NF ACS 0–1 years	0.08	0.27	-0.19
P-NF ACS 1–2 years	0.08	0.25	-0.17
Stable post-ACS	0.73	1.44	-0.72
P-NF stroke 0–1 years	0.01	0.06	-0.04
P-NF stroke 1–2 years	0.01	0.05	-0.04
Stable P-NF stroke	0.10	0.24	-0.13
Total	16.00	14.58	1.42

ACS, acute coronary syndrome; HeFH, heterozygous familial hypercholesterolaemia; NF, non-fatal; P-NF, post-non-fatal; QALY, quality-adjusted life-year

Table 93: Summary of QALY gain by health state – HeFH secondary prevention

Health state	QALY intervention (alirocumab plus statins plus ezetimibe)	QALY comparator (statins plus ezetimibe)	Increment
Baseline	7.11	3.61	3.49
P-NF ACS 0–1 years	1.03	1.23	-0.20
P-NF ACS 1–2 years	0.26	0.57	-0.31
Stable CHD	0.27	0.49	-0.22

Health state	QALY intervention (alirocumab plus statins plus ezetimibe)	QALY comparator (statins plus ezetimibe)	Increment
Stable post-revascularisation	1.98	2.22	-0.24
P-NF stroke 0 - 1 years	0.02	0.06	-0.04
P-NF stroke 1–2 years	0.02	0.06	-0.04
Stable P-NF stroke	0.13	0.24	-0.11
Total	10.82	8.49	2.33

ACS, acute coronary syndrome; CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolaemia; NF, non-fatal; P-NF, post-non-fatal; QALY, quality-adjusted life-year

Table 94: Summary of QALY gain by health state – High Risk CVD

Health state	QALY intervention (alirocumab plus statins)	QALY comparator (Statins)	Increment
Baseline	8.23	5.77	2.46
P-NF ACS 0–1 years	0.09	0.23	-0.14
P-NF ACS 1–2 years	0.09	0.18	-0.09
Stable CHD	0.51	0.68	-0.17
Stable post-revascularisation	0.26	0.39	-0.13
P-NF stroke 0-1 years	0.03	0.08	-0.05
P-NF stroke 1–2 years	0.03	0.07	-0.04
Stable P-NF stroke	0.19	0.27	-0.08
Total	9.43	7.68	1.75

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; NF, non-fatal; P-NF, post-non-fatal; QALY, quality-adjusted life-year; HS1, health state 1; HS2, health state 2; NF, non-fatal

Table 95: Summary of QALY gain by health state – Recurrent events/ polyvascular disease

Health state	QALY intervention (alirocumab plus statins)	QALY comparator (Statins)	Increment
Baseline	6.46	4.44	2.02
P-NF ACS 0–1 years	0.23	0.27	-0.04
P-NF ACS 1–2 years	0.12	0.23	-0.11
Stable CHD	0.11	0.17	-0.06
Stable post-	0.57	0.56	0.01

Health state	QALY intervention (alirocumab plus statins)	QALY comparator (Statins)	Increment
revascularisation			
P-NF stroke 0 - 1 years	0.06	0.11	-0.05
P-NF stroke 1–2 years	0.06	0.09	-0.04
Stable P-NF stroke	0.34	0.43	-0.09
Total	7.95	6.30	1.64

Table 96: Summary of costs by health state – HeFH primary prevention

Health state	Cost intervention (alirocumab plus statins plus ezetimibe)	Cost comparator (statins plus ezetimibe)	Increment (£)
Baseline	[redacted]	[redacted]	[redacted]
P-NF ACS 0–1 years	[redacted]	[redacted]	[redacted]
P-NF ACS 1–2 years	[redacted]	[redacted]	[redacted]
Stable CHD	[redacted]	[redacted]	[redacted]
Stable post-revascularisation	[redacted]	[redacted]	[redacted]
P-NF stroke 0-1 years	[redacted]	[redacted]	[redacted]
P-NF stroke 1–2 years	[redacted]	[redacted]	[redacted]
Stable P-NF stroke	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; NF, non-fatal; P-NF, post-non-fatal; QALY, quality-adjusted life-year; HS1, health state 1; HS2, health state 2; NF, non-fatal

Table 97: Summary of costs by health state – HeFH secondary prevention

Health state	Cost intervention (alirocumab plus statins plus ezetimibe)	Cost comparator (statins plus ezetimibe)	Increment (£)
Baseline	[redacted]	[redacted]	[redacted]
P-NF ACS 0–1 years	[redacted]	[redacted]	[redacted]
P-NF ACS 1–2 years	[redacted]	[redacted]	[redacted]
Stable CHD	[redacted]	[redacted]	[redacted]
Stable post-revascularisation	[redacted]	[redacted]	[redacted]
P-NF stroke 0-1 years	[redacted]	[redacted]	[redacted]
P-NF stroke 1–2 years	[redacted]	[redacted]	[redacted]

Health state	Cost intervention (alirocumab plus statins plus ezetimibe)	Cost comparator (statins plus ezetimibe)	Increment (£)
Stable P-NF stroke	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; NF, non-fatal; P-NF, post-non-fatal; QALY, quality-adjusted life-year; HS1, health state 1; HS2, health state 2; NF, non-fatal

Table 98 Summary of costs by health state – Recurrent events/ polyvascular

Health state	Cost intervention (alirocumab plus statins)	Cost comparator (statins)	Increment (£)
Baseline	[redacted]	[redacted]	[redacted]
P-NF ACS 0–1 years	[redacted]	[redacted]	[redacted]
P-NF ACS 1–2 years	[redacted]	[redacted]	[redacted]
Stable CHD	[redacted]	[redacted]	[redacted]
Stable post-revascularisation	[redacted]	[redacted]	[redacted]
P-NF stroke 0 -1 years	[redacted]	[redacted]	[redacted]
P-NF stroke 1–2 years	[redacted]	[redacted]	[redacted]
Stable P-NF stroke	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; NF, non-fatal; P-NF, post-non-fatal; QALY, quality-adjusted life-year; HS1, health state 1; HS2, health state 2; NF, non-fatal

5.9 Subgroup analysis

We have explored, as per the scope, cost-effectiveness in patients with and without familial hypercholesterolaemia, patients with established CVD and patients who have an even higher level of risk within CVD, and patients on a background of statin therapy and those not.

As described above we present results for patients who have hypercholesterolaemia on maximally tolerated existing therapy. We present below in Table 99 analyses according to different baseline LDL-C levels. Unsurprisingly, alirocumab is more cost-effective at higher starting baseline LDL-C levels, due to the higher CV risk in these groups and the higher absolute LDL-C reduction achieved.

Table 99: Subgroup analyses by LDL-C levels

Patient population	Baseline LDL-C (mmol/L)	Incremental costs £	Incremental QALY	ICER
HeFH primary prevention	2.59	[redacted]	1.42	[redacted]
	3.36	[redacted]	1.64	[redacted]
	4.13	[redacted]	1.79	[redacted]
HeFH secondary prevention	2.59	[redacted]	2.33	[redacted]
	3.36	[redacted]	2.48	[redacted]
	4.13	[redacted]	2.74	[redacted]
High Risk CVD	2.59	[redacted]	1.37	[redacted]
	3.36	[redacted]	1.76	[redacted]
	4.13	[redacted]	2.15	[redacted]
Recurrent events / Polyvascular disease	2.59	[redacted]	1.64	[redacted]
	3.36	[redacted]	2.09	[redacted]
	4.13	[redacted]	2.54	[redacted]

HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life-year

5.10 Validation

Validation of *de novo* cost-effectiveness analysis

Three advisory boards were held as part of the development of the model. Additional consultation was also taken with health economic and clinical experts on key parameters of the model. Internal validity checks were undertaken including extreme value checks, use of Markov traces and tracing of QALYs and costs over time, and structural sensitivity analyses, Probabilistic and Deterministic analyses were undertaken to investigate model sensitivity and the impact of different scenarios on results.

5.11 Interpretation and conclusions of economic evidence

Previous evaluations of lipid-lowering therapies have evaluated primary or secondary prevention as large groups, whereas with a more specialised treatment the objective of this analysis was to focus on identifying specific high risk patient groups who are not controlled on current therapy and analyse the cost-effectiveness of alirocumab in these groups.

There are two main sources of uncertainty in the results; their importance reflects the inherent uncertainty in the estimates we have today and their impact on the model results:

5.11.1 Baseline CV risk

One of the key difficulties has been accurately establishing the current (not historical) baseline risk in key patient populations, most notably HeFH. The data currently included in the submission represents data from patients identified through an algorithm for Dutch Lipid criteria, not confirmed through genotyping or clinical diagnosis. Nevertheless, given the limitations of current publications and other data sources identified, and with a sample size of almost 3000 patients, we believe this is the most robust, UK-specific data we can use.

One limitation of the model is that it does not account for multiple events occurring within the same cycle. In the CV risk analysis conducted in THIN, patients were censored at their first event. These data are used to inform the model, and with one

year cycle lengths, this structure does not account for the potential impact on costs or quality of life of patients having multiple events in one year. Analyses of THIN data suggested that this is the case and that some patients do indeed suffer several events within the same year. This is not captured within the model, and in this sense the model estimates may be conservative. The issue of patients having repeated events within the same year will of course impact on hospital services and capacity as well as patients' quality of life.

5.11.2 Outcomes data

A second challenge is the lack of final outcomes data. This necessarily results in uncertainty in the analysis and indeed the link between LDL-C reduction and CV event reduction is the largest source of uncertainty. Nevertheless, there is strong data supporting the LDL-C hypothesis which means we consider it is appropriate to rely on this as a surrogate outcome. Moreover, data from genetic studies of PCSK9 mutations have shown a clear relationship between PCSK9 function, LDL-C, and CV events - in loss-of-function mutations, LDL-C is reduced and so is CV event risk [4, 10] [3, 52], while CV risk is increased in people with a PCSK9 gain-of-function mutation. Therefore, we considered it appropriate to use the meta-analysis by Navarese et al of PCSK9 inhibitor outcomes data to date. This necessarily has large confidence intervals due to the current immaturity of the data. Nevertheless, as an analysis of PCSK9 inhibitors we consider it the most appropriate source to inform this relationship. The results of the CVOT trial will inform future reviews of this guidance.

5.11.3 Other assumptions

The model is relatively robust to other assumptions around utility, costs, treatment discontinuation and duration.

6 Assessment of factors relevant to the NHS and other parties

6.1 Eligible patient population

The eligible population of alirocumab is estimated based on patients who have inadequately controlled LDL-C on current treatment, including patients on maximal tolerated dose of statins and those who are completely statin intolerant and receiving non-statin based lipid lowering therapies.

Similar to the CV risk study described in the cost-effectiveness model Section, a study was undertaken to understand the epidemiology of hyperlipidaemia in the UK. This study also used the THIN database, with similar coding and methodology to that described in Appendices 10 and 11. The inclusion criteria for the study were adults (≥18 years as of index date), with a high cardiovascular (CV) risk condition and continuous representation in THIN database for at least 2 years prior to the index date. The THIN study cohort was divided into mutually exclusive groups of different high CV risk conditions. These strata were further categorised according to LDL-C level.

These estimates were then scaled to the UK using published national prevalence figures based on the BHF 2014 cardiovascular disease (CVD) statistics for CHD and stroke. According to the Royal College of Physicians' National Sentinel Stroke Audit 2010, 88% of strokes are ischaemic in nature, so this percentage was applied to the BHF figure. HeFH was assumed to have a prevalence of 1 in 500 in the general population. An optimisation algorithm (Excel Solver) was used to estimate scaling factors for each mutually exclusive disease profile by minimising the difference between the weighted extrapolated totals for aggregate conditions, such as coronary heart disease (CHD) or ischaemic stroke, and their established national prevalence based on published sources. The scaling factors were then multiplied by the number of people within the THIN cohort with the respective patient profile.

Table 100 contains the total estimated patient numbers in the mutually exclusive strata.

Table 100 Extrapolated UK Country-Level Values for Mutually Exclusive Hierarchical CVD Sub-Populations, divided by LDL-C Level

1.	Condition							
	HeFH		Any record of ACS at any time*		Other CHD		Ischaemic stroke	
LDL-C level	Patient numbers	% of total	Patient numbers	% of total	Patient numbers	% of total	Patient numbers	% of total
Any	101,003	100	946,705	100	1,340,868	100	791,974	100
>1.81 mmol/L	96,753	95.79	567,118	59.90	896,315	66.85	497,699	62.84
≥2.59 mmol/L	86,098	85.24	225,344	23.80	404,576	30.17	217,520	27.47
≥3.36 mmol/L	70,590	69.89	74,781	7.90	149,674	11.16	76,065	9.60
≥3.62 mmol/L	65,238	64.59	48,903	5.17	102,393	7.64	51,421	6.49
≥3.88 mmol/L	61,473	60.86	36,834	3.89	76,531	5.71	36,709	4.64
≥4.14 mmol/L	56,921	56.36	23,496	2.48	49,052	3.66	24,047	3.04

*Includes ACS ≤ 12 months prior to index and ACS 12-24 months prior to index, as well as patients with a history of MI/UA.

6.1.1 HeFH

The prevalence of HeFH was estimated as 1:500, with a diagnosis rate of 15%, based on the UK national FH audit. In the decision problem we consider alirocumab for patients who are not able to reach LDL-C targets on maximal current therapy. Therefore, alirocumab will not be initiated at HeFH diagnosis, rather patients will cycle through different treatments to control their lipids (different statins, with the likely addition of ezetimibe). To estimate this we used Adelphi real-world data on the proportion of patients who were on third-line therapy. The patient flow for HeFH is show in Figure 39.

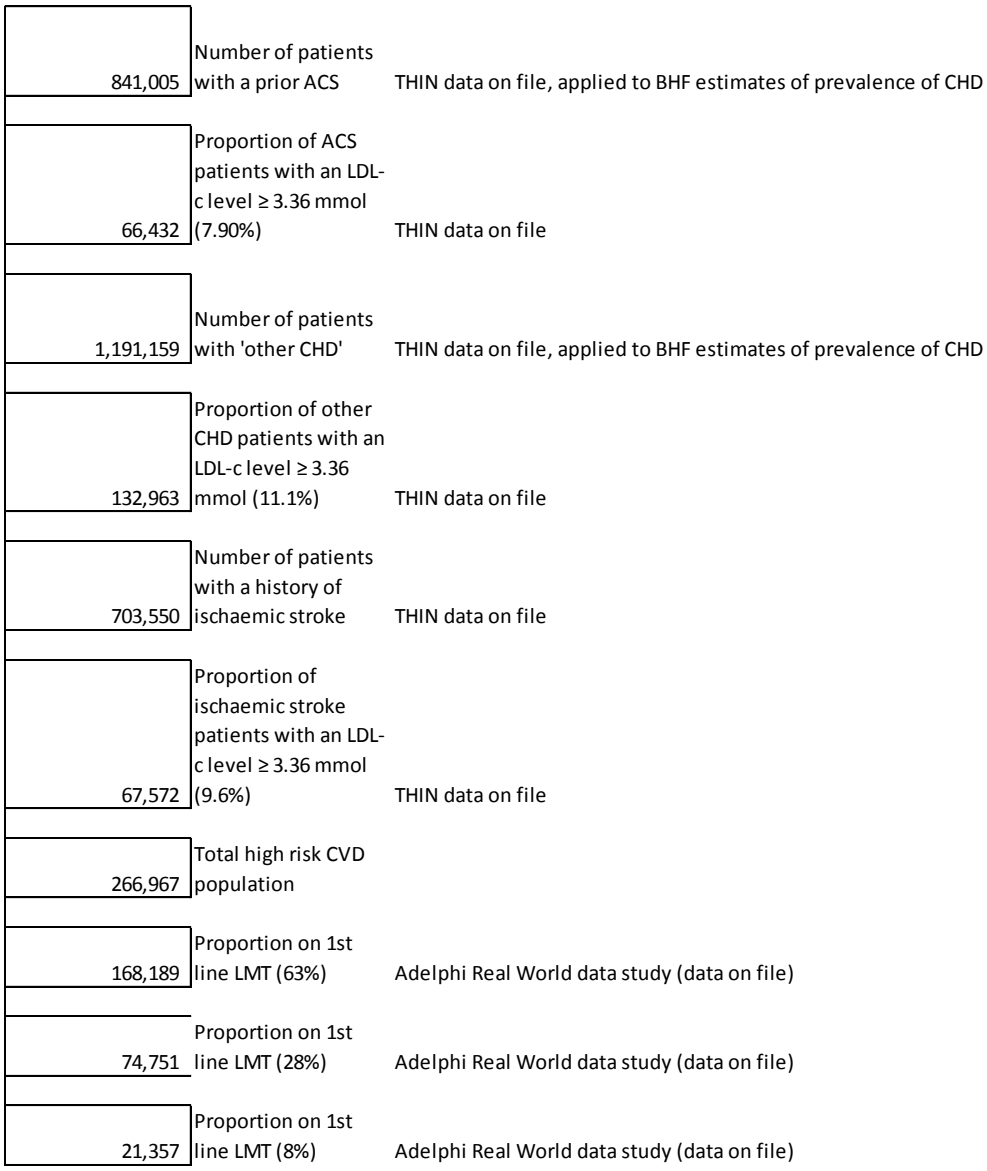
Figure 39: Patient flow for HeFH

Population flow	Estimate	Reference
56,948,229	Population of England and Wales (56948229)	Office for National Statistics (ONS) Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2013 - SUPERSEDED. File name used MYE2_population_by_sex_and_age_for_local_authorities_UK.xls
42,099,960	Adult population (18 - 79; 73.9%)	Office for National Statistics (ONS) Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2013 - SUPERSEDED. File name used MYE2_population_by_sex_and_age_for_local_authorities_UK.xls
84,369	Prevalence of HeFH (1:500)	The National Audit of the Management of Familial Hypercholesterolaemia 2010 NATIONAL REPORT December 2010 (Pedersen 2010)
12,655	Diagnosis rate of HeFH (15%)	The National Audit of the Management of Familial Hypercholesterolaemia 2010 NATIONAL REPORT December 2010 (Pedersen 2010)
7,340	Proportion on 1st line LMT (58%)	Adelphi Real World data study (data on file)
3,037	Proportion on 1st line LMT (24%)	Adelphi Real World data study (data on file)
1,772	Proportion on 1st line LMT (14%)	Adelphi Real World data study (data on file)
1,772	PCSK9 eligible population	

6.1.2 High risk CVD

2014 BHF figures on the prevalence of CHD, stroke and PAD were used. According to the Royal College of Physicians' National Sentinel Stroke Audit 20103, 88% of strokes are ischaemic in nature, so this percentage was applied to the BHF figure. An analysis of the THIN database was undertaken to identify patients with a history of ACS (at any time), other forms of CHD, stroke and PAD, using the same codes as were used for the analysis of CV risk reported above (see 5.3.2 and Appendix 11 and 12). This analysis was undertaken in a hierarchical fashion (i.e. groups were mutually exclusive) to avoid double-counting patients with a history of more than one event type. In addition to CV history, data on LDL-C levels was also collected. Scaling factors from the total UK prevalence figures were used to calculate the total number of patients by LDL-C levels. Again, in line with the assumption that patients would be trialled on different statins and potentially ezetimibe before being considered for alirocumab, real-world data on current treatment pathways showing the proportion of patients who have received at least 3 different lipid lowering therapies was then used. The patient flow for high risk CVD is shown in Figure 40.

Figure 40: Patient flow for high risk CVD



6.1.3 Recurrent events/ polyvascular disease

This is a subset of the high-risk CVD population. CV risk data from THIN showed approximately the same number of patients with polyvascular disease (ACS event, AND a history of ischaemic stroke OR PAD) as in the ischaemic stroke group. Therefore, the prevalence of ischaemic stroke was used as a proxy for this group. If patients with recurrent coronary events are included, the size of this group will be greater.

Again, in line with the assumption that patients would be trialled on different statins and potentially ezetimibe before being considered for alirocumab, real-world data on current treatment pathways showing the proportion of patients who have received at least 3 different lipid lowering therapies was then used. The patient flow is shown in Figure 41.

Figure 41: Patient flow for Recurrent events/ polyvascular disease

703,550	Number of patients with polyvascular disease	Estimates of ischaemic stroke population, used as proxy based on
193,234	Proportion of patients with an LDL-C ≥ 2.59 mmol/L (27%)	THIN data on file
121,737	Proportion on first-line (63%)	Adelphi Real world data study (data on file)
54,105	Proportion on second-line (28%)	Adelphi Real world data study (data on file)
15,459	Proportion on third-line (8%)	Adelphi Real world data study (data on file)

6.2 Current treatment options and uptake of technologies

An annual increase of 0.6% was assumed based on the predicted growth rate in the UK population. The numbers above came from mid-2013 estimates, so this increase rate was applied to provide prevalence estimates over the next 5 years as shown below in Table 101.

Table 101: Patient populations over next 5 years

	2016	2017	2018	2019	2020
HeFH (LDL-C ≥ 2.59 mmol/L)	1,804	1,815	1,826	1,836	1,848
High risk CVD (LDL-C ≥ 3.36 mmol/L)	21,744	21,875	22,006	22,138	22,271
Recurrent events/ polyvascular disease (LDL-C ≥ 2.59 mmol/L)	15,739	15,833	15,928	16,024	16,120

6.3 Current treatment options and uptake of technologies

Alirocumab will be used as an adjunct to current maximal therapy therefore no therapies will be displaced. Anticipated uptake rates are as follows. It is anticipated there will be a higher uptake rate in HeFH as compared to CVD as a whole (Table 102).

Table 102: Uptake assumptions

	2016	2017	2018	2019	2020
HeFH (LDL-C ≥ 2.59 mmol/L)	9%	12%	16%	22%	29%
High risk CVD (LDL-C ≥ 3.36 mmol/L)	2%	5%	14%	15%	16%
Recurrent events/ polyvascular disease (LDL-C ≥ 2.59 mmol/L)	2%	5%	14%	15%	16%

Estimates of patient numbers anticipated to receive alirocumab are provided below (Table 103).

Table 103: Numbers of patients estimated to receive alirocumab

	2016	2017	2018	2019	2020
HeFH (LDL-C ≥ 2.59 mmol/L)	158	214	291	395	537

High risk CVD (LDL-C ≥ 3.36 mmol/L)	326	984	2,971	3,321	3,563
Recurrent events/ polyvascular disease (LDL-C ≥ 2.59 mmol/L)	236	712	2,150	2,404	2,579

This gives an estimated drug cost budget as outlined in the table below, applying the UK list price. In estimating the NHS budget impact we conservatively assume 100% compliance, in line with the cost-effectiveness model (Table 104).

Note that there is overlap between the High Risk CVD and the Polyvascular/ Recurrent events population. Therefore results are presented disaggregated between populations.

Table 104: Drug cost budget

	2016	2017	2018	2019	2020
HeFH (LDL-C ≥ 2.59 mmol/L)	£691,789	£939,519	£1,275,961	£1,732,883	£2,353,428
High risk CVD (LDL-C ≥ 3.36 mmol/L)	£1,429,565	£4,314,427	£13,020,942	£14,554,519	£15,617,970
Recurrent events/ polyvascular disease (LDL-C ≥ 2.59 mmol/L)	£1,034,736	£3,122,835	£9,424,715	£10,534,737	£11,304,475

6.4 Other costs

In line with the assumptions in the economic analysis we do not consider alirocumab will be associated with other significant costs given routine monitoring of the high risk patients likely to be prescribed alirocumab and a rate of adverse events comparable to placebo in clinical trials.

6.5 Cost savings

In line with the economic analysis, it is estimated that alirocumab will reduce the risk of CV events and thereby lead to NHS savings on CV event costs. In the economic model we model event risks and events avoided over a lifetime. It is challenging to accurately translate this into cost savings to the NHS on an annual basis and to do so would require a number of simplifying assumptions. Therefore, we have focused on estimating the drug budget, as provided above.

In addition to CV events avoided, a potential impact of alirocumab on the NHS is to reduce the requirement for apheresis. This is a high cost treatment which some severe HeFH patients require. There is restricted capacity within the NHS to provide apheresis and anecdotally some patients who could benefit from apheresis do not. Reductions in apheresis requirements may improve capacity allowing more patients to benefit from currently scarce NHS resources.

6.6 Annual NHS budget impact

The budget impact based on the list price is therefore as estimated in Table 104.

6.8 Limitations of budget impact analysis

As described a key limitation of this analysis is the challenge in estimating the savings associated with avoiding CV events. In addition there is uncertainty about the potential uptake and about the long-term adherence to alirocumab. Nevertheless we consider the above estimates demonstrate a manageable budget impact. Alirocumab will be prescribed in a specialised care setting to patients who are at high CV risk, and who are unable to achieve LDL-c targets with any currently available therapy.

References

Reference List

1. Poirier,S. & Mayer,G. The biology of PCSK9 from the endoplasmic reticulum to lysosomes: new and emerging therapeutics to control low-density lipoprotein cholesterol. *Drug Des Devel. Ther.* **7**, 1135-1148 (2013).

2. Abifadel,M., Rabes,J.P., Boileau,C., & Varret,M. [After the LDL receptor and apolipoprotein B, autosomal dominant hypercholesterolemia reveals its third protagonist: PCSK9]. *Ann. Endocrinol. (Paris)* **68**, 138-146 (2007).

3. Cohen,J.C., Boerwinkle,E., Mosley,T.H., Jr., & Hobbs,H.H. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N. Engl. J. Med.* **354**, 1264-1272 (2006).

4. Goldstein,J.L. & Brown,M.S. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell* **161**, 161-172 (2015).

5. Libby,P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* **104**, 365-372 (2001).

6. Genest,J. 9th ed: 2011, Philadelphia, PA: Elsevier Saunders. in *Braunwald's Heart Disease - A Textbook of Cardiovascular Medicine.* (ed. Robert O.Bonow,M.D.L.M.M.F.D.P.Z.M.a.P.L.M.) (Elsevier Health Sciences, 2011).

7. Hubert,H.B., Feinleib,M., McNamara,P.M., & Castelli,W.P. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* **67**, 968-977 (1983).

8. Lewington,S. *et al.* Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* **370**, 1829-1839 (2007).

9. Sharrett,A.R. *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* **104**, 1108-1113 (2001).

10. Ference,B.A. *et al.* Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J. Am. Coll. Cardiol.* **60**, 2631-2639 (2012).

11. Humphries,S.E. *et al.* Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk. *J. Med. Genet.* **43**, 943-949 (2006).

12. Boekholdt,S.M. *et al.* Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J. Am. Coll. Cardiol.* **64**, 485-494 (2014).

13. Cannon,C.P. IMPROVE-IT trial: a comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes after acute coronary syndrome. Circulation 130, 2105.-2126. 2014.
Ref Type: Abstract

14. Cannon,C.P. *et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N. Engl. J. Med* **372**, 2387-2397 (2015).

15. CTT *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* **366**, 1267-1278 (2005).

16. CTT *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* **376**, 1670-1681 (2010).

17. CTT *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* **380**, 581-590 (2012).

18. CTT *et al.* Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* **385**, 1397-1405 (2015).

19. Gould,A.L., Davies,G.M., Alemao,E., Yin,D.D., & Cook,J.R. Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. *Clin. Ther.* **29**, 778-794 (2007).

20. Law,M.R., Wald,N.J., & Rudnicka,A.R. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* **326**, 1423 (2003).

21. Robinson,J.G., Smith,B., Maheshwari,N., & Schrott,H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J. Am. Coll. Cardiol.* **46**, 1855-1862 (2005).

22. Gould,A.L., Rossouw,J.E., Santanello,N.C., Heyse,J.F., & Furberg,C.D. Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation* **97**, 946-952 (1998).

23. NICE. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease; Clinical Guideline 181. 2014.
Ref Type: Online Source

24. NICE. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia, NICE technology appraisal guidance [TA132].

2007.
Ref Type: Online Source

25. NICE. Identification and management of familial hypercholesterolaemia, 2008 Clinical Guideline 71, https://www.nice.org.uk/guidance/cg71. 2008.
Ref Type: Online Source

26. Neil,A. *et al.* Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur. Heart J.* **29**, 2625-2633 (2008).

27. Benn,M., Watts,G.F., Tybjaerg-Hansen,A., & Nordestgaard,B.G. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *J. Clin. Endocrinol. Metab* **97**, 3956-3964 (2012).

28. Mundal,L. *et al.* Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992-2010. *J. Am. Heart Assoc.* **3**, e001236 (2014).

29. Reiner,Z. *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.* **32**, 1769-1818 (2011).

30. Pederson N, Humphries SE, Roughton M, & Besford. The National Audit of the Management of Familial Hypercholesterolaemia 2010 NATIONAL REPORT; Royal College of Physicians. 2010.
Ref Type: Online Source

31. Bonaca,M.P. *et al.* Long-term use of ticagrelor in patients with prior myocardial infarction. *N. Engl. J. Med.* **372**, 1791-1800 (2015).

32. Smolina,K., Wright,F.L., Rayner,M., & Goldacre,M.J. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. *Circ. Cardiovasc. Qual. Outcomes.* **5**, 532-540 (2012).

33. Bhatt,D.L. *et al.* Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur. Heart J.* **30**, 1195-1202 (2009).

34. Wilson,P.W. *et al.* An international model to predict recurrent cardiovascular disease. *Am. J. Med.* **125**, 695-703 (2012).

35. Subherwal,S. *et al.* Polyvascular disease and long-term cardiovascular outcomes in older patients with non-ST-segment-elevation myocardial infarction. *Circ. Cardiovasc. Qual. Outcomes.* **5**, 541-549 (2012).

36. Halcox,J.P. *et al.* Low rates of both lipid-lowering therapy use and achievement of low-density lipoprotein cholesterol targets in individuals at

high-risk for cardiovascular disease across Europe. *PLoS. One.* **10**, e0115270 (2015).

37. Bhatnagar,P., Wickramasinghe,K., Williams,J., Rayner,M., & Townsend,N. The epidemiology of cardiovascular disease in the UK 2014. *Heart* **101**, 1182-1189 (2015).

38. Robinson,J.G. *et al.* Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N. Engl. J. Med.* **372**, 1489-1499 (2015).

39. Navarese,E.P. *et al.* Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. *Ann. Intern. Med.* **163**, 40-51 (2015).

40. NICE. Cardiovascular Disease Prevention' NICE pathway. 2015.
Ref Type: Generic

41. NICE. 'Familial Hypercholesterolaemia' NICE pathway. 2015.
Ref Type: Generic

42. Joint Health Surveys Unit of Social and Community Planning Research and University College London. Health Survey for England. 2003. [Computer File] (3rd ed.). 2005. Colchester, Essex: UK Data Archive, [distributor], 2005. SN: 5098.
Ref Type: Generic

43. Joint Health Surveys Unit of Social and Community Planning Research and University College London. Health Survey for England. 2003. [Computer File] (3rd ed.). 2008. Colchester, Essex: UK Data Archive, [distributor], 2005. SN: 5098.
Ref Type: Generic

44. Abifadel et.al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia, Nature Genetics. 34(2), 154-156. 2003.
Ref Type: Generic

45. Foody,J.M. Familial hypercholesterolemia: an under-recognized but significant concern in cardiology practice. *Clin. Cardiol.* **37**, 119-125 (2014).

46. Raal,F., Panz,V., Immelman,A., & Pilcher,G. Elevated PCSK9 levels in untreated patients with heterozygous or homozygous familial hypercholesterolemia and the response to high-dose statin therapy. *J. Am. Heart Assoc.* **2**, e000028 (2013).

47. Gaudet,D. *et al.* Effect of alirocumab, a monoclonal proprotein convertase subtilisin/kexin 9 antibody, on lipoprotein(a) concentrations (a pooled analysis of 150 mg every two weeks dosing from phase 2 trials). *Am. J. Cardiol.* **114**, 711-715 (2014).

48. FDA. Praluent Prescribing information USA. 2015.
Ref Type: Online Source

49. HEART UK. LDL-Apheresis. 2015.
Ref Type: Online Source

50. Davidson,M.H. *et al.* Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists. *J. Clin. Lipidol.* **5**, 338-367 (2011).

51. Jarcho,J.A. & Keaney,J.F., Jr. Proof That Lower Is Better--LDL Cholesterol and IMPROVE-IT. *N. Engl. J. Med.* **372**, 2448-2450 (2015).

52. Packard,C.J., Weintraub,W.S., & Laufs,U. New metrics needed to visualize the long-term impact of early LDL-C lowering on the cardiovascular disease trajectory. *Vascul. Pharmacol.* **71**, 37-39 (2015).

53. Ference,B.A., Majeed,F., Penumetcha,R., Flack,J.M., & Brook,R.D. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both: a 2 x 2 factorial Mendelian randomization study. *J. Am. Coll. Cardiol.* **65**, 1552-1561 (2015).

54. Jacobson,T.A. *et al.* National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. *J. Clin. Lipidol.* **8**, 473-488 (2014).

55. Kastelein,J.J. *et al.* Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation* **117**, 3002-3009 (2008).

56. Boekholdt,S.M. *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* **307**, 1302-1309 (2012).

57. Di Angelantonio E. *et al.* Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* **302**, 1993-2000 (2009).

58. Di Angelantonio E. *et al.* Lipid-related markers and cardiovascular disease prediction. *JAMA* **307**, 2499-2506 (2012).

59. Erqou,S. *et al.* Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* **302**, 412-423 (2009).

60. Matza,L.S. *et al.* Acute and chronic impact of cardiovascular events on health state utilities. *BMC. Health Serv. Res.* **15**, 173 (2015).

61. Matza,L.S. *et al.* Acute and chronic impact of cardiovascular events on health state utilities. *BMC. Health Serv. Res* **15**, 173 (2015).

62. Slack,J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. *Lancet* **2**, 1380-1382 (1969).

63. Mohrschladt,M.F., Westendorp,R.G., Gevers Leuven,J.A., & Smelt,A.H. Cardiovascular disease and mortality in statin-treated patients with familial hypercholesterolemia. *Atherosclerosis* **172**, 329-335 (2004).

64. JBS3 Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* **100 Suppl 2**, ii1-ii67 (2014).

65. Ference,B.A. & Mahajan,N. The role of early LDL lowering to prevent the onset of atherosclerotic disease. *Curr. Atheroscler. Rep.* **15**, 312 (2013).

66. Packard,C.J., Ford,I., Murray H, & McCowan C. Lifetime clinical and economic benefits of statin-based LDL lowering in the 20-year follow-up of the West of Scotland Coronary Prevention Study. American Heart Associations scientific sessions . 2014.
Ref Type: Abstract

67. Hebert,P.R., Gaziano,J.M., Chan,K.S., & Hennekens,C.H. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *JAMA* **278**, 313-321 (1997).

68. Stone,N.J. *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. *Circulation* **129**, S1-45 (2014).

69. Eckel,R.H. Approach to the patient who is intolerant of statin therapy. *J. Clin. Endocrinol. Metab* **95**, 2015-2022 (2010).

70. Alfirevic,A. *et al.* Phenotype standardization for statin-induced myotoxicity. *Clin. Pharmacol. Ther.* **96**, 470-476 (2014).

71. Simons,L.A., Levis,G., & Simons,J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. *Med. J. Aust.* **164**, 208-211 (1996).

72. Nair RK, Karadi RL, & Kilpatrick ES Managing patients with 'statin intolerance': a retrospective study. *The British Journal of Cardiology* **15**, 158-160 (2008).

73. Guyton,J.R., Bays,H.E., Grundy,S.M., Jacobson,T.A., & The National Lipid Association An assessment by the Statin Intolerance Panel: 2014 update. *J. Clin. Lipidol.* **8**, S72-S81 (2014).

74. NICE. **Lipid-modifying drugs** NICE advice [KTT3]. 2015.
Ref Type: Online Source

75. JBS2 JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* **91 Suppl 5**, v1-52 (2005).

76. Soran,H., Schofield,J.D., & Durrington,P.N. Cholesterol, not just cardiovascular risk, is important in deciding who should receive statin treatment. *Eur. Heart J.*(2015).

77. Sanofi DOF. Data on File - UK Hospital vs Retail Ezetimibe Sales, September 2015, [SAGB.ALI.15.09.1061]. 2015.
Ref Type: Generic

78. NHS Choices. High Cholesterol. 2015.
Ref Type: Online Source

79. Higgins JPT & Green S. Cochrane Handbook for Systematic Reviews of Interventions. 2011.
Ref Type: Online Source

80. Moher,D., Liberati,A., Tetzlaff,J., & Altman,D.G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J. Clin. Epidemiol.* **62**, 1006-1012 (2009).

81. Stein,E.A. *et al.* Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. *Lancet* **380**, 29-36 (2012).

82. McKenney,J.M. *et al.* Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J. Am. Coll. Cardiol.* **59**, 2344-2353 (2012).

83. Moriarty,P.M. *et al.* Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. *J. Clin. Lipidol.* **8**, 554-561 (2014).

84. Stroes,E. *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.* **63**, 2541-2548 (2014).

85. Roth,E.M., McKenney,J.M., Hanotin,C., Asset,G., & Stein,E.A. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N. Engl. J. Med.* **367**, 1891-1900 (2012).

86. Kastelein,J.J. *et al.* ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur. Heart J.*(2015).

87. Kereiakes,D.J. *et al.* Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. *Am. Heart J.* **169**, 906-915 (2015).

88. Cannon,C.P. *et al.* Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled

hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur. Heart J.* **36**, 1186-1194 (2015).

89. Bays,H. *et al.* Alirocumab as Add-On to Atorvastatin Versus Other Lipid Treatment Strategies: ODYSSEY OPTIONS I Randomized Trial. *The Journal of Clinical Endocrinology & Metabolism* **100**, 3140-3148 (2015).

90. Moriarty,P.M. *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*.

91. Roth,E.M. *et al.* Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. *Int. J. Cardiol.* **176**, 55-61 (2014).

92. EuroQol Group. EQ-5D. 2015.
Ref Type: Online Source

93. Grundy,S.M. *et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* **110**, 227-239 (2004).

94. Broome S Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* **303**, 893-896 (1991).

95. World Health Organisation (WHO). Familial Hypercholesterolaemia (FH): Report of a second
WHO consultation. 1998.
Ref Type: Online Source

96. Perk,J. *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.* **33**, 1635-1701 (2012).

97. Little,R.J. *et al.* The prevention and treatment of missing data in clinical trials. *N. Engl. J. Med.* **367**, 1355-1360 (2012).

98. Bland,J.M. & Altman,D.G. Multiple significance tests: the Bonferroni method. *BMJ* **310**, 170 (1995).

99. Cochrane. Cochrane Collaboration's tool for assessing risk of bias. 2015.
Ref Type: Online Source

100. NICE. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease; Clinical Guideline 181 Appendices. 2014.

Ref Type: Online Source

101. Dolan P, Gudex C, Kind P, & Williams A. A social tariff for EuroQol: results from a UK general population survey;Discussion paper 138. 1995.
Ref Type: Online Source

102. Zhang,X.L. *et al.* Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. *BMC. Med.* **13**, 123 (2015).

103. Li,C. *et al.* 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.* **4**, e001937 (2015).

104. Stroup,D.F. *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **283**, 2008-2012 (2000).

105. Jadad,A.R. *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin. Trials* **17**, 1-12 (1996).

106. Higgins,J.P., Thompson,S.G., Deeks,J.J., & Altman,D.G. Measuring inconsistency in meta-analyses. *BMJ* **327**, 557-560 (2003).

107. Fleiss,J.L. Analysis of data from multiclinic trials. *Control Clin. Trials* **7**, 267-275 (1986).

108. Beynon,R. *et al.* Search strategies to identify diagnostic accuracy studies in MEDLINE and EMBASE. *Cochrane. Database. Syst. Rev.* **9**, MR000022 (2013).

109. Robinson,J.G. *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* **311**, 1870-1882 (2014).

110. Koren,M.J. *et al.* Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. *J. Am. Coll. Cardiol.* **63**, 2531-2540 (2014).

111. Raal,F.J. *et al.* PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* **385**, 331-340 (2015).

112. Blom,D.J. *et al.* A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N. Engl. J. Med.* **370**, 1809-1819 (2014).

113. Sabatine,M.S. *et al.* Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N. Engl. J. Med.* **372**, 1500-1509 (2015).

114. Schwartz,G.G. *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.* **168**, 682-689 (2014).

115. O'Keefe et.al. Optimal low-density lipoprotein is 50 to 70 mg/dl Lower is better and physiologically normal. J Am Coll Cardiol 43(11), 2142-2146. 2004.
Ref Type: Generic

116. National Institute for Health and Care Excellence. Ticagrelor for the treatment of acute coronary syndromes. NICE Technology Appraisal Guidance 236. 2015.
Ref Type: Online Source

117. National Institute for Health and Care Excellence. Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome> NICE Technology Appraisal Guidance 335. 2015.
Ref Type: Online Source

118. Alnasser et.al. Late Consequences of Acute Coronary Syndromes: Global Registry of Acute Coronary Events (GRACE) Follow-up. The American Journal of Medicine 128, 766-775. 2015.
Ref Type: Generic

119. Jernberg et.al. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. European Heart Journal . 2014.
Ref Type: Generic

120. THIN. The Health Improvement Network (THIN). 2015.
Ref Type: Online Source

121. Hippisley-Cox,J. *et al.* Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* **336**, 1475-1482 (2008).

122. Office for National Statistics. Interim Life Tables, United Kingdom. Based on data from 2011-2013. 2014.
Ref Type: Online Source

123. Office for National Statistics. Mortality Statistics: Deaths Registered in England and Wales (Series DR), 2013. 2014.
Ref Type: Online Source

124. Sanofi DOF. Data on File - Ezetimibe Formulary Access in England, September 2015, [SAGB.ALI.15.09.1060]. 2015.
Ref Type: Generic

125. Herrett,E. *et al.* Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ* **346**, f2350 (2013).

126. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. *Atherosclerosis* **142**, 105-112 (1999).

127. Besseling et.al. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: A study of a cohort of 14,000 mutation carriers, Atherosclerosis. 233, 219-223. 2014.
Ref Type: Generic

128. Versmissen,J. *et al.* Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* **337**, a2423 (2008).

129. Ara,R. & Wailoo AJ. NICE DSU Technical Support Document 12: The use of health state utility values in decision models. 2011.
Ref Type: Online Source

130. Ara,R. & Brazier,J.E. Populating an economic model with health state utility values: moving toward better practice. *Value. Health* **13**, 509-518 (2010).

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Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Dear Charlie,

The Evidence Review Group, Aberdeen HTA Group and the technical team at NICE have now had an opportunity to take a look at the submission received on the 1 October by Sanofi. 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** on **6 November**. 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 via this link:
https://appraisals.nice.org.uk/request/8737

If you have any further queries on the technical issues raised in this letter then please contact Jasdeep Hayre, Technical Lead (jasdeep.hayre@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

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Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **PRIORITY**. Two systematic reviews have been conducted by the company. Review 1 focused on patients at high risk of cardiovascular disease (CVD) and included a total of 32 studies from 30 papers (Figure 5, page 51). A separate modified review, Review 2, focused on patients at moderate or high CVD risk and identified 20 studies published in 18 papers (Figure 6, page 55). Please state which review (Review 1, Review 2 or both) identified the 10 relevant RCTs from ODYSSEY included in the company's evidence submission.

A2. **PRIORITY.** The company states on page 52 that "None of the included studies were conducted in patients who were intolerant to statins or for whom statins are not appropriate (defined as population 2 in the PICOS framework). Several alirocumab and evolocumab studies were identified in this population, but included patients with moderate CV risk as well as high CV risk patients (ODYSSEY ALTERNATIVE, GAUSS, GAUSS-2) and hence were not included in the review (Review 1)." ALTERNATIVE is among the relevant RCTs (Table 2, page 20) assessed in the submission and statin intolerant patients were included in this trial. Please clarify why ALTERNATIVE was subsequently considered appropriate for inclusion in the submission?

A3. Review 1 included studies with homozygous familial hypercholesterolaemia patient populations such as Gagne 2002 and Raal 2015 (Appendix 8.2.3.1, page 10). Please clarify if homozygous familial hypercholesterolaemia was considered as a part of the relevant patient population for this systematic literature review.

A4. Table 8, page 57: The table includes only trials from ODYSSEY. Please clarify why trials of evolocumab, ezetimibe plus statins and Teramoto 2014 included in Review 1 and Review 2, were subsequently excluded from the list of relevant RCTs.

A5. Results for OPTIONSI and OPTIONSII (Table 2, page 20): Using results from Tables 25 and 26 (pages 134 to 137) the estimates should have negative signs as they represent the differences in the 'change from baseline' between alirocumab and its comparator. Please provide the correct effect estimates for OPTIONSI and OPTIONSII.

A6. **PRIORITY.** Table 2, page 20: Please provide 95% CIs to the reported effect estimates for all trials.

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A7. Table 8, page 57: List of relevant RCTs: Please clarify whether the following Phase II trials were retrieved from Review 1 or from Review 2.

Trial number	**Source of trial**
DFI11566	
CL-1018	
DFI12361	
CL-1308	
EFC13786	
EFC 13672	

A8. **PRIORITY.** Tables 19 to 30 show the estimates of percentage (%) change from baseline for each treatment group. Please provide the estimates and the associated 95% CI for the difference in % change in LDL-C between alirocumab and comparators.

A9. **PRIORITY.** Please provide the equivalent of Table 31, page 142 (EQ-5D data) for each of the trials separately and for each of the treatment groups.

A10. **PRIORITY.** Table 36, page 156: Please provide 95% CI for each of the estimates for in the table.

A11. **PRIORITY**. In the UK there were 36 NHS centres across 6 trials (FHI, FHII, LONG TERM, OPTIONSI, OPTIONSII, ALTERNATIVE). Please provide the number of patients per trial and for each treatment group from the UK.

A12. **PRIORITY**. Appendix 8.2.3.1, page 10, The company's submission only includes the ODYSSEY phase III trials in the review of clinical effectiveness and ignores Phase II trials assessing alirocumab. Please give the rationale for including Phase II trials in the safety analyses but not in the efficacy analyses. Please include the reason why ODYSSEY phase II results were not included in the review of clinical effectiveness.

A13. **PRIORITY**. Figure 9, page 109 shows the estimates of calculated LDL-C and measured LDL-C for LONGTERM. The submission states that the two methods show similar results but Figure 9 shows that the calculated LDL-C values are greater than the measured LDL-C values for alirocumab. However, calculated LDL-C is less than measured LDL-C for placebo. Consequently, the choice of using calculated LDL-C,

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instead of measured LDL-C, is likely to increase the difference between intervention groups. Please explain why calculated LDL-C was used throughout the submission.

Section B: Clarification on cost-effectiveness data

B1. **PRIORITY.** Please provide more detail on the THIN data analysis cohort relating to the type of medications that patients were receiving. Please include the proportion of patients on high dose, high intensity statins or other types of lipid modification therapy.

B2. **PRIORITY.** Please provide more detail on how CV-related deaths have been calculated in the THIN data analysis for those patients whose cause of death is not recorded.

B3. Table 60, page 207: The standard errors around the mean percent reduction in LDL-C in Table 60 of the submission are different from those in the model for "vs placebo". For example, the standard error values for "FH" were 1.9% in Table 60 (2.1% in the model), and for "monotherapy" for "High CV Risk" 1.6% (1.4% in the model) and "as add-on to statin" 3.2% (2.3% in the model). Please indicate which mean percent reduction in LDL-C and standard errors for "Vs. Placebo" are correct.

B4. **PRIORITY:** Page 209. Please provide further justification for the approach used to estimate the relationship between absolute LDL-C reductions (per 1 mmol/L) and reductions in CV events for PCSK9 inhibitors (section 5.3.1 in the submission); Please include the rationale for assuming a steeper log-linear relationship between LDL-C reductions and the relative risks of CV events with PCSK9 inhibitors as compared with statins.

B5. **PRIORITY:** Page 211. Please provide more detail on how the mean value of 1.6 mmol/L reduction in LDL-C has been estimated from the trials included in Navarese et al. Please state if all trials been used to estimate this reduction or only trials used in the meta-analysis of MI events.

B6. **PRIORITY.** Base case analysis: No results were presented in the Navarese et al.meta-analysis for the effect of PCSK9 inhibitors on ischaemic stroke (IS) (Table 61, page 211) and was assumed to be the same as for other non-fatal CV events. Please provide the rationale for applying the same hazard ratio for non-fatal myocardial infarction (MI) to IS.

B7. **PRIORITY.** Page 211**:** Please clarify how the 95% CIs for the estimated hazard ratios, per mmol/L reduction LDL-C, have been calculated using data from Navarese et al.

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B8. Please detail the methods by which the annual age adjustment for CV risk (3%) and for non-fatal CV events (5%) were selected (based on Wilson et al. 2012). Please state if alternative sources were considered.

B9. In the model "Introduction Worksheet", "Descriptive CV Risk" tab, the values for the "CV Event Probabilities* (Hierarchical Sub-Populations)" and "CV Event Probabilities* (Prevalent Sub-Populations)" are inconsistent with the results presented in Appendix 11, Analysis of THIN of CV risk. Please clarify which set of CV event probabilities are correct. Please supply more detail of the "descriptive Kaplan-Meier analyses from the THIN database" (section 5.3.2 in the submission) which is used to calculate CV risk in the model.

B10. **PRIORITY.** The submission states that health–related quality of life was assessed in 7 ODYSSEY trials using the EQ-5D. Please confirm if country-specific value sets were used (for example that the set of weights that represent the UK general population's values were applied to generate the EQ-5D utilities in the 36 UK centres).

B11. Table 63, page 218: Please provide baseline utilities from ODYSSEY for UK subjects compared with non-UK subjects.

B12. Table 65, page 222: The mean values for CV event based utilities do not correspond to the values in the model. Please clarify which CV event disutility multipliers are the correct. Similarly, some of the multipliers in Table 66, page 223 and those used in the model show small discrepancies. Please clarify which values are considered correct.

Table 65	**Submission**	**Model**
NF MI/UA/ACS first year	0.765	0.763
Ischaemic stroke	0.775	0.773
NF MI Second Year/Stable beyond 2	0.906	0.903
UA Second Year/Stable beyond 2 years	0.960	0.957
ACS Second Year/Stable beyond 2 years	0.924	0.922
IS second year	0.822	0.820

Table 66	**Submission**	**Model**
HeFH (secondary prevention)	0.924	0.922
ACS (0-12 months)	0.765	0.763
ACS (13-24 months)	0.924	0.922
CHD	0.924	0.922
PAD	0.924	0.922
History of IS	0.822	0.820

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B13. Table 85, page 250: Please justify the selection of the 3 to 8% discontinuation rate per year for sensitivity analyses. Does this reflect the average discontinuation rates associated with all the ODYSSEY trials of 52 weeks follow-up or longer (i.e. including LONGTERM)?

B14. Please provide the year (and sources) used to estimate cost data in the economic model Table 68, page 228: Please provide more information on drug acquisition costs; e.g. tablet pack sizes and prices, and version of the BNF source.

B15. Please provide the rationale for the "Cohort Proportions on Statin as Background Therapy (%)" used in the model for atorvastatin: 40mg (20%), 80mg (50%), and Rosuvastatin: 20mg (10%), 40 mg (20%).

B16. **PRIORITY**. Please explain why ongoing (post-event) costs were applied for up to 3 years following the event and not in the longer term.

B17. In Table 87, page 252 after applying 8% discontinuation rate, the estimated ICER for the HeFH secondary prevention population decreased compared to the basecase (using a 0% discontinuation rate). Scenario analyses of increased discontinuation in other populations increase the estimated ICERs compared to the basecase(s). Please explain why higher discontinuation rates in the HeFH secondary prevention population decreases the estimated ICERs.

B18. Table 99, page 264: Please clarify whether the baseline LDL value of 4.13 should be 4.14 as described in Table 57, page 203.

B19. **PRIORITY.** Table 60, page 206: Please list the trials/source for each mean % changes in LDL-C values Please insert an additional column indicating the specific clinical studies that were pooled and what assumptions have been made – it is not clear why the pooled estimates for the high CV risk group reported in Table 60 do not seem to match those reported in Tables 36 and 37 in the clinical effectiveness chapter.

B20. Page 191: Please provide a reference for applying 3.36 mmol/L as the baseline LDL-C threshold in patients with high risk CVD.

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Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Section A: Clarification on effectiveness data

A1. **PRIORITY**. Two systematic reviews have been conducted by the company. Review 1 focused on patients at high risk of cardiovascular disease (CVD) and included a total of 32 studies from 30 papers (Figure 5, page 51). A separate modified review, Review 2, focused on patients at moderate or high CVD risk and identified 20 studies published in 18 papers (Figure 6, page 55). Please state which review (Review 1, Review 2 or both) identified the 10 relevant RCTs from ODYSSEY included in the company's evidence submission.

Review 1 identified 8 alirocumab Phase III RCTs: FH I, FH II, High FH, LONG-TERM, COMBO I, COMBO II, OPTIONS I and OPTIONS II.

Review 2 identified the above 8 RCTs and also included MONO and ALTERNATIVE.

A2. **PRIORITY.** The company states on page 52 that "None of the included studies were conducted in patients who were intolerant to statins or for whom statins are not appropriate (defined as population 2 in the PICOS framework). Several alirocumab and evolocumab studies were identified in this population, but included patients with moderate CV risk as well as high CV risk patients (ODYSSEY ALTERNATIVE, GAUSS, GAUSS-2) and hence were not included in the review (Review 1)." ALTERNATIVE is among the relevant RCTs (Table 2, page 20) assessed in the submission and statin intolerant patients were included in this trial. Please clarify why ALTERNATIVE was subsequently considered appropriate for inclusion in the submission?

Review 1 was designed to identify studies focussing on patients at high cardiovascular risk, and therefore excluded MONO and ALTERNATIVE, as MONO was conducted in patients with moderate CV risk (100%) and ALTERNATIVE included some patients at moderate CV risk (17.6% of the total trial population). The objective of Review 2 was to identify studies of all PCSK9 inhibitors (alirocumab and evolocumab) and in this review it was considered relevant not to restrict solely to patients at high CV risk. This was particularly in light of the fact that evolocumab trials did not exclude patients at low or moderate CV risk (whereas ODYSSEY, except for ALTERNATIVE and MONO, did exclude such patients) and in the PROFICIO programme 40% of patients in the integrated cohort submitted to the EMA were moderate CV risk, and 13% were low CV risk. This also allowed the inclusion of ALTERNATIVE (see discussion below).

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ALTERNATIVE is the main source of evidence to inform the efficacy and safety of alirocumab used as a monotherapy (or as an adjunct to non-statin-based LMT) in statin-intolerant patients. ALTERNATIVE was excluded from the original review 1 on the basis that it included moderate CV risk patients. However, this does not mean it is not informative for the decision problem in this submission, particularly given that it is the main trial in statin-intolerant population. Moreover, a high proportion (82.4%) of patients in ALTERNATIVE were at high CV risk.

A3. Review 1 included studies with homozygous familial hypercholesterolaemia patient populations such as Gagne 2002 and Raal 2015 (Appendix 8.2.3.1, page 10). Please clarify if homozygous familial hypercholesterolaemia was considered as a part of the relevant patient population for this systematic literature review.

Review 1 included patients at high CV risk, including patients with familial hypercholesterolaemia. This definition includes patients with homozygous familial hypercholesterolaemia, and therefore studies conducted in these patients were included. However, given that there are no trials evaluating alirocumab in this patient population, and that the alirocumab licence does not include homozygous familial hypercholesterolaemia, studies in this population are not considered as relevant to the decision problem addressed in this submission.

A4. Table 8, page 57: The table includes only trials from ODYSSEY. Please clarify why trials of evolocumab, ezetimibe plus statins and Teramoto 2014 included in Review 1 and Review 2, were subsequently excluded from the list of relevant RCTs.

The reason for this is that the pivotal trial programme provides sufficient evidence to address the relative effectiveness of alirocumab. As outlined in our submission (section 1.5), we do not consider evolocumab to be a relevant comparator, because it is not standard NHS practice, and because it is still in the appraisal process with NICE. We consider the most appropriate evaluation is of alirocumab as an adjunct to existing maximal therapy (i.e. maximal tolerated dose of statins plus ezetimibe, or maximal tolerated dose statins alone, or as an adjunct to ezetimibe monotherapy in statin-intolerant patients). This means a comparison versus no additional active comparator. The ODYSSEY programme provides data evaluating alirocumab as an adjunct to:

- maximal tolerated dose of statins plus ezetimibe
- maximal tolerated dose of statins (without ezetimibe)
- non-statin-based lipid lowering therapy

We evaluate comparisons directly versus ezetimibe in scenario analyses. ODYSSEY also provides data directly comparing alirocumab versus ezetimibe both on a

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background of statin-based therapy and on a background of non-statin-based therapy. Therefore, in both of these situations, there is direct evidence available from the pivotal Phase III trial programme, so the additional trials of ezetimibe plus statins captured in the systematic review are not necessary to inform the decision problem.

A5. Results for OPTIONSI and OPTIONSII (Table 2, page 20): Using results from Tables 25 and 26 (pages 134 to 137) the estimates should have negative signs as they represent the differences in the 'change from baseline' between alirocumab and its comparator. Please provide the correct effect estimates for OPTIONSI and OPTIONSII.

These are provided in the answer to question A7 below in an updated Table 2. Note that with regards to question A7, the results from OPTIONS have 99% and 98.75% CIs due to the powering of these trials.

A6. **PRIORITY.** Table 2, page 20: Please provide 95% CIs to the reported effect estimates for all trials.

These are shown in a revised version of table 2 below. There were some slight errors due to rounding in the numbers presented in the original table 2 which are corrected below (e.g. 34.3% not 34.2% for the difference between alirocumab and rosuvastatin uptitration in OPTIONS II).

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Table 1: Revised version of Table 2 from submission

Trial no. (acronym) Patient Numbers (N)	Intervention/ Comparator	Population	High/Very High CV risk patients (%)	Primary Outcome – Mean percentage change in LDL-C from baseline at Week 24	
				vs Placebo	vs Ezetimibe
EFC12492 (FH I) N = 486	Alirocumab vs Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs	100	-57.9% (p<0.0001) (95% CI: -63.3 to -52.6)	
CL-1112 (FH II) N = 249	Alirocumab vs Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs	100	-51.4% (p<0.0001) (95% CI: -58.1 to -44.9)	
EFC12732 (HIGH FH) N = 107	Alirocumab vs Placebo	Patients with HeFH not adequately controlled with statin ± other LMTs and with LDL-C ≥160 mg/dL (4.14 mmol/L)	100	-39.1% (p<0.0001) (95% CI: -51.1 to -27.1)	
EFC11568 (COMBO I) N = 316	Alirocumab vs Placebo	Patients at high CV risk with hypercholesterolaemia not adequately controlled with statin ± other LMTs	100	-45.9% (p<0.0001) (95% CI: -52.5 to -39.3)	
EFC11569 (COMBO II) N = 720	Alirocumab vs Ezetimibe	Patients at high CV risk with hypercholesterolaemia not adequately controlled with statin therapy	100		-29.8% (p<0.0001) (95% CI: -34.4 to -25.3)
LTS11717 (LONG TERM) N = 2341	Alirocumab vs Placebo	Patients with HeFH or non-FH at high CV risk not adequately controlled with a statin ± other LMTs	100	-61.9% (p<0.0001) (95% CI: -64.3 to -59.4),	
CL-1119 (ALTERNATIVE) N = 314	Alirocumab vs Ezetimibe, Atorvastatin	Patients with primary hypercholesterolaemia and moderate, high, or very high CV risk who are intolerant to statins.	82.4		-30.4% (p<0.0001) (95% CI: -30.6 to -24.2)
EFC11716 (MONO) N =103	Alirocumab vs Ezetimibe	Patients at moderate CV risk with LDL-C ≥100 mg/dL	0		-31.6% (p<0.0001) (95% CI: -40.2 to -23.0)

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		(2.59 mmol/L) and ≤190 mg/dL (4.91 mmol/L)			
				vs Statin Up-titration	vs Ezetimibe
CL-1110 (OPTIONS I) N = 355	Alirocumab + Atorvastatin vs Atorvastatin+Ezetimibe; Atorvastatin (up-titrated); Rosuvastatin (switch)	Patients at high CV risk with non-FH or HeFH not adequately controlled with atorvastatin (20 mg or 40 mg) ± other LMT excluding ezetimibe	100	1. Atorva 20mg: -39.1% (p<0.0001) (99% CI: -55.9 to -22.2) 2. Atorva 40mg -49.2% (p<0.0001) (99% CI: -65.0 to -33.5); 3. Rosuva Switch: -32.6% (p<0.0001) (99% CI:-48.4 to -16.9)	1. - 23.6% (p<0.0001) (99% CI: -40.7 to -6.5) 2. -31.4% (p<0.0001) (99% CI: -47.4 to -15.4)
CL-1118 (OPTIONS II) N = 305	Rosuvastatin+Alirocumab vs Rosuvastatin+Ezetimibe; Rosuvastatin (up-titrated)	Patients at high CV risk with non-FH or HeFH not adequately controlled with rosuvastatin (10 mg or 20 mg) ± other LMT excluding ezetimibe	100	1. Rosuva 10mg: -34.2% (p<0.0001) (98.75% CI [-49.2 to -19.3); 2. Rosuva 20mg: -20.3 % (p=0.0453) (98.75% CI: -45.8 to 5.1)	1. -36.1% (p<0.0001) (98.75% CI: -51.5 to -20.7) 2. - 25.3% (p=0.0136) (98.75% CI: -50.9 to 0.3)

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A7. Table 8, page 57: List of relevant RCTs: Please clarify whether the following Phase II trials were retrieved from Review 1 or from Review 2.

Sources for these are provided in Table 2.

Table 2: Sources for Phase II and additional Phase III RCTs

Trial number	Source of trial
DFI11565	Review 1
CL-1003	Review 1
DFI11566	Review 1
CL-1018	Not yet published – company trial
DFI12361	Not yet published – company trial
CL-1308	Not yet published - company trial
EFC13786	Not yet published – company trial
EFC 13672	Not yet published – company trial

A8. **PRIORITY.** Tables 19 to 30 show the estimates of percentage (%) change from baseline for each treatment group. Please provide the estimates and the associated 95% CI for the difference in % change in LDL-C between alirocumab and comparators.

These values are provided in table 3 – 5 below.

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Table 3: Mean percentage change in calculated LDL-C for alirocumab versus comparator – ITT analyses

Comparison	Mean percentage change in calculated LDL-C for alirocumab versus comparator from pivotal Phase III trials (95% CI)							
	FH I	FH II	High FH	LONG-TERM	COMBO I	COMBO II	ALTERNATIVE	MONO
	Week 12							
Versus placebo	-49.5% (95% CI: -54.2 to -44.8);	-48.4% (95% CI, -54.7% to -42.2%)	-40.3% (95% CI: -51.4 to -29.3)	-64.8 % (95% CI: -67.2 to -62.4)	-49.3% (95% CI: -55.3 to -43.3)			
Versus ezetimibe						-29.4% (95% CI: -33.7 to -25.1)	-31.5 (95% CI: -36.9 to -26.1)	-28.5% (95% CI: -35.7 to -21.2)
	Week 24							
Versus placebo	-57.9% (95% CI: -63.3 to -52.6)	-51.5% (95% CI: -58.1 to -44.9)	-39.1% (95% CI: -51.1 to -27.1)	-61.9% (95% CI: -64.3 to -59.4)	-45.9% (95% CI: -52.5 to -39.3)	-	-	-
Versus ezetimibe	-	-	-	-	-	-29.8% (95% CI: -34.4 to -25.3)	-30.4% (95% CI: -30.6 to -24.2)	-31.6% (95% CI: -40.2 to -23.0)
	Week 52							
Versus placebo	-56.2% (95% CI: -	-58.8% (95% CI: -	-39.1% (95% CI: -	-61.3% (95% CI: -	-43.0% (95% CI: -			

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	62.4 to -50.0)	66.8 to -50.8)	53.6 to -24.6)	64.1 to -58.4)	51.6 to -34.3)			
Versus ezetimibe						-31.2% (95% CI: -36.3 to -26.1)	NR	NR

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Table 4: Mean percentage change in calculated LDL-C for alirocumab versus comparator – OPTIONS I – trial – ITT analysis

Comparison:	Mean percentage change from baseline (%)
	OPTIONS I
Week 12	
Alirocumab + atorvastatin 20 mg versus atorvastatin uptitration to 40 mg	-39.8% (95% CI: -54.0 to -25.6)
Alirocumab + atorvastatin 20 mg versus addition of ezetimibe to atorvastatin 20 mg	-25.8% (95% CI: -40.0 to -11.6)
Alirocumab + atorvastatin 40 mg versus atorvastatin uptitration to 80 mg	-36.0% (95%CI: -47.7 to -24.3)
Alirocumab + atorvastatin 40 mg versus addition of ezetimibe to atorvastatin 40 mg	-20.9% (95%CI: -32.8 to -8.9)
Alirocumab + atorvastatin 40 mg versus switch to rosuvastatin 40 mg	-27.3% (95% CI: -39.2 to -15.4)
Week 24	
Alirocumab + atorvastatin 20 mg versus atorvastatin uptitration to 40 mg	-39.1% (95% CI: -55.9 to -22.2)
Alirocumab + atorvastatin 20 mg versus addition of ezetimibe to atorvastatin 20 mg	-23.6% (95% CI: -40.7 to -6.5)
Alirocumab + atorvastatin 40 mg versus atorvastatin uptitration to 80 mg	-49.2% (95% CI: -65.0 to -33.5)
Alirocumab + atorvastatin 40 mg versus addition of ezetimibe to atorvastatin 40 mg	-31.4% (95% CI: -47.4 to -15.4)
Alirocumab + atorvastatin 40 mg versus switch to rosuvastatin 40 mg	-32.6% (95%CI: -48.4 to -16.9)

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Table 5: Mean percentage change in calculated LDL-C for alirocumab versus comparator – OPTIONS II – ITT analysis

Comparison:	Mean percentage change from baseline (%)
	OPTIONS II
Week 12	
Alirocumab + rosuvastatin 10 mg versus rosuvastatin uptitration to 20 mg	-35.3% (95% CI: -48.2 to -22.5)
Alirocumab + rosuvastatin 10 mg versus addition of ezetimibe to rosuvastatin 10 mg	-32.3% (95% CI: -45.6 to -19.0)
Alirocumab + rosuvastatin 20 mg versus rosuvastatin uptitration to 40 mg	-24.5% (95% CI:-49.2 to 0.2)
Alirocumab + rosuvastatin 20 mg versus addition of ezetimibe to rosuvastatin 20 mg	-24.9% (95% CI: -49.6 to -0.3)
Week 24	
Alirocumab + rosuvastatin 10 mg versus rosuvastatin uptitration to 20 mg	-34.2% (95% CI:-49.2 to -19.3)
Alirocumab + rosuvastatin 10 mg versus addition of ezetimibe to rosuvastatin 10 mg	-36.1% (95% CI:-51.5 to -20.7)
Alirocumab + rosuvastatin 20 mg versus rosuvastatin uptitration to 40 mg	-20.3% (95% CI:-45.8 to 5.1)
Alirocumab + rosuvastatin 20 mg versus addition of ezetimibe to rosuvastatin 20 mg	-25.3% (95% CI: -50.9 to 0.3)

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A9. **PRIORITY.** Please provide the equivalent of Table 31, page 142 (EQ-5D data) for each of the trials separately and for each of the treatment groups.

Data for mean EQ-5D at baseline are provided in the table 5 below.

Table 6: Baseline EQ-5D by trial

Trial	Control		Alirocumab	
	n	Mean EQ-5D (SD)	n	Mean EQ-5D (SD)
FH I	162	0.912 (0.127)	314	0.908 (0.139)
FH II	81	0.903 (0.128)	163	0.919 (0.162)
High FH	35	0.883 (0.208)	73	0.926 (0.122)
LONG-TERM	758	0.840 (0.210)	1490	0.858 (0.197)
COMBO I	102	0.847 (0.204)	200	0.826 (0.208)
COMBO II	233	0.832 (0.188)	458	0.837 (0.191)

A10. **PRIORITY.** Table 36, page 156: Please provide 95% CI for each of the estimates for in the table.

These are provided below. We also provide these for Table 37.

Table 7: Table 36 from submission updated with 95% CIs – On-treatment analyses

Dose	Alirocumab + background statin Mean change from baseline (SE, 95% CI)	Placebo + background statin Mean change from baseline (SE, 95% CI)	Difference Mean change from baseline (SE, 95% CI)
Week 12			
75 mg (pooling FH I + FH II + COMBO I)	–45.1% (0.9) (95% CI: -46.9 to -43.3)	+4.3% (1.3) (95% CI:+1.7 to +6.9)	–49.3% (1.6) (95% CI: -52.5 to -46.1)
Week 24			

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Dose	Alirocumab + background statin Mean change from baseline (SE, 95% CI)	Placebo + background statin Mean change from baseline (SE, 95% CI)	Difference Mean change from baseline (SE, 95% CI)
75/150 mg (up-titration studies, pooling FH I + FH II + COMBO I)	–49.7% (1.0) (95% CI: -51.8 to -47.7)	+4.4% (1.5) (95% CI: +1.5 to +7.2)	–54.1% (1.8) (95% CI: -57.6 to -50.6)
150 mg (pooling LONG TERM + HIGH FH)	–62.1% (0.7) (95% CI: -63.4 to -60.7)	+0.4% (1.0) (95% CI: -1.5 to +2.3)	–62.5% (1.2) (95% CI: -64.8 to -60.2)
Week 12			
75 mg (pooling FH I + FH II)	–44.0% (1.1) (95% CI: -46.1 to -41.8)	+5.3% (S.6) (95% CI: +2.3 to +8.4)	–49.3% (1.9) (95% CI: -53.1 to -45.5)
Week 24			
75/150 mg (up-titration studies, pooling FH I + FH II)	–49.3% (1.2) (95% CI: -51.8 to -46.9)	+6.8% (1.7) (95% CI: +3.3 to +10.2)	–56.1% (2.1) (95% CI: -60.3 to -51.9)

Table 8: Table 37 from submission updated with 95% CIs – on treatment analyses

	ALTERNATIVE (monotherapy) Mean change from baseline (SE, 95% CI)		Difference Mean change from baseline (SE, 95% CI)	Pooling of COMBO II + OPTIONS I + OPTIONS II Mean change from baseline (SE, 95% CI)		Difference Mean change from baseline (SE, 95% CI)
Dose	Alirocumab	Ezetimibe		Alirocumab + statin	Ezetimibe + statin	
	Week 12					
75 mg	–51.2% (1.7) (95% CI: -54.5 to -47.8)	–18.0% (1.8) (95% CI: -21.6 to -14.5)	-33.1% (2.5) (95% CI: -38.0 to -28.2)	–51.0% (1.1) (95% CI: -53.2 to -48.9)	–23.9% (1.4) (95% CI: -26.5 to -21.2)	-27.2% (1.8) (95% CI: -30.6 to -23.7)
	Week 24					

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	ALTERNATIVE (monotherapy) Mean change from baseline (SE, 95% CI)		Difference Mean change from baseline (SE, 95% CI)	Pooling of COMBO II + OPTIONS I + OPTIONS II Mean change from baseline (SE, 95% CI)		Difference Mean change from baseline (SE, 95% CI)
Dose	Alirocumab	Ezetimibe		Alirocumab + statin	Ezetimibe + statin	
75/150 mg (up-titration studies)	–52.2% (2.0) (95% CI: -56.0 to -48.3)	–17.1% (2.0) (95% CI: -21.1 to -13.0)	-35.1% (2.8) (95% CI: -40.7 to -29.5)	–51.6% (1.3) (95% CI: -54.1 to -49.0)	–21.6% (1.6) (95%CI: -24.8 to -18.5)	-29.9% (2.1) (95% CI: -34.0 to -25.9)

A11. **PRIORITY**. In the UK there were 36 NHS centres across 6 trials (FHI, FHII, LONG TERM, OPTIONSI, OPTIONSII, ALTERNATIVE). Please provide the number of patients per trial and for each treatment group from the UK.

This information is provided in the table below.

Table 9: UK patients in ODYSSEY trials

Trial	Placebo (N)	Alirocumab (N)
FH I	7	16
FH II	8	17
LONG TERM	167	317
OPTIONS I	Atorvastatin 80mg: 1 Rosuvastatin 40mg: 3	Alirocumab + atorva 20mg: 1 Alirocumab + atorva 40mg: 2
OPTIONS II	Rosuva 10mg + ezetimibe: 2 Rosuva 20mg: 2 Rosuva 20mg + ezetimibe: 1 Rosuva 40mg: 2	Alirocumab + rosuva 10mg: 4

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Trial	Placebo (N)	Alirocumab (N)
ALTERNATIVE	Atorvastatin: 3 Ezetimibe: 8	Alirocumab: 8

A12. **PRIORITY**. Appendix 8.2.3.1, page 10, The company's submission only includes the ODYSSEY phase III trials in the review of clinical effectiveness and ignores Phase II trials assessing alirocumab. Please give the rationale for including Phase II trials in the safety analyses but not in the efficacy analyses. Please include the reason why ODYSSEY phase II results were not included in the review of clinical effectiveness.

The ten Phase III trials presented in the submission form the basis of the summary of clinical efficacy presented to the regulators. Although the Phase II studies do provide information on clinical efficacy, they were of shorter duration than the Phase III studies, and assessed doses other than the licensed dose (three of the five Phase II studies were dose-finding), and primary analyses were performed on an mITT basis. Efficacy results from the Phase II studies were in line with those observed in Phase III. Given the size and strength of the Phase III programme, the Phase II studies do not provide substantial additional information to inform the decision problem. Of the five Phase II trials, three were dose-finding studies, conducted to inform the optimal dose for evaluation in Phase III trials. One assessed the combination of alirocumab and high doses of atorvastatin, and the fifth was conducted specifically looking at alirocumab in patients with a gain of function mutation in the PCSK9 gene or a loss of function mutation in the ApoB gene

To understand the safety of a product, it is relevant to include information from as many treated patients as possible, to provide the greatest exposure to the investigational product. Therefore, Phase II trials were included in the safety database provided to the regulators and this was considered the most relevant information to present in the NICE submission. Of note, CL-1018 was not included in the integrated safety database as it was an exploratory nature in a unique patient population.

A table of the Phase II trials is presented on the following page.

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Table 10: Phase II trials

Trial	Population	Primary objective	Alirocumab dose (n)	Control (n)	Design	Treatment duration	Primary efficacy results - % change from baseline in MITT popn
DFI11565	Patients with hypercholesterolaemia and LDL-C ≥100 mg/dL (2.59 mmol/L) treated with a stable dose of atorvastatin (10 mg, 20 mg, or 40 mg)	Evaluate the effect of alirocumab on LDL-C levels after 12 weeks of treatment in comparison with placebo.	50 mg Q2W (n = 30) 100 mg Q2W (n = 31) 150 mg Q2W (n = 31) 200 mg Q4W (n = 30) 300 mg Q4W (n = 30)	Placebo for alirocumab Q2W (n = 31)	Randomised, double-blind, placebo-controlled, parallel-group study	12 weeks	50 mg Q2W: -39.62 100 mg Q2W: -64.17 150 mg Q2W: -72.37 200 mg Q4W: -43.21 300 mg Q4W : -47.74 Placebo: -5.11
CL-1003	Patients with HeFH on a stable daily statin dose (with or without ezetimibe) and with LDL-C levels 100 mg/dL (2.59 mmol/L)	Evaluate the effect of alirocumab on LDL-C levels after 12 weeks of treatment in comparison with placebo	150 mg Q4W (n = 15) 200 mg Q4W (n = 16) 300 mg Q4W (n = 15) 150 mg Q2W (n = 16)	Placebo for alirocumab Q2W (n = 15)	Randomised, double-blind, placebo-controlled, parallel-group study	12 weeks	150 mg Q4W: -28.87 200 mg Q4W: -31.54 300 mg Q4W: -42.53 150 mg Q2W: -67.90 Placebo: -10.65
DFI11566	Patients with hypercholesterolaemia and LDL-C ≥100 mg/dL (2.59 mmol/L) treated with a stable dose of atorvastatin (10 mg)	Evaluate the effect of alirocumab on LDL-C levels after 8 weeks of treatment in comparison with placebo when co-administered with 80 mg of atorvastatin.	150 mg Q2W + atorvastatin 10 mg (n = 31) 150 mg Q2W + high dose of atorvastatin (80 mg) (n = 30)	Placebo for alirocumab + high dose of atorvastatin (80 mg) (n = 31)	Randomised, double-blind, placebo-controlled, parallel-group study	8 weeks	150 mg Q2W + atorvastatin 10 mg: -66.2% 150 mg Q2W + high dose of atorvastatin (80 mg) (n = 30): -73.2% Placebo + 80 mg atorvastatin: -17.3%
CL-1018	Patients with autosomal dominant hypercholesterolaemia (ADH): gain-of-function mutation (GOFm) in 1 or both alleles of the PCSK9 gene (cohort 1) and patients with either	Assess the pharmacodynamic (PD) effect of alirocumab on serum LDL-C during 14 weeks SC with primary	Group A: 150 mg Q2W on Day 1, 15, 29, 43 and 71 + Placebo on Day 57, 85, and 99 (n = 6)	Refer to column "alirocumab dose"	Randomised, double-blind, placebo-controlled study	14 weeks (double-blind period)	Group A: -62.48% Group B: -8.77% Group C: -48.21 Group D: -4.93%

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Trial	Population	Primary objective	Alirocumab dose (n)	Control (n)	Design	Treatment duration	Primary efficacy results - % change from baseline in MITT popn
	GOFm in 1 or both alleles of the PCSK9 gene or loss-of-function mutation (LOFm) in 1 or more alleles of the Apo B gene (cohort 2).	endpoint on Day 15.	Group B: 150 mg Q2W on Day 15, 29, 43, 57 and 85 + Placebo on Day 1, 71, and 99 (n =7) Group C: 150 mg Q2W on Day 1, 15, 29, 43 and 71 + Placebo on Day 57, 85, and 99 (n =5) Group D: 150 mg Q2W on Day 15, 29, 43, 57 and 85 + Placebo on Day 1, 71, and 99 (n = 5)				
DFI12631	Patients with hypercholesterolemia (non-FH) and LDL-C ≥100 mg/dL (2.59 mmol/L) treated with a stable dose of atorvastatin (5 to 20 mg) for at least 6 weeks	Evaluate the effect of alirocumab on LDL-C levels after 12 weeks of treatment in comparison with placebo	50 mg Q2W (n=25) 75 mg Q2W (n=25) 150 mg Q2W (n=25)	Placebo for alirocumab Q2W (n=25)	Multicenter, randomized, double-blind, 4 parallel-group, placebo-controlled, study conducted in Japan	12 weeks	50 mg Q2W: -54.9% 75 mg Q2W: -62.3% 150 mg Q2W: -71.8% Placebo: -2.7%

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A13. **PRIORITY**. Figure 9, page 109 shows the estimates of calculated LDL-C and measured LDL-C for LONG-TERM. The submission states that the two methods show similar results but Figure 9 shows that the calculated LDL-C values are greater than the measured LDL-C values for alirocumab. However, calculated LDL-C is less than measured LDL-C for placebo. Consequently, the choice of using calculated LDL-C, instead of measured LDL-C, is likely to increase the difference between intervention groups. Please explain why calculated LDL-C was used throughout the submission.

Calculated LDL-C was used throughout the submission because it was the primary efficacy endpoint in all the ODYSSEY trials. In clinical practice, calculated LDL-C is more commonly used and evaluated than measured LDL-C. This was the main reason for using calculated LDL-C as the primary parameter in the ODYSSEY trial programme. The use of calculated LDL-C is more relevant to what is expected to occur in UK clinical practice when assessing the efficacy of lipid-lowering therapies.

Measured LDL-C using the beta-quantification method was also evaluated in the LONG-TERM study, and in 7 other phase III studies (FH I, FH II, COMBO I, COMBO II, OPTIONS I, OPTIONS II, High FH, ALTERNATIVE). This approach was agreed with the regulatory bodies. The rationale for assessing measured LDL-C as well as calculated LDL-C is that the Friedewald equation loses accuracy at levels of high fasting TGs and there is also the potential of some discrepancy at the low end of the LDL-C spectrum (although typically only with LDL-C <40 mg/dL /1.04 mmol/L])[1].

In both LONG-TERM and the other Phase III studies, very similar values were observed for measured and calculated LDL-C throughout, with a close correlation between the two measurements (see Figure 1). In LONG-TERM, there was a slightly greater decrease in calculated LDL-C as compared with the directly measured LDL-C for alirocumab, and a slightly lower increase in calculated LDL-C as compared with the directly measured LDL-C for placebo. However, the percentage reduction in LDL-C for alirocumab versus placebo (i.e. the placebo-adjusted comparison) is very similar (-61.8% with calculated versus -61.3% with measured LDL-C). Overall, across all Phase III trials, there was no systematic difference - differences between the 2 methods were small, and sometimes in favour of measured LDL-C.

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Table 11: Calculated versus measured LDL-C changes – ITT population

Trial	Comparison	Difference at week 24 between alirocumab and control	
		Calculated LDL-C	Measured LDL-C
FH I	Alirocumab versus placebo	-57.9%	-62.7%
FH II	Alirocumab versus placebo	-51.4%	-49.9%
COMBO I	Alirocumab versus placebo	-45.9%	-45.9%
COMBO II	Alirocumab versus ezetimibe	-29.9%	-28.8%
LONG-TERM	Alirocumab versus placebo	-61.8%	-61.3%
OPTIONS I	Alirocumab versus atorvastatin uptitration from 20 mg to 40 mg	-39.1%	-52.8%
	Alirocumab versus addition of ezetimibe to atorvastatin 20 mg	-23.6%	-34.4%
	Alirocumab versus uptitration from atorvastatin 40 mg to 80 mg	-49.2%	-50.8%
	Alirocumab versus addition of ezetimibe to atorvastatin 40 mg	-31.4%	-31.9%
	Alirocumab versus switch to rosuvasatin 40 mg	-32.6%	-33.7%
OPTIONS II	Alirocumab versus uptitration from rosuvastatin 10 mg to rosuvastatin 20 mg	-34.3%	-37.9%
	Alirocumab versus addition of ezetimibe to rosuvastatin 20 mg	-36.2%	-31.8%
	Alirocumab versus addition of ezetimibe to rosuvastatin 40 mg	-25.3%	-27.7%
ALTERNATIVE	Alirocumab versus ezetimibe	-30.4%	-32.9%

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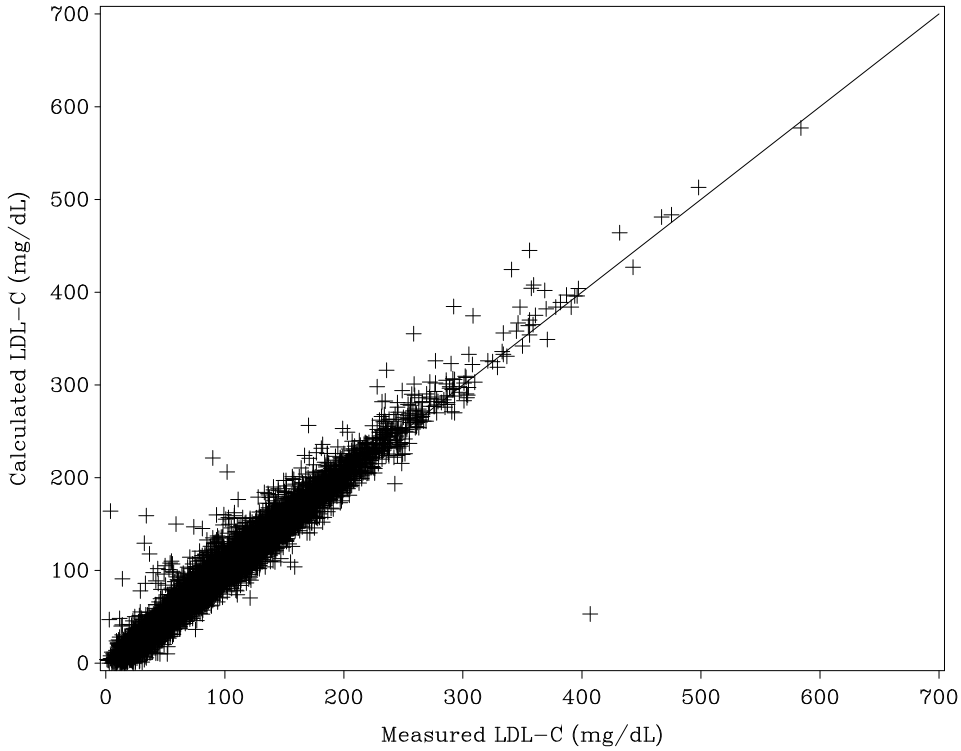
Figure 1 - **Scatter plot of calculated LDL-C versus measured LDL-C - Pool of phase 3 studies (all treatment groups combined)**



PGM=PRODOPS/SAR236553/OVERALL/POOL_2014_01/REPORT/PGM/MFCLAO_eff_corldlcm_i_g.sas
OUT=REPORT/OUTPUT/MFCLAO_eff_corldlcm_i_g_x.rtf (21OCT2014 - 12:21)

Section B: Clarification on cost-effectiveness data

B1. **PRIORITY.** Please provide more detail on the THIN data analysis cohort relating to the type of medications that patients were receiving. Please include the proportion of patients on high dose, high intensity statins or other types of lipid modification therapy.

These data are provided in Table 12 below. Lipid-lowering therapies were categorised in line with CG181 [2]. High-intensity statins were classified as: atorvastatin 20,40 and 80mg; rosuvastatin 10, 20 and 40mg; simvastatin 80mg. Medium intensity statins were classified as atorvastatin 10mg; fluvastatin 80mg; rosuvastatin 5mg; simvastatin 20 and 40mg. Low-intensity statins: fluvastatin 20 and 40mg; pravastatin 10, 20 and 40mg; simvastatin 10mg. Non-statin lipid-lowering therapies (LLT) were classified as ezetimibe; niacin; bile acid sequestrants.

Current treatment status by LLT as of index date (Jan 1, 2010) was ascertained as far as is possible.

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Table 12: Lipid-lowering therapies in THIN CV risk cohort

	Hierarchical Categorisation for Established CV Disease					Established CV Disease (N=148,051)	HeFH[1]	
	ACS ≤ 12 Months Prior to Index (N=4,717)	Ischaemic Stroke (N=15,835)	ACS 12-24 Months Prior to Index (N=4,107)	Other CHD (N=104,408)	PAD (N=18,984)		Primary Prevention (N=2,972)	Secondary Prevention[2] (N=1,421)
Currently on High-Intensity Statin	16.9%	3.3%	10.4%	4.4%	2.1%	4.6%	3.1%	13.3%
Monotherapy	14.3%	2.6%	8.9%	3.3%	1.5%	3.5%	1.9%	7.1%
+ Ezetimibe	0.7%	0.5%	0.8%	0.8%	0.4%	0.7%	1.0%	5.2%
+ Other LLT	1.9%	0.2%	0.7%	0.3%	0.2%	0.3%	0.2%	1.0%
Currently on Medium-Intensity Statin	16.3%	14.7%	18.5%	18.2%	12.5%	17.0%	10.7%	25.5%
Monotherapy	14.1%	13.1%	15.9%	15.9%	11.1%	14.9%	8.9%	19.8%
+ Ezetimibe	1.0%	1.0%	1.4%	1.5%	0.8%	1.3%	1.3%	4.4%
+ Other LLT	1.2%	0.6%	1.2%	0.9%	0.5%	0.8%	0.5%	1.4%
Currently on Low-Intensity Statin	52.3%	59.4%	57.5%	55.0%	51.1%	55.0%	33.0%	39.8%
Monotherapy	50.5%	57.6%	55.5%	52.9%	49.6%	53.0%	31.6%	36.0%
+ Ezetimibe	1.5%	1.5%	1.7%	1.7%	1.1%	1.6%	1.1%	3.7%
+ Other LLT	0.3%	0.3%	0.3%	0.4%	0.3%	0.4%	0.2%	0.1%
Currently on Non-Statin LLT	1.7%	2.2%	1.8%	2.4%	1.9%	2.3%	2.0%	3.9%
Ezetimibe Only	1.1%	1.5%	1.2%	1.5%	1.2%	1.4%	1.0%	2.2%

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Other Non-Statin LLT Only	0.5%	0.7%	0.5%	0.8%	0.7%	0.7%	0.8%	1.3%
Ezetimibe + Other Non-Statin LLT	0.0%	0.1%	0.1%	0.1%	0.0%	0.1%	0.1%	0.5%
No Current Treatment with LLT	12.8%	20.3%	11.8%	20.0%	32.4%	21.2%	51.2%	17.5%
Previously on Statins	7.7%	11.5%	8.8%	11.7%	12.6%	11.6%	10.5%	12.9%
Previously on Non-statin LLT	0.1%	0.1%	0.0%	0.1%	0.2%	0.1%	0.1%	0.0%
No Treatment with LLT	5.0%	8.7%	3.0%	8.2%	19.6%	9.5%	40.5%	4.5%

[1] As identified by the application of the Dutch Lipid Criteria (score ≥6)
[2] Subset of the population with established CV disease

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B2. **PRIORITY.** Please provide more detail on how CV-related deaths have been calculated in the THIN data analysis for those patients whose cause of death is not recorded.

In the current analysis we estimated CV-death rates by multiplying the estimated all-cause mortality rates by 62% (Appendix 11 of submission). Although all-cause mortality information is recorded accurately in the THIN database, a cause is recorded only for a subset (approximately 15% in our study cohort) of deaths. The estimate of 62% is based on the proportion of deaths that were CV related in the CTT meta-analysis. This was considered as one of the largest data sources to inform the proportion of deaths that were cardiovascular in a relevant patient population[3]. This proportion was reported to be 66% for the subgroup with prior CV disease. We also explored the proportion of deaths that are CV-related in other recent real-world cohort analyses, registries, and RCTs that have been conducted in relevant populations. These provided similar or somewhat higher proportions, indicating that our estimate was relatively conservative. The following Table provides a summary of this information.

Table 13: Additional sources estimating proportion of CV deaths

Study/ Database	Reference	Population	Study Type	Country	% Deaths that are CV related
GRACE	Alnasser et al. 2015[4]	Recent ACS	Registry	Multinational	64%
US MarketScan	Steen et al. 2015[5]	Recent ACS	Real-world cohort	U.S.	77%
US MarketScan	Steen et al. 2015[5]	CV disease	Real-world cohort	U.S.	77%
EMPA-REG OUTCOME	Zinman et al. 2015[6]	CV disease with diabetes	RCT	Multinational	71%
SOLID-TIMI 52	O'Donoghue et al. 2014[7]	Recent ACS	RCT	Multinational	66%
STABILITY	Stability Investigators et al. 2014[8]	Stable CHD	RCT	Multinational	81%
REACH	Steg et al. 2007[9]	CV disease	Registry	Multinational	65%
REACH	Steg et al. 2007[9]	Stable CHD	Registry	Multinational	67%

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We also explored an alternate methodology for estimating the proportion of deaths that are CV related by utilising the UK lifetable data. Standard UK lifetables provide all-cause mortality rates by age and gender for the UK general population, and the proportion of deaths that are CV related. We estimated CV death rates for subpopulations in the THIN study cohort by subtracting the rate of non-CV death from the life tables (matched for average age and gender split) from the all-cause mortality rate from the THIN study cohort (see Table below). The estimated CV mortality rates aligned closely with estimates obtained by applying the 62% factor, with the exception of HeFH primary prevention without diabetes, where the all-cause mortality observed in the THIN study cohort was relatively lower. Overall, estimates of CV death rates were slightly higher using the life table approach compared to the results by applying the 62% factor, suggesting that the latter base-case approach is more conservative.

Table 14: Estimates of CV death rates obtained from life tables

Subpopulation	Mean age from THIN	All-cause mortality rate from THIN	Non-CV death rate from life table	Estimated CV death rate via difference	CV death rates by utilising 62% factor
With Diabetes					
Dutch Lipid Secondary prevention	67.3	5.5%	0.97%	4.5%	3.4%
ACS ≤ 12 months prior to index	70.9	9.6%	1.43%	8.2%	6.0%
Ischemic Stroke	74.5	6.6%	2.01%	4.6%	4.1%
ACS 12-24 months prior to index	70.7	6.6%	1.43%	5.2%	4.1%
Other CHD	72.1	3.9%	1.61%	2.3%	2.4%
PAD	73.1	5.9%	1.74%	4.2%	3.7%
Dutch Lipid Primary prevention	61.1	1.6%	0.57%	1.0%	1.0%
Diabetes without ASCVD	61.7	2.0%	0.64%	1.4%	1.2%
Without Diabetes					
Dutch Lipid Secondary prevention	65.8	2.1%	0.86%	1.2%	1.3%
ACS ≤ 12 months prior to index	69.5	4.7%	1.25%	3.5%	2.9%
Ischemic Stroke	74.5	5.8%	2.01%	3.8%	3.6%
ACS 12-24 months prior to index	69.4	3.6%	1.19%	2.4%	2.2%
Other CHD	72.6	3.1%	1.74%	1.4%	1.9%
PAD	73.0	4.7%	1.74%	2.9%	2.9%
Dutch Lipid Primary prevention	57.2	0.3%	0.39%	-0.09%	0.2%

B3. Table 60, page 207: The standard errors around the mean percent reduction in LDL-C in Table 60 of the submission are different from those in the model for “vs placebo”.

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For example, the standard error values for “FH” were 1.9% in Table 60 (2.1% in the model), and for “monotherapy” for “High CV Risk” 1.6% (1.4% in the model) and “as add-on to statin” 3.2% (2.3% in the model). Please indicate which mean percent reduction in LDL-C and standard errors for “Vs. Placebo” are correct.

The table in the submission included rows for the efficacy of uptitration. However, the inclusion of these rows was an error, as the model calculates efficacy based on uptitration and this is dependent on the percentage of patients assumed to undergo uptitration in the model (which is dependent on the population in the model and initial LDL-C level). This is the reason for the discrepancy in standard error values observed. Otherwise, the values presented in this table match the values in the model (B412 – I424 in the Intro sheet).

See further answer to question B19 below.

B4. **PRIORITY:** Page 209. Please provide further justification for the approach used to estimate the relationship between absolute LDL-C reductions (per 1 mmol/L) and reductions in CV events for PCSK9 inhibitors (section 5.3.1 in the submission); Please include the rationale for assuming a steeper log-linear relationship between LDL-C reductions and the relative risks of CV events with PCSK9 inhibitors as compared with statins.

The rationale for using a steeper log-linear relationship with PCSK9 inhibitors as compared with statins is that this is what the PCSK9 data available to date show. We based this on an independent meta-analysis by Navarese et al[10] of outcomes reported in 24 PCSK9 trials to date, including 10,159 patients.

There is extensive evidence from genetic, epidemiological, and pharmacological studies to demonstrate a relationship between LDL-C and CV events. This includes evidence from genetic studies demonstrating a central role for PCSK9 in LDL-C regulation. PCSK9 Loss of Function mutations are associated with lower LDL-C levels and with CV event reduction. In the large prospective ARIC study[11], mutations in the *PCSK9* gene that lowered LDL-C by ~0.5 mmol/L were associated with a 47% reduction in the incidence of CHD, while mutations that lowered LDL-C by ~1mmol/L were associated with an 88% reduction in the incidence of CHD.

The figure below, taken from Ference et al 2015[12], shows the relationship observed for LDL-C reduction and CV risk reduction from genetic studies (including PCSK9 genetic studies) as well as pharmacological studies, mainly the statin trials but also including the IMPROVE-IT trial. The steeper relationship observed with the genetic studies is hypothesised to be due to the impact of lifelong cholesterol reduction.

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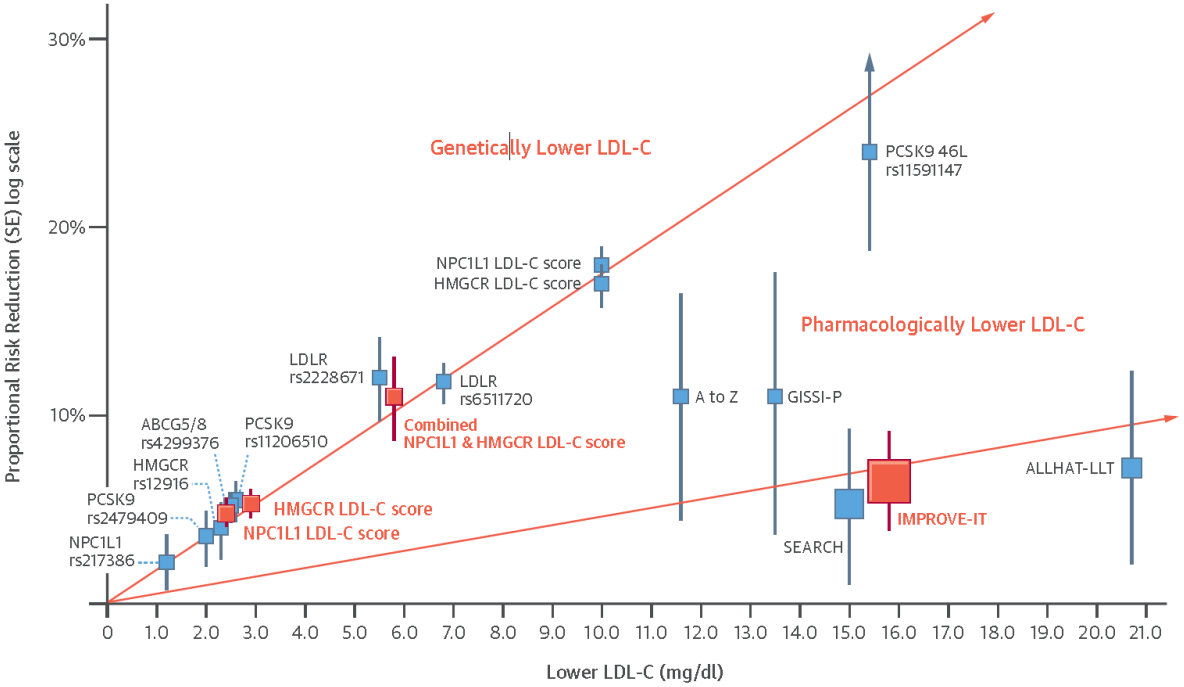
Figure 2: Figure from Ference et al 2015



Boxes represent proportional risk reduction (1–OR) of CHD for each exposure allele, genetic score, or randomised trial plotted against the absolute magnitude of lower LDL-C associated with that allele or genetic score; or the absolute difference in LDL-C between treatment groups for each trial. Vertical lines represent 1 SE above and below point estimate of proportional risk reduction. SNPs, genetic scores, and trials are plotted in order of increasing absolute magnitude of effect on lower LDL-C. The lines(which are forced to pass through the origin) represent the increase in proportional risk reduction of CHD per unit lower LDL-C. In the top line, the red boxes represent results of the 2x2 factorial mendelian randomisation study and the blue boxes represent results derived from CARDIoGRAMplusC4D consortia data. In the lower line, the red box represents the results of the IMPROVE-IT trial and the blue boxes represent the results of prior statin trials.

CHD, coronary heart disease; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SE, standard error; SNP, single-nucleotide polymorphism

The majority of evidence linking pharmacological LDL-C reduction to CV event reduction comes from statin trials. In addition, meta-analyses including non-statin therapies [13, 14] as well as the IMPROVE-IT trial of ezetimibe [15] have also shown a reduction in CV events linked to LDL-C reduction. The CTT meta-analysis of statin trials is the most well-known source of evidence evaluating pharmacological reduction with LDL-C [3]. This individual patient data analysis is a large and robust meta-analysis which clearly shows a relationship between LDL-C lowering and CV event reduction. However, there are some aspects that do not necessarily apply to the PCSK9 target

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population which may explain a steeper log-linear relationship between LDL-C reductions and the relative risks of CV events with PCSK9 inhibitors observed in the PCSK9 data so far. The CTT meta-analysis pulls together CVOT results from a very broad set of patient populations that are not part of the intended alirocumab population. In particular, there are trials that examined the effect of statins in novel patient populations that were later shown not to be impacted by lipid lowering therapy, such as trials in patients with end-stage renal disease and renal transplant patients. By contrast, the data from the PCSK9 trials are taken from studies including patient populations that have been shown to benefit from LDL-C reduction and represent specifically the intended population for alirocumab therapy.

In addition to these potential limitations of the CTT meta-analysis for describing the relationship between LDL-C reduction and CV event reduction for PCSK9 inhibitors, there are potentially additional effects of PCSK9 inhibitors that may contribute to a steeper relationship. While it is not possible to draw definitive conclusions to explain the preliminary effects seen with PCSK9 inhibitors in terms of reducing relative risk of CV events, several recent studies have explored the potential positive benefits of PCSK9 inhibition on parameters directly related to atherosclerosis progression, beyond the effect of reducing LDL-C concentrations. In particular, PCSK9 inhibitors decrease the serum concentration of Lipoprotein(a) by around 25%[16]. The robust and specific association between elevated Lp(a) levels and increased cardiovascular disease (CVD)/coronary heart disease (CHD) risk, together with recent genetic findings, indicates that elevated Lp(a), like elevated LDL-cholesterol, is causally related to premature CVD/CHD. The association is continuous without a threshold or dependence on LDL- or non-HDL-cholesterol levels. Mechanistically, elevated Lp(a) levels may either induce a prothrombotic/anti-fibrinolytic effect as apolipoprotein(a) resembles both plasminogen and plasmin but has no fibrinolytic activity, or may accelerate atherosclerosis because, like LDL, the Lp(a) particle is cholesterol-rich, or both[17]. Yet no available therapies in Europe (including statins) have shown a reduction in Lp(a) concentrations. Therefore, it has been hypothesised that the ability of PCSK9 inhibitors to reduce levels of Lp(a) may have an incremental effect on reducing relative risk of CV events.

We therefore use PCSK9 data as the most relevant data source for modelling the effect of PCSK9 inhibitors. A further advantage of the Navarese et al meta-analysis is that the patients included in the trials were already receiving maximal tolerated dose of statins and therefore the results reflect the impact of additional lipid-lowering therapy with PCSK9 inhibitors on top of this background. Clearly, one limitation is the immaturity of the data, resulting in wide confidence intervals. This uncertainty is explored through the PSA.

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We have modelled scenario analyses which assume the same relationship between LDL-C lowering and CV event reduction as that observed with the statins (i.e. based on the CTT meta-analysis).

B5. **PRIORITY:** Page 211. Please provide more detail on how the mean value of [redacted] mmol/L reduction in LDL-C has been estimated from the trials included in Navarese et al. Please state if all trials been used to estimate this reduction or only trials used in the meta-analysis of MI events.

Appendix Table 6 in the Navarese publication provides the baseline and final LDL-C level for PCSK9 and non-PCSK9 treatments. Using this and the sample size for each treatment group the mean difference in LDC-C level at final assessment between PCSK9 and non-PCSK9 treatments was estimated at 1.6 mmol/L. All trials were used to estimate this reduction, weighted by sample size.

We also looked at the LDL-C reduction in trials used only for the specific event meta-analysis. This leads to a 1.3 mmol/L reduction for CV death and 1.8 mmol/L reduction for MI. This would lead to an alpha value of 0.58 for CV death and an alpha value of 0.68 for MI (instead of 0.64 for both).

B6. **PRIORITY.** Base case analysis: No results were presented in the Navarese et al.meta-analysis for the effect of PCSK9 inhibitors on ischaemic stroke (IS) (Table 61, page 211) and was assumed to be the same as for other non-fatal CV events. Please provide the rationale for applying the same hazard ratio for non-fatal myocardial infarction (MI) to IS.

We considered two alternative ways for modelling this – either to apply the same ratio as for other non-fatal CV events, or to assume no effect. The rationale for applying the same ratio as for other non-fatal CV events was that, as an ischaemic CV event that is typically included in the definition of major adverse cardiovascular events (MACE), ischaemic stroke would be expected to be reduced by LDL-C lowering as would other ischaemic cardiovascular events. The same ratio was applied for this in the interests of simplicity. However, we accept that no results were presented in the Navarese meta-analysis for ischaemic stroke and we therefore present below scenario analyses assuming no impact on stroke. The impact of this is as would be expected to increase the ICER. However, the changes observed are relatively small, demonstrating that the model is not particularly sensitive to this assumption (Table 15).

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Table 15

Patient population	Base-case ICER (without PAS)	Scenario assuming no impact on ischaemic stroke	Base-case ICER (with PAS)	Scenario assuming no impact on ischaemic stroke
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	[redacted]	[redacted]	36,793	39,611
HeFH secondary prevention (LDL-C ≥2.59 mmol/L)	[redacted]	[redacted]	16,896	17,567
High risk CVD (LDL-C ≥3.36 mmol/L)	[redacted]	[redacted]	19,791	21,469
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	[redacted]	[redacted]	19,447	21,136

B7. **PRIORITY.** Page 211**:** Please clarify how the 95% CIs for the estimated hazard ratios, per mmol/L reduction LDL-C, have been calculated using data from Navarese et al.

To calculate the 95% CI, the lower and upper limit of the 95%CI of the relative risk (from Navarese et al) was used with the same 1.6 mmol/l reduction in LDL-C, to give the 95% CI on the rate ratio of 0.64.

B8. Please detail the methods by which the annual age adjustment for CV risk (3%) and for non-fatal CV events (5%) were selected (based on Wilson et al. 2012). Please state if alternative sources were considered.

We considered several different alternative sources for this. Previous models in cardiovascular disease have used varied sources and varied rates. In the recent appraisal of ezetimibe, much lower age-related increases were applied (0.03% for male and 0.008% for female). This is based on Ward 2007 using a regression analysis of data from the Health Survey for England. A recent model developed for

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ACS applied age-related annual increases in risk for non-fatal events of 8.7% to 10.7% (Bayer –rivaroxaban, Table 47).

The Wilson reference was used partly because it is based on a high risk patient group (cohort of patients with cardiovascular disease at baseline) which should align more closely to the high risk groups included in the alirocumab model. A second reason was that it splits the age adjustment into fatal and non-fatal CV events. Advice from clinical experts was that the increase in age was likely to be different for fatal and non-fatal events.

B9. In the model "Introduction Worksheet", "Descriptive CV Risk" tab, the values for the "CV Event Probabilities* (Hierarchical Sub-Populations)" and "CV Event Probabilities* (Prevalent Sub-Populations)" are inconsistent with the results presented in Appendix 11, Analysis of THIN of CV risk. Please clarify which set of CV event probabilities are correct. Please supply more detail of the "descriptive Kaplan-Meier analyses from the THIN database" (section 5.3.2 in the submission) which is used to calculate CV risk in the model.

Appendix 11 provides results directly from the descriptive K-M analyses from the THIN database. However, while THIN is a large, real-world, well-validated primary care record database, there is evidence that it does not capture 100% of events. Analyses by Herrett et al[18] investigated the percentage of MI events that were captured by a primary care record database (CPRD, analogous to THIN), and/ or by Hospital Episode statistics (HES) and/ or by the Myocardial Ischaemia National Audit Group registry (MINAP). They found that all three data-sets captured most, but not all, events. The primary care database captured approximately 75% of MI events. There is no systematic difference between CPRD and THIN in terms of event recording and therefore we expect that this 25% undercoding figure would apply to THIN as to CPRD. For this reason, we apply an adjustment factor based on Herrett et al to the non-fatal event estimates that we obtained from THIN (c.f. section 5.3.2.1 of the submission). The values included in the Descriptive CV risk tab in the model incorporate this adjustment factor. No adjustment factor is applied for fatal events.

B10. **PRIORITY.** The submission states that health–related quality of life was assessed in 7 ODYSSEY trials using the EQ-5D. Please confirm if country-specific value sets were used (for example that the set of weights that represent the UK general population's values were applied to generate the EQ-5D utilities in the 36 UK centres).

The standard UK value set was applied to the EQ-5D responses from ODYSSEY to generate the EQ-5D utilities used. All patients were included in this analysis, it was not specific to the UK patients included in ODYSSEY. This was because there is no reason to suppose that UK patients would be systematically different to non-UK

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patients as regards utility. Further, this provided a larger sample size to perform an analysis specifically by CV event history and FH status as was provided in the submission.

B11. Table 63, page 218: Please provide baseline utilities from ODYSSEY for UK subjects compared with non-UK subjects

Table 16 shows the number of UK patients with EQ-5D data by trial. Table 17 shows the mean EQ-5D at baseline for UK and non-UK subjects. Values are similar.

Table 16: Number of UK subjects providing EQ-5D data by trial

	Placebo (N=181)	Alirocumab (N=337)
EFC12492 - FH I	7 (3.9%)	16 (4.7%)
LTS11717 – Long-term	166 (91.7%)	304 (90.2%)
R727-CL-1112 - FH II	8 (4.4%)	17 (5.0%)

Table 17: Mean EQ-5D data for UK versus non-UK subjects

Utility score	non-UK subjects N=3546	UK subjects N=518
Baseline		
Number	3546	518
Mean (SD)	0.86 (0.18)	0.84 (0.23)
Median	1.00	1.00
Q1 : Q3	0.76 : 1.00	0.73 : 1.00
Min : Max	-0.2 : 1.0	-0.2 : 1.0

B12. Table 65, page 222: The mean values for CV event based utilities do not correspond to the values in the model. Please clarify which CV event disutility multipliers are the correct. Similarly, some of the multipliers in Table 66, page 223 and those used in the model show small discrepancies. Please clarify which values are considered correct.

The values in the model are correct. The multipliers are calculated as age-adjusted multipliers relative to an age-adjusted baseline. However, gender is also included in the age-based regression equation from Ara 2010[19]. Therefore, the multipliers vary slightly dependent on the gender balance in the population being assessed. In the submission, the multipliers presented were calculated based on a 50/50 male/ female

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split. The model calculates these based on the gender split in the population being evaluated – this is an assumption of 50% male in the heFH populations and 60% males and 40% females in high CVD and recurrent event/polyvascular populations.

B13. Table 85, page 250: Please justify the selection of the 3 to 8% discontinuation rate per year for sensitivity analyses. Does this reflect the average discontinuation rates associated with all the ODYSSEY trials of 52 weeks follow-up or longer (i.e. including LONGTERM)?

In considering this, it was challenging to accurately estimate rates given that discontinuation rates in trials may be different to those in the real world. Overall, however, the impact of discontinuations is relatively small as it impacts both the benefit and the alirocumab costs.

In LONG-TERM, 14.2% of patients discontinued treatment at week 52 in both arms. 6.3% discontinued due to adverse events and 7.9% due to other reasons. Typically, patients who discontinue due to treatment-related adverse events discontinue earlier and are overall likely to discontinue in the first year. Therefore, it is assumed that the 7.9% rate for other reasons is more reflective of the long-term annual discontinuation rate. This is the rationale for the 8%. Comparable results for discontinuations at 52 weeks were observed in other trials (Table 18).

Table 18: Discontinuations by week 52 in trials with 52 week follow-up

Trial	Did not complete the 52 week study period Control	Did not complete the 52 week study period Alirocumab
LONG-TERM	14.2%	14.2%
FH I	9.2%	10.5%
FH II	2.4%	6.6%
High FH	17.1%	20.8%
COMBO II	13.7%	14.8%

B14. Please provide the year (and sources) used to estimate cost data in the economic model Table 68, page 228: Please provide more information on drug acquisition costs; e.g. tablet pack sizes and prices, and version of the BNF source.

All drug acquisition costs were taken from the BNF 2015 (January). Annual costs were calculated on the basis of daily usage. Atorvastatin was assumed to be used in its generic form. The values are checked in the table below against the October BNF. There are some small discrepancies versus the costs from January but these are very minor (Table 19).

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Table 19: Drug acquisition costs

Treatment	Dose	Annual cost in model (£)	Pack price from BNF October 2015	Annual cost based on October BNF version (£)
Ezetimibe	10 mg	342.97	Ezetimibe 10 mg daily – Ezetrol - £26.31 per 28 tablet pack, annual cost = £26.31/ 28 x 365 days	342.97
Atorvastatin (Lipitor)	10 mg	15.51	Cost of 28 tab pack = £1.15	14.99
	20 mg	18.90	Cost of 28 tab pack = £1.38	17.99
	40 mg	21.77	Cost of 28 tab pack = £1.57	20.47
	80 mg	34.94	Cost of 28 tab pack = £2.73	35.59
Rosuvastatin (Crestor)	5 mg	235.03	Cost of 28 tab pack = £18.03	235.03
	10 mg	235.03	Cost of 28 tab pack = £18.03	235.03
	20 mg	339.19	Cost of 28 tab pack = £26.02	339.19
	40 mg	386.51	Cost of 28 tab pack = £29.69	387.03

B15. Please provide the rationale for the "Cohort Proportions on Statin as Background Therapy (%)" used in the model for atorvastatin: 40mg (20%), 80mg (50%), and Rosuvastatin: 20mg (10%), 40 mg (20%).

This was based on market research data. As this submission focusses on the use of alirocumab in patients treated with current maximal therapy, we did not include lower intensity statins such as pravastatin, as we assumed patients who would be considered candidates for alirocumab (and who could tolerate statins) would be receiving high intensity statins such as atorvastatin and rosuvastatin. Because statins are part of the background therapy and relatively cheap as generic products, changes to the proportions assumed do not have a substantial impact on the ICER (<1k).

B16. **PRIORITY**. Please explain why ongoing (post-event) costs were applied for up to 3 years following the event and not in the longer term.

Following a cardiovascular event, patients are likely to need additional medical care and therefore the NHS will incur additional costs, subsequent to the first year. For example, patients suffering a debilitating stroke are likely to require additional healthcare resources over their remaining lifetime. However, we were not certain as to whether it is appropriate to apply these to all patients over the entire lifetime. The approach taken was judged to be conservative. Overall, post-event costs, which are

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relatively small and subject to discounting, have a very limited impact on the ICER. Because the model is relatively stable to this input, we did not focus on it in great detail. A scenario analysis assuming post-event costs apply in perpetuity, is presented below (Table 20).

Table 20: Scenario analyses assuming post-CV event costs in perpetuity

Patient population	Base-case ICER (without PAS)	Scenario assuming post-CV event costs in perpetuity (without PAS)	Base-case ICER (with PAS)	Scenario assuming post-CV event costs in perpetuity (with PAS)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	[redacted]	[redacted]	36,793	36,422
HeFH secondary prevention (LDL-C ≥2.59 mmol/L)	[redacted]	[redacted]	16,896	16,869
High risk CVD (LDL-C ≥3.36 mmol/L)	[redacted]	[redacted]	19,791	19,689
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	[redacted]	[redacted]	19,447	19,468

B17. In Table 87, page 252 after applying 8% discontinuation rate, the estimated ICER for the HeFH secondary prevention population decreased compared to the basecase (using a 0% discontinuation rate). Scenario analyses of increased discontinuation in other populations increase the estimated ICERs compared to the basecase(s). Please explain why higher discontinuation rates in the HeFH secondary prevention population decreases the estimated ICERs.

This was a typo in the submission. The ICER assuming an 8% discontinuation rate should read [redacted]. The same pattern applies for this population as for the others. A corrected table is presented below (Table 21).

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Table 21

Base case			[redacted]
Discontinuation rate	0%	3%	
		8%	

B18. Table 99, page 264: Please clarify whether the baseline LDL value of 4.13 should be 4.14 as described in Table 57, page 203.

Yes, this is correct, the value should be 4.14.

B19. **PRIORITY.** Table 60, page 206: Please list the trials/source for each mean % changes in LDL-C values Please insert an additional column indicating the specific clinical studies that were pooled and what assumptions have been made – it is not clear why the pooled estimates for the high CV risk group reported in Table 60 do not seem to match those reported in Tables 36 and 37 in the clinical effectiveness chapter.

Trials were pooled depending on background therapy (monotherapy or as add-on to statin), Alirocumab dose (up-titration studies or 150mg) and comparator (placebo or Ezetimibe). Further pooled analyses were performed depending on the populations (heFH, high CV risk).

For the model, slightly different pooled analyses were conducted in order to more precisely match the populations and comparisons included in the model. Namely, a pooled analysis of High FH and the HeFH patients included in Long-term was performed to model the efficacy of 150 mg alirocumab dose in FH patients. Thus the results in Table 60 do not precisely match the results in Table 36 and 37.

Table 60 is re-presented below (Table 22) with an explanation of the sources for each estimate. Results are presented separately for different populations (FH and High CV risk) and for different doses (75 mg and 150 mg).

The analyses presented below were utilised in order to more precisely match the populations and comparator scenarios in the model. In some situations, there are several different approaches that could have been taken. However, as is clear from the table, efficacy results are very similar across different trials and patient populations, with the 75 mg dose producing a ~50% reduction, the 150 mg dose producing a ~60% reduction, and ezetimbe showing a ~20% reduction versus baseline.

Several other points of explanation on this analysis:

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- There is no trial solely evaluating the 75 mg dose. Therefore, to calculate the efficacy of the 75 mg dose, values from week 12 are used because after week 12, patients could undergo uptitration to 150 mg dose. For other situations, the week 24 value is used.

- Values are presented as reduction versus placebo for the comparisons versus placebo. However, for comparisons versus ezetimibe, the values presented are reductions from baseline. Corresponding reductions from baseline are provided for ezetimibe and so when comparing against ezetimibe the result in the model reflects the difference in efficacy between alirocumab and ezetimibe.

- Data are not available for all possible sets of combinations and populations. For example, for FH, there is no data for monotherapy. Where such data are not available reasonable assumptions have been made – for example, it is assumed that data for combination therapy in FH apply also to the monotherapy setting. Although these are assumptions, it is notable that percentage reductions are consistent across populations and settings, with the only difference being the difference in efficacy between the 75 mg and 150 mg dose.

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Table 22: Revised version of submission Table 60

			Percent Reduction in LDL-C		Standard Error		
			As Monotherapy	As Add-On To Statin	As Monotherapy	As Add- On To Statin	Source
Comparison vs Placebo [1]	**FH**	Alirocumab (75 mg)	49.3%	49.3%	1.9%	1.9%	Pooled FH I and FH II prior to uptitration (week 12) – values versus placebo
		Alirocumab (150 mg)	59.6%	59.6%	2.3%	2.3%	Pooled High FH and HeFH patients from LONG-TERM – values versus placebo at week 24
	High CV Risk	Alirocumab (75 mg)	49.3%	49.3%	1.6%	1.6% (NB previously stated 3.2% - in error)	FH I and FH II and COMBO I pooled prior to up titration (week 12) – values versus placebo
		Alirocumab (150 mg)	62.5%	62.5%	1.2%	1.2%	LONG-TERM – values versus placebo at week 24
Comparison vs Ezetimibe [2]	**FH**	Alirocumab (75 mg)	51.2%	51.0%	1.7%	1.1%	Assumed same as high CV risk.
		Alirocumab (150 mg)	59.6%	59.6%	2.3%	2.3%	Assumed same as vs placebo

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			Percent Reduction in LDL-C		Standard Error		
			As Monotherapy	As Add-On To Statin	As Monotherapy	As Add- On To Statin	Source
							Pooled High FH and HeFH patients from LONG-TERM – values versus placebo at week 24
	High CV Risk	Alirocumab (75 mg)	51.2%	51.0%	1.7%	1.1%	Values are percent reduction from baseline prior to uptitration (at week 12). For monotherapy, value from ALTERNATIVE was used. For combination therapy, pooled from COMBO II, OPTIONS I and OPTIONS II
		Alirocumab (150 mg)	62.5%	62.5%	1.2%	1.2%	Assumed same as vs placebo
Ezetimibe (10 mg)			18.0%	23.9%	1.8%	1.4%	Represents percent reduction from baseline for ezetimibe. For monotherapy, value from ALTERNATIVE; for combination therapy, pooled from COMBO II, OPITIONS I and II

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B20. Page 191: Please provide a reference for applying 3.36 mmol/L as the baseline LDL-C threshold in patients with high risk CVD.

The high risk CVD population is a broad population at high risk of CV events. Given that this is a relatively large group, we consider that clinically and economically it is reasonable to consider a threshold for PCSK9 usage for patients whose cholesterol level is clearly far from existing targets. LDL-C influences cardiovascular risk. Patients with a higher minimum baseline LDL-C represent a higher risk population within the broad high CV risk population. Selecting on the basis of cardiovascular risk reflects the approach taken by previous NICE guidelines – for example CG181, which took into account clinical and economic considerations when providing recommendations on the whether a 10% or 20% 10-year risk score that should be used to guide statin initiation in primary prevention[20].

Patients with an LDL of at least 3.36 mmol/L on a maximum tolerated dose of lipid-modifying therapy are clearly far from existing lipid targets and they are at very high risk because of their LDL-C levels. We set out below further rationale for the threshold of 3.36 mmol/L at baseline.

Patients with a history of cardiovascular events (secondary prevention) and an LDL-C level greater than 3.36 mmol/L (130 mg/dL) are at significant high risk of a new cardiovascular event. Indeed, in these patients, as shown below, the risk of coronary events is 3 times greater than for patients with LDL-C levels of 1.81 mmol/L (70 mg/dL)[21].

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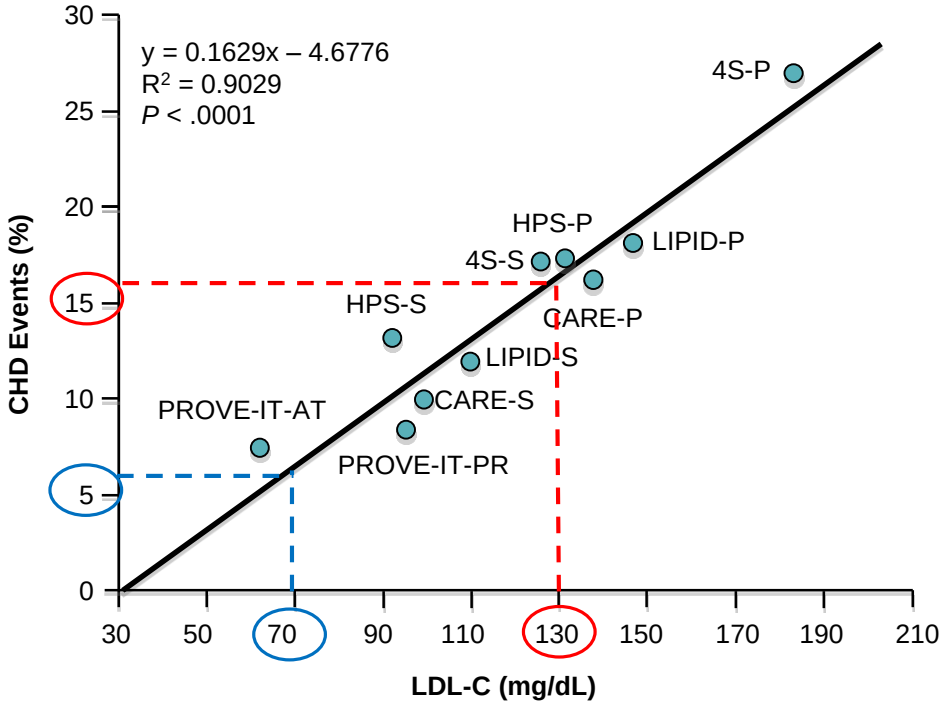
Figure 3: Relationship between LDL-C and CV event risk (Figure adapted from O'Keefe 2004 - scale shown is in mg/dL; 70 mg/dL = 1.81mmol/L, 130 mg/dL = 3.36 mmol/L)



In another meta-analysis, taking into account individual patient data including more recent trials with statins (8 RCTs, N=38,153), the residual risk of major CV events, on statins, is directly related to the achieved LDL-C levels as illustrated on the following table [22].

TABLE 1 Risk for Major Cardiovascular Events, by Achieved LDL-C Concentration

	Achieved On-Trial LDL-C Concentration, mg/dl (mmol/l)						
	<50 (<1.29) (n = 4,375)	50-<75 (1.29-<1.94) (n = 10,395)	75-<100 (1.94-<2.58) (n = 10,091)	100-<125 (2.58-<3.23) (n = 8,953)	125-<150 (3.23-<3.88) (n = 3,128)	150-<175 (3.88-<4.52) (n = 836)	≥175 (≥4.52) (n = 375)
Major cardiovascular events	194 (4.4)	1,185 (11.4)	1,664 (16.5)	1,480 (16.5)	557 (17.8)	184 (22.0)	123 (32.8)
Unadjusted HR (95% CI)	0.20 (0.16-0.25)	0.40 (0.33-0.48)	0.50 (0.42-0.60)	0.48 (0.40-0.58)	0.51 (0.42-0.62)	0.64 (0.51-0.81)	1.00 (ref)
Adjusted HR (95% CI)*	0.44 (0.35-0.55)	0.51 (0.42-0.62)	0.56 (0.46-0.67)	0.58 (0.48-0.69)	0.64 (0.53-0.79)	0.71 (0.56-0.89)	1.00 (ref)
Major coronary events	129 (2.9)	918 (8.8)	1,431 (14.2)	1,336 (14.9)	492 (15.7)	170 (20.3)	107 (28.5)
Unadjusted HR (95% CI)	0.15 (0.12-0.20)	0.36 (0.29-0.43)	0.50 (0.41-0.61)	0.51 (0.42-0.62)	0.53 (0.43-0.65)	0.69 (0.54-0.88)	1.00 (ref)
Adjusted HR (95% CI)*	0.47 (0.36-0.61)	0.53 (0.43-0.65)	0.58 (0.48-0.71)	0.62 (0.51-0.75)	0.67 (0.55-0.83)	0.78 (0.61-0.99)	1.00 (ref)
Major cerebrovascular events	72 (1.6)	315 (3.0)	302 (3.0)	205 (2.3)	91 (2.9)	21 (2.5)	23 (6.1)
Unadjusted HR (95% CI)	0.47 (0.29-0.74)	0.62 (0.41-0.95)	0.52 (0.34-0.79)	0.38 (0.25-0.58)	0.47 (0.30-0.75)	0.41 (0.23-0.74)	1.00 (ref)
Adjusted HR (95% CI)*	0.36 (0.22-0.59)	0.46 (0.30-0.71)	0.49 (0.32-0.75)	0.45 (0.29-0.69)	0.58 (0.36-0.91)	0.43 (0.24-0.78)	1.00 (ref)

Values are n (%) unless otherwise indicated. *Adjusted for sex, age, smoking status, presence of diabetes mellitus, systolic blood pressure, high-density lipoprotein cholesterol concentration, and trial. The highest low-density lipoprotein cholesterol (LDL-C) category was used as the reference category.

CI = confidence interval; HR = hazard ratio.

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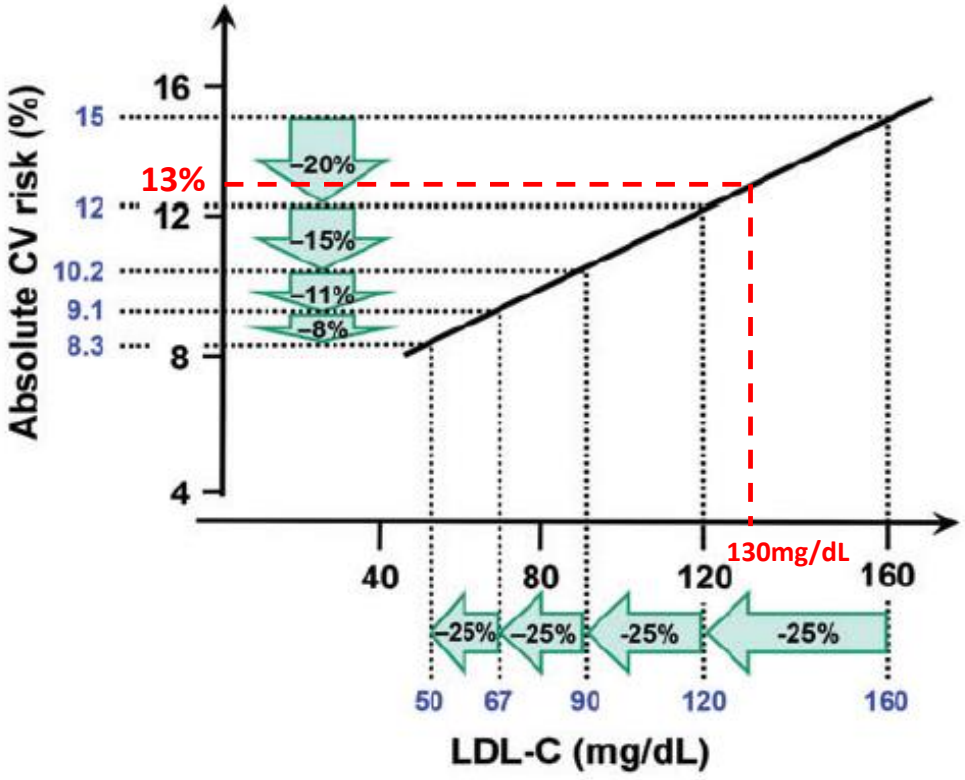
Furthermore, the higher the baseline LDL-C, the greater the absolute LDL-C reduction that is achieved. In a patient whose baseline LDL-C is 4 mmol/L, a 50% reduction in LDL-C due to alirocumab will reduce LDL-C by 2 mmol/L. In a patient whose baseline LDL-C is 2 mmol/L, their LDL-C will be reduced by 1mmol/L. Epidemiological, genetic and pharmacological evidence shows a linear/ log-linear relationship between LDL-C and CV event reduction. Therefore, in patients with a higher baseline-LDL-C, there will be a greater the absolute risk reduction in CV events and consequently a lower number needed to treat (NNT). This is illustrated in Figure 4.

Figure 4: Relationship between LDL-C and absolute CV risk reduction (adapted from Laufs 2014[23])



Patients should be on maximal tolerated dose of existing treatment before being considered for alirocumab. However, a further point is around the potential of existing treatments to get patients to target. In patients with an LDL-C of >3.36 mmol/L, a reduction of ~50% is needed to get them to recommended (absolute) LDL-C target of 1.81 mmol/L [24] – see also discussion in section 3.6 of our submission. No current therapeutic options can enable this, other than PCSK9 inhibitors. If a patient has an LDL-C of 3.36 mmol/L on maximal tolerated dose of statins without ezetimibe, adding in ezetimibe will not get them to the 1.81 mmol/L target. In contrast, if a patient has

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an LDL-C of 2.0 mmol/L for example, on maximal tolerated dose of statins without ezetimibe, adding in ezetimibe would be an option.

We specifically select 3.36 mmol/L (equivalent to 130 mg/dL) as opposed to say 3.4 mmol/L, because this reflects both guideline levels and pre-specified analyses in ODYSSEY. In various guidelines including the previous NCEP-ATPIII Cholesterol Guidelines, the different LDL-C targets, which were set up according to the different patients' CV risk profiles, were segmented into <70 mg/dL, <100 mg/dL, <130 mg/dL, <160 mg/dL (<1.81 mmol/L, <2.59 mmol/L, <3.36 mmol/L, <4.14 mmol/L).

For those reasons, ODYSSEY prespecified subgroup analyses followed this segmentation of <1.81 mmol/L, <2.59 mmol/L, <3.36 mmol/L, <4.14 mmol/L.

In addition, the most recent American National Lipid Association (NLA) recommendations for the management of dyslipidaemia (2015), also present the LDL-C thresholds into those segments with a distance of 30mg/dL (0.78 mmol/L) of LDL-C each time the risk is different. On a related note the sub-populations we present in our dossier are in line with those new NLA recommendations which are the first to address the priority target populations for PCSK9 inhibitors before the availability of CVOT results. Those recommendations are summarised in Figure 5 below. Our approach of selecting higher LDL-C thresholds was more conservative, mainly for economic reasons.

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Figure 5: Recommendations from NLA guidelines[25]

Candidates for PCSK9 inhibitors according to the new NLA recommendations (Prior to the outcomes data)

Segment	Specific population	LDL-C (mg/dL) on maximally-tolerated statin (±ezetimibe)
He FH	1. Heterozygous FH patients without ASCVD	≥ 130 (3.36 mmol/L)
ASCVD	2. ASCVD not at Goal	≥ 100 (2.58 mmol/L)
	3. Selected ASCVD patients such as those with recurrent CV events	≥ 70 (1.81 mmol/L)
Statin Intolerance	4. high or very high risk patients who meet the NLA definition of statin intolerance	Not mentioned

NLA : National Lipid Association
He FH: Heterozygous Familial Hypercholesterolemia
ASCVD : Atherosclerotic Cardiovascular Disease

Jacobson et al. J Clin Lipidol 2015 Online

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Reference List

1. Lindsey,C., Graham,M., Johnston,C., Kiroff,C., & Freshley,A. A Clinical Comparison of Calculated versus Direct Measurement of Low-Density Lipoprotein Cholesterol Level. Pharmacotherapy 24, 167-172. 2004.

2. NICE. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease; Clinical Guideline 181. 2014.

3. CTT 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 380, 581-590 (2012).

4. Alnasser et.al. Late Consequences of Acute Coronary Syndromes: Global Registry of Acute Coronary Events (GRACE) Follow-up. The American Journal of Medicine 128, 766-775. 2015.

5. Steen,D., Khan,I., & Song,X. Cardiovascular Event Rates in a High-Risk Managed Care Population in the United States. ACC . 2015.

6. Zinman,B., Warner,C., & Lachin,J. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N.Engl.J.Med Epub ahead of print. 2015.

7. O'Donoghue,M., Braunwald,E., & White,H. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. JAMA 312, 1006-1015. 2014.

8. Stability Investigators, White,H., Held,C., & Stewart,R. Darapladib for preventing ischemic events in stable coronary heart disease. N.Engl.J.Med 370, 1702-1711. 2014.

9. Steg,P.G., Bhatt,D.L., & Wilson,P.W. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 297, 1197-1206. 2007.

10. Navarese,E.P. et al. Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. Ann. Intern. Med. 163, 40-51 (2015).

11. Cohen,J.C., Boerwinkle,E., Mosley,T.H., Jr., & Hobbs,H.H. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N. Engl. J. Med. 354, 1264-1272 (2006).

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12. Ference,B.A., Majeed,F., Penumetcha,R., Flack,J.M., & Brook,R.D. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both: a 2 x 2 factorial Mendelian randomization study. J. Am. Coll. Cardiol. 65, 1552-1561 (2015).

13. Gould,A.L., Davies,G.M., Alemao,E., Yin,D.D., & Cook,J.R. Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. Clin. Ther. 29, 778-794 (2007).

14. Law,M.R., Wald,N.J., & Rudnicka,A.R. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 326, 1423 (2003).

15. Cannon,C.P. et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N. Engl. J. Med 372, 2387-2397 (2015).

16. Raal,F., Giugliano,R.P., & Sabatine,M.S. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. J.Am.Coll.Cardiol. 63, 1278-1288. 2014.

17. Nordestgaard,B.G., Chapman,M.J., Ray,K., & Boren,J. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur.Heart J. 31, 2844-2853. 2010.

18. Herrett,E. et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ 346, f2350 (2013).

19. Ara,R. & Brazier,J.E. Populating an economic model with health state utility values: moving toward better practice. Value. Health 13, 509-518 (2010).

20. NICE. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease; Clinical Guideline 181 Appendices. 2014.

21. O'Keefe et.al. Optimal low-density lipoprotein is 50 to 70 mg/dl Lower is better and physiologically normal. J Am Coll Cardiol 43(11), 2142-2146. 2004.

22. Boekholdt,S.M. et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J. Am. Coll. Cardiol. 64, 485-494 (2014).

23. Laufs,U. Eur.Heart J. 35, 1996-2000. 2014.

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24. Reiner Z, Catapano AL, De BG, et al (2011) 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. 32: 1769-1818

25. Jacobson,T.A., Maki,K.C., Orringer,C.E., & Jones,P.H. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. J Clin Lipidol . 2015.

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Patient/carer organisation submission (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

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]

Name of your organisation: HEART UK

Your position in the organisation: [redacted]

Brief description of the organisation: HEART UK- The Cholesterol Charity- is the UK's only 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.

(For example: who funds the organisation? How many members does the organisation have?)

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 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. 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.

Taken in conjunction with a statin and Ezetimibe, or by itself if intolerant to current medications, 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.

It 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.

HEART UK has not undertaken any research into this.

5. 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)
- 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, often confused with reports in the mainstream media. HEART UK offers literature and information on lifestyle choices and medication options.

Please list any concerns patients or carers have about the treatment being appraised.

Patients are often concerned about the life-long financial consequences of paying for prescriptions. Patients perceive an unfairness compared with other long-term conditions when prescriptions are not paid for. .

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.

None known

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.

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 known

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)?

X 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.

9. Other issues

Do you consider the treatment to be innovative?

X 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?

Access 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 medications does not reduce their cholesterol sufficiently, therefore add on treatments are necessary to avoiding the development of CVD

- Patients will need support when initiating treatment given the new method of administration (injection)
- Alirocumab 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

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia 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: [redacted]

Name of your organisation: British Cardiovascular Society

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- 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)?
- **other? (please specify)**
    - **A specialist (consultant cardiologist) with expertise in dyslipidemia in relation to cardiovascular risk and in the management of cardiovascular risk.**

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia 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?

For the treatment of primary hypercholesterolemia and mixed dyslipidemia
The description of the conditions in which alirocumab may be used is quite a broad one and covers number of conditions. Current approaches to cholesterol reduction incorporate a number of factors that include:

1. Any known underlying genetic defect
2. The level of LDL cholesterol, or variant (e.g. non-HDL cholesterol)
3. Other features of dyslipidemia
4. Drug intolerance / interactions
5. Additional indications e.g. for secondary prevention of cardiovascular disease

a) Apheresis – Used in severe cases. Expensive – invasive – impacts quality of life.

b) Statin drugs – Effective – large evidence base. Outcome data in primary and secondary prevention. Safe and effective. Serious side effects are rare. Intolerance relatively common but highly subjective.

c) Ezetimibe – Less efficacious. Well tolerated. Outcome data positive in secondary prevention.

d) PCSK-9 inhibitors – emerging class, Highly efficacious but limited outcome data.

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?

High LDL-cholesterol is a risk factor for cardiovascular disease At the level of LDL-cholesterol attained in studies to date, there appears to be a linear relationship in primary and secondary prevention populations between CV risk and LDL-cholesterol. At some point that relationship will breakdown.

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 is an injectable monoclonal antibody therapy.
It is likely to be expensive. Based on relatively small number of patients in published studies, the early safety profile seems to be good. I would anticipate Initial use in specialist clinics, especially pending outcome data.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

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?

Not applicable – new drug

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.

Not applicable – new drug

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 key here is the increased efficacy of this drug in lowering LDL-cholesterol, particularly when used in conjunction with statins.

How and whether this will translate into outcome benefits is not yet known and will likely depend in part on the patient groups in which it is studied.

For patients with severe hypercholesterolemia e.g. in heterozygous FH, there is a clear consensus that LDL-c should be lowered to reduce cardiovascular risk. The extent to which that should be pursued has not been defined by clinical trials.

In patients with established atherosclerotic disease lowering LDL with statins and ezetimibe + statin lowers CV mortality / major adverse cardiovascular events. However, it is unclear whether, or to what extent, further LDL-reduction would reduce cardiovascular events in that population. The secondary prevention outcome trials for PCSK-9 inhibition are awaited.

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.

I am not aware that any such tests e.g. plasma biomarkers (over and above LDL-c) are of use in this situation, though they would be desirable.

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?

Alirocumab has been used in several clinical trials in various groups of patients with dyslipidemias. It is highly efficacious in lowering LDL-cholesterol. This reduction appears to be sustained for the duration of treatment. Consistent with what is understood of the mechanism of action, changes to other lipoprotein classes are minimal.

Because alirocumab is given by injection the effects observed in trials should reflect closely the 'real-world' effects - assuming, of course, that patients in the real world are adherent to such a therapeutic regime.

There is good reason (from trials of statins and ezetimibe) to suppose the LDL-cholesterol reduction will translate into lower cardiovascular risk. However, this is not inevitable and trials of nicotinic acid and CETP inhibition with torcetrapib lowered LDL-cholesterol but with overall adverse outcomes – presumably due to "off-target" effects. However, one might reasonably assume that the potential for off-target effects of a monoclonal antibody (which is inherently specific in its targeting) would be low and that the LDL-c benefits would exert the dominant effect.

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?

I am not aware of any such information. Refer to clinical trials

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.

I am not aware of any such information

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

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)?

This is an injectable preparation that is administered subcutaneously. I would expect the additional training resources to be relatively modest and easily communicated. There should be precedence from implementation of other monoclonal therapies e.g. in cancer and rheumatological diseases

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.

I am not aware of any such potential.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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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: [redacted]

Name of your organisation: Royal College of Pathologists
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- 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)?
- other? (please specify)

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia 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.

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.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

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?

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.

The submission does not include homozygous familial hypercholesterolaemia. A recent trial (see attached)has shown has shown effective cholesterol lowering. The response in homozygous familial hypercholesterolaemia reflects the residual receptor function. Those with no residual receptor function (null) do not respond but these are in the minority. Up to 40% reduction was achieved in this trial. Alirocumab, therefore has a potential role as an additional treatment for patients on LDL apheresis or may reduce the frequency of apheresis. This is important because there is a lack of capacity for apheresis in England and most patients are treated sub-optimally every two weeks rather than weekly. Replacement of a session of apheresis by use of Alirocumab would have cost benefits

A certain mutation leading to receptor dysfunction on homozygous familial hypercholesterolaemia causes over production of PCSK9 protein. Patients homozygous for this mutation or with this mutation combined with another mutation even if that second mutation is null would be expected to have a very favourable response to inhibition of the PCSK9 protein and this has been demonstrated.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *The Lancet*, 2015:385;341-350.

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)?

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia 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: ALAN REES

Name of your organisation HEART UK

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.)? **YES. MEDICAL DIRECTOR OF HEART UK (pro bono position in a Medical Charity)**
- other? (please specify) **PREVIOUS CO-AUTHOR OF JBS-1 & JBS-3 NATIONAL GUIDELINES, PREVIOUS CHAIR OF TRUSTEES OF HEART UK, PAST PRESIDENT OF SECTION OF LIPIDS, METABOLISM AND VASCULAR RISK SECTION OF THE RSM, PAST CHAIR OF WELSH ENDOCRINE AND DIABETES SOCIETY, CURRENT CHAIR OF THE SOCIETY OF PHYSICIANS IN WALES, CURRENT VICE PRESIDENT OF THE RCP FOR WALES, PREVIOUS MEMBER AND CO-AUTHOR OF: 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).**
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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 both in secondary and primary care. Specialist lipid clinics are not ubiquitous in the UK and many patients with FH are not fully evaluated and simply receive statin therapy following screening (NHS Health Check) or after review by general cardiology or diabetes/endocrine services. **National and international consensus guidelines exist on the management of FH. Most guidelines follow NICE CG71 and TA132 on recommendations for diagnosis, and treatment with statin and/or ezetimibe therapy. Some controversy exists 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% recomendation as achieving LDL-C targets in the general population 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 of LDL-C may have very high LDL-C (overlapping with genetically diagnosed HeFH) and do not respond fully to current therapies despite proof of adequate adherence. They often show 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 poor 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 both in Canada and also 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 low-efficacy alternative medications.**
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.Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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 will 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 old 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-it is being used in some patients in clinical trials and in trial extensions
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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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 Hypercholesterolaema) 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/relevant
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?
Alirocumab 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 Alirocumab 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 (old data) 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 Alirlocumab. 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

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 Alirocumab. 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

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Single Technology Appraisal (STA)

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 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.

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Single Technology Appraisal (STA)

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.

The intruiging finding from the Aliroocumab 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 mmo/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, Averna 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.

<u>Criteria for the diagnosis of homozygous familial hypercholesterolaemia</u>

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***

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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.
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 PCSK9 mabs 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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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)?

Suitable patients would already be attending LIPID CLINICS but there would be extra resource issues

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Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by British Cardiovascular Society and consequently I will not be submitting a personal statement.

Name: .....Robin Choudhury.....

Signed: .....[redacted].....

Date: .....6 Jan 15.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779]

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: Karen hasid
Name of your nominating organisation: Heart UK
Do you know if your nominating organisation has submitted a statement?

☐X Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☐X Yes ☐ No

(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?

☐X Yes ☐ No

- a carer of a patient with the condition?

☐X Yes ☐ No

- a patient organisation employee or volunteer?

☐X Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☐X 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.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

As a patient and carer of FH my experience is a constant battle of maintaining healthy cholesterol numbers whilst experiencing raised ALT, raised Amylase causing pains in the abdomen caused by current medication. A catch 22, lower medication may equal less side effects but this raises the LDL.

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.

The treatment outcomes for me would be to have a drug that could reduce our risk as a family from early onset heart conditions caused by raised LDL. This drug would enable the reduction without having to use any invasive, time consuming procedures such as apheresis. I especially think of my children's futures who should have the right to normal lifestyle, for example college, university, travelling without having to worry about missing lectures because they have to be hooked up to a machine twice a month for apheresis leaving them feeling weak afterwards for a few days following. Treatment.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

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.

Lowering raised LDL leading to early onset heart conditions giving a better quality of life.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Non debilitating, non invasive plus it is cheaper than apheresis whilst giving quality of life.

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.

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.

People can't tolerate statins and need alternatives in FH

Please list any concerns you have about the treatment being appraised.

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.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Yes, patients who are unable to tolerate statins and of course the rare HOFH patients with the PCSK9 fault who from the studies that have already taken place have shown that when the new PCSK9 drug have been added to the statin regime in HOFH patients they have had a very good improvement.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

People who tolerate statins and have had a good result from their current treatment.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☐ 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?

☐x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

This treatment is non invasive or debilitating to the patient whilst lowering cholesterol significantly.

Is there anything else that you would like the Appraisal Committee to consider?

How much apheresis costs in comparison to this drug

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Quality of Life
- Longevity of life
- Avoiding the invasive apheresis treatments with al its concomitant problems i.e travelling, time consuming, debilitating, invasive etc…
- Price comparison to Apheresis
- Freeing up the paid time of the professional healthcare specialised staff at the hospital who would administer apheresis, rather than the ease of self administering of the drug at home.

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Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by HEART UK and consequently I will not be submitting a personal statement.

Name: Karen Hasid.....

Signed: .....Karen Hasid.....

Date: .....08/01/16.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by HEART UK and consequently I will not be submitting a personal statement.

Name: SIMON WILLIAMS

Signed: [redacted]

Date: 7/1/15

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/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/Pharmaceuticalpriceregulationscheme/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-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.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-pmg9).

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.

Response

Brand Name:	Praluent®
Approved Name:	Alirocumab
Therapeutic Class:	PCSK9 Inhibitor
Disease Area:	Hypercholesterolaemia

3.2 Please outline the rationale for developing the patient access scheme.

Response

The patient access scheme was developed to improve the cost-effectiveness of alirocumab across all populations covered by the licensed indication

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Response

As defined in the 2014 PPRS, with reference to the 2009 PPRS, the patient access scheme is a ‘simple discount scheme’.

The scheme takes the form of a confidential fixed price at the point of invoice and as such qualifies as a simple discount scheme as it imposes no significant ongoing additional burden on the NHS.

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:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

Response

The patient access scheme will apply to all patient populations within the licensed 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? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

Response

The scheme will apply to all patients within the licensed indication.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Response

N/A

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

Response

The simple patient access scheme takes the form of a confidential fixed price at the point of invoice.

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.

Response

The simple patient access scheme takes the form of a confidential fixed price at the point of invoice. No additional information will, therefore, need to be collected.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Response

N/A

3.10 Please provide details of the duration of the scheme.

Response

We anticipate the simple PAS will be in place at least until the point where NICE reviews the guidance on alirocumab (until subsequent publication of final guidance from the review). The only circumstance in which we would withdraw the simple PAS is if the list price changes to a level at or below the simple PAS price. In such a circumstance the simple PAS would obviously be unnecessary and we would withdraw it.

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?

Response

N/A

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.

Response

A condition of supply letter outlining the nature of the PAS and expectation of confidentiality will be provided to relevant NHS stakeholders. No signatures are required.

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.

N/A

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.

Response

The population to whom the scheme applies is identical to that presented in the main manufacturer/sponsor submission of evidence for the technology appraisal.

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.

Response

N/A

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.

Response

The patient access scheme is reflected in the model by a reduction in the annual price of alirocumab based on the confidential fixed price at the point of invoice detailed in 3.7. The price per year is based on multiplying the unit price for 14 days of

treatment to 365.25 days. The cells, for reference, are F490 and F491 in the Introduction Tab of the de novo economic model.

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.

Response

Please refer to Sections 4 of the company evidence submission document: Single technology appraisal - Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779] for general details of the clinical effectiveness data.

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'.

Response

N/A – simple discount

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.

Response

N/A

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

Table 1 - Cost-effectiveness base case results without PAS, by population. This table is a composite of Tables 72-77 in the main submission; cross-reference information is provided in the first column of Table 1.

- the results for the intervention with the patient access scheme.

Table 2a - Cost-effectiveness base case results with PAS, by population (duplicate of Table 1 – without PAS). This table is a composite of Tables 72-77 in the main submission; cross-reference information is also provided in the first column of Table 2a.

Table 2b-d - Summary of costs by health state, by population. These are duplicates of Tables 96-98 in the main submission.

Table 2e - Subgroup analyses by LDL-C levels. This table is a composite of Table 99 in the main submission.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 1 Incremental cost-effectiveness results – Basecases without Patient Access Scheme

Sub Ref	Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
Table 72 page 238	**HeFH primary prevention (LDL-C ≥2.59 mmol/L)**	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	[redacted]	1.62	1.42	[redacted]
		Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
Table 72 page 238	**HeFH secondary prevention (LDL-C ≥2.59 mmol/L)** *Baseline risk data from Morschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	[redacted]	3.04	2.33	[redacted]
		Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
Table 72 page 238	**HeFH secondary prevention (LDL-C ≥2.59 mmol/L)** *Baseline risk data from THIN*	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	[redacted]	2.85	2.14	[redacted]
		Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
Table 73 page 240	**High risk CVD (LDL-C ≥3.36 mmol/L)**	Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	[redacted]	2.38	1.76	[redacted]
		Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				
Table 73 page 240	**Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)**	Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	[redacted]	2.42	1.64	[redacted]
		Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 1 (Continued) Incremental cost-effectiveness results – Basecases without Patient Access Scheme

Sub Ref	Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
Table 75 page 243	**HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L)**	Alirocumab + statins	[redacted]	[redacted]	[redacted]	[redacted]	1.07	0.95	[redacted]
		Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Table 75 page 243	**HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L)**	Alirocumab + statins	[redacted]	[redacted]	[redacted]	[redacted]	2.21	1.70	[redacted]
		Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Table 76 page 243	**High-risk CVD (baseline LDL-C ≥3.36 mmol/L)**	Alirocumab + statins	[redacted]	[redacted]	[redacted]	[redacted]	1.75	1.29	[redacted]
		Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Table 76 page 243	**Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)**	Alirocumab + statins	[redacted]	[redacted]	[redacted]	[redacted]	1.83	1.25	[redacted]
		Ezetimibe + statins	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 1 (Continued) Incremental cost-effectiveness results – Basecases without Patient Access Scheme

Sub Ref	Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
STATIN INTOLERANT									
Table 74 page 240	**High-risk CVD (baseline LDL-C ≥3.36mmol/L)**	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	2.76	2.04	[redacted]
		Ezetimibe	[redacted]	[redacted]	[redacted]				
Table 74 page 240	**Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)**	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	3.52	2.40	[redacted]
		Ezetimibe	[redacted]	[redacted]	[redacted]				
Table 77 page 244	**High-risk CVD (baseline LDL-C ≥3.36 mmol/L)**	Alirocumab	[redacted]	[redacted]	[redacted]	[redacted]	2.40	1.78	[redacted]
		Ezetimibe	[redacted]	[redacted]	[redacted]				
Table 77 page 244	**Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)**	Alirocumab	[redacted]	[redacted]	[redacted]	[redacted]	3.12	2.14	[redacted]
		Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 2a Incremental cost-effectiveness results – Basecases with Patient Access Scheme

Sub Ref	Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
Table 72 page 238	**HeFH primary prevention (LDL-C ≥2.59 mmol/L)**	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	52,256	1.62	1.42	36,793
		Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
Table 72 page 238	**HeFH secondary prevention (LDL-C ≥2.59 mmol/L)** *Baseline risk data from Morschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	39,306	3.04	2.33	16,896
		Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
Table 72 page 238	**HeFH secondary prevention (LDL-C ≥2.59 mmol/L)** *Baseline risk data from THIN*	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	40,733	2.85	2.14	19,060
		Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
Table 73 page 240	**High risk CVD (LDL-C ≥3.36 mmol/L)**	Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	34,684	2.38	1.76	19,751
		Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				
Table 73 page 240	**Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)**	Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	31,953	2.42	1.64	19,447
		Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 2a (Continued) Incremental cost-effectiveness results – Basecases with Patient Access Scheme

Sub Ref	Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
Table 75 page 243	**HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L)**	Alirocumab + statins	[redacted]	[redacted]	[redacted]	45,962	1.07	0.95	48,193
		Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Table 75 page 243	**HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L)**	Alirocumab + statins	[redacted]	[redacted]	[redacted]	34,632	2.21	1.70	20,352
		Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Table 76 page 243	**High-risk CVD (baseline LDL-C ≥3.36 mmol/L)**	Alirocumab + statins	[redacted]	[redacted]	[redacted]	31,195	1.75	1.29	24,175
		Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Table 76 page 243	**Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)**	Alirocumab + statins	[redacted]	[redacted]	[redacted]	28,781	1.83	1.25	23,078
		Ezetimibe + statins	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 2a (Continued) Incremental cost-effectiveness results – Basecases without Patient Access Scheme

Sub Ref	Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
STATIN INTOLERANT									
Table 74 page 240	**High-risk CVD (baseline LDL-C ≥3.36mmol/L)**	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	35,146	2.76	2.04	17,256
		Ezetimibe	[redacted]	[redacted]	[redacted]				
Table 74 page 240	**Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)**	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	32,798	3.52	2.40	13,669
		Ezetimibe	[redacted]	[redacted]	[redacted]				
Table 77 page 244	**High-risk CVD (baseline LDL-C ≥3.36 mmol/L)**	Alirocumab	[redacted]	[redacted]	[redacted]	30,829	2.40	1.78	17,295
		Ezetimibe	[redacted]	[redacted]	[redacted]				
Table 77 page 244	**Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)**	Alirocumab	[redacted]	[redacted]	[redacted]	28,820	3.12	2.14	13,469
		Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 2b Summary of costs by health state – HeFH primary prevention
(Submission Table 96, page 270)

Health state	Cost intervention (alirocumab plus statins plus ezetimibe)	Cost comparator (statins plus ezetimibe)	Increment (£)
Baseline	[redacted]	[redacted]	[redacted]
P-NF ACS 0–1 years	[redacted]	[redacted]	[redacted]
P-NF ACS 1–2 years	[redacted]	[redacted]	[redacted]
Stable CHD	[redacted]	[redacted]	[redacted]
Stable post-revascularisation	[redacted]	[redacted]	[redacted]
P-NF stroke 0-1 years	[redacted]	[redacted]	[redacted]
P-NF stroke 1–2 years	[redacted]	[redacted]	[redacted]
Stable P-NF stroke	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	£52,256

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; NF, non-fatal; P-NF, post-non-fatal; QALY, quality-adjusted life-year; HS1, health state 1; HS2, health state 2; NF, non-fatal

Table 2c Summary of costs by health state – HeFH secondary prevention
(Submission Table 97, page 270-1)

Health state	Cost intervention (alirocumab plus statins plus ezetimibe)	Cost comparator (statins plus ezetimibe)	Increment (£)
Baseline	[redacted]	[redacted]	[redacted]
P-NF ACS 0–1 years	[redacted]	[redacted]	[redacted]
P-NF ACS 1–2 years	[redacted]	[redacted]	[redacted]
Stable CHD	[redacted]	[redacted]	[redacted]
Stable post-revascularisation	[redacted]	[redacted]	[redacted]
P-NF stroke 0-1 years	[redacted]	[redacted]	[redacted]
P-NF stroke 1–2 years	[redacted]	[redacted]	[redacted]
Stable P-NF stroke	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	£39,422

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; NF, non-fatal; P-NF, post-non-fatal; QALY, quality-adjusted life-year; HS1, health state 1; HS2, health state 2; NF, non-fatal

Table 2d Summary of costs by health state – Recurrent events/ polyvascular
(Submission Table 98, page 272)

Health state	Cost intervention (alirocumab plus statins)	Cost comparator (statins)	Increment (£)
Baseline	[redacted]	[redacted]	[redacted]
P-NF ACS 0–1 years	[redacted]	[redacted]	[redacted]
P-NF ACS 1–2 years	[redacted]	[redacted]	[redacted]
Stable CHD	[redacted]	[redacted]	[redacted]
Stable post-revascularisation	[redacted]	[redacted]	[redacted]
P-NF stroke 0 -1 years	[redacted]	[redacted]	[redacted]
P-NF stroke 1–2 years	[redacted]	[redacted]	[redacted]
Stable P-NF stroke	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	£31,953

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; NF, non-fatal; P-NF, post-non-fatal; QALY, quality-adjusted life-year; HS1, health state 1; HS2, health state 2; NF, non-fatal

Table 2e Subgroup analyses by LDL-C levels
(Submission Table 99, page 273)

Patient population	Baseline LDL-C (mmol/L)	Incremental costs £	Incremental QALY	ICER
HeFH primary prevention	2.59	52,256	1.42	36,793
	3.36	52,005	1.64	31,750
	4.13	51,804	1.79	28,923
HeFH secondary prevention	2.59	39,306	2.33	16,896
	3.36	39,224	2.48	15,838
	4.13	39,023	2.74	14,242
High Risk CVD	2.59	34,701	1.37	25,287
	3.36	34,684	1.76	19,751
	4.13	34,493	2.15	16,043
Recurrent events / Polyvascular disease	2.59	31,953	1.64	19,447
	3.36	32,085	2.09	15,332
	4.13	32,013	2.54	12,606

HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life-year

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.

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.

N/A – no fully incremental analyses in submission.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

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.

HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe

Table 3 HeFH primary prevention, deterministic sensitivity analysis (Submission Table 81 page 252)

Parameter	Variation	ICER (£/QALY)
Base case with PAS		**36,793**
Annual CV risk	–20%	47,504
Annual CV risk	+20%	30,047
Adjustment of CV risk by age	–20%	37,023
Adjustment of CV risk by age	+20%	36,428
CV costs	–20%	37,094
CV costs	+20%	36,492
CV event costs	Doubled	35,287
Alirocumab efficacy (LDL-C lowering)	Lower CI	38,146
Alirocumab efficacy (LDL-C lowering)	Upper CI	35,659
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	33,828
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	39,413
Rate ratio per 1 mmol/L for treatment effect	Lower CI	29,787
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	36,448
Acute CV disutilities	Upper CI	37,144
Baseline utilities	Lower CI	36,793
Baseline utilities	Upper CI	36,793
Chronic CV disutilities	Lower CI	35,751
Chronic CV disutilities	Upper CI	37,897

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio

HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe

Table 4 HeFH secondary prevention, deterministic sensitivity analysis (Submission Table 82 page 253)

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**16,896**
Annual CV risk	–20%	20,018
Annual CV risk	+20%	14,806
Adjustment of CV risk by age	–20%	16,932
Adjustment of CV risk by age	+20%	16,919
CV costs	–20%	17,192
CV costs	+20%	16,600
CV event costs	Doubled	15,416
Alirocumab efficacy (LDL-C lowering)	Lower CI	17,690
Alirocumab efficacy (LDL-C lowering)	Upper CI	16,222
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	16,020
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	17,622
Rate ratio per 1 mmol/L for treatment effect	Lower CI	12,477
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	16,756
Acute CV disutilities	Upper CI	17,038
Baseline utilities	Lower CI	17,574
Baseline utilities	Upper CI	16,268
Chronic CV disutilities	Lower CI	16,722
Chronic CV disutilities	Upper CI	17,074

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio;

High Risk CVD - alirocumab + statins versus statins

Table 5 High risk CVD, deterministic sensitivity analysis
(Submission Table 83 page 254)

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**19,751**
Annual CV risk	–20%	23,910
Annual CV risk	+20%	17,009
Adjustment of CV risk by age	–20%	19,710
Adjustment of CV risk by age	+20%	19,784
CV costs	–20%	19,979
CV costs	+20%	19,522
CV event costs (doubled)		18,608
Alirocumab efficacy (LDL-C lowering)	Lower CI	20,600
Alirocumab efficacy (LDL-C lowering)	Upper CI	19,021
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	18,650
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	20,689
Rate ratio per 1 mmol/L for treatment effect	Lower CI	14,518
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	19,621
Acute CV disutilities	Upper CI	19,882
Baseline utilities	Lower CI	20,549
Baseline utilities	Upper CI	19,012
Chronic CV disutilities	Lower CI	19,578
Chronic CV disutilities	Upper CI	19,926

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio

Recurrent events/ Polyvascular Disease - alirocumab + statins versus statins

Table 6 Recurrent events/ polyvascular, deterministic sensitivity analysis (Submission Table 84 page 255)

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**19,447**
Annual CV risk	–20%	22,901
Annual CV risk	+20%	17,153
Adjustment of CV risk by age	–20%	18,799
Adjustment of CV risk by age	+20%	20,096
CV costs	–20%	19,649
CV costs	+20%	19,245
CV event costs	Doubled	18,435
Alirocumab efficacy (LDL-C lowering)	Lower CI	20,623
Alirocumab efficacy (LDL-C lowering)	Upper CI	18,460
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	18,919
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	19,872
Rate ratio per 1 mmol/L for treatment effect	Lower CI	13,268
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Domniated
Acute CV disutilities	Lower CI	19,331
Acute CV disutilities	Upper CI	19,564
Baseline utilities	Lower CI	20,585
Baseline utilities	Upper CI	18,429
Chronic CV disutilities	Lower CI	19,358
Chronic CV disutilities	Upper CI	19,537

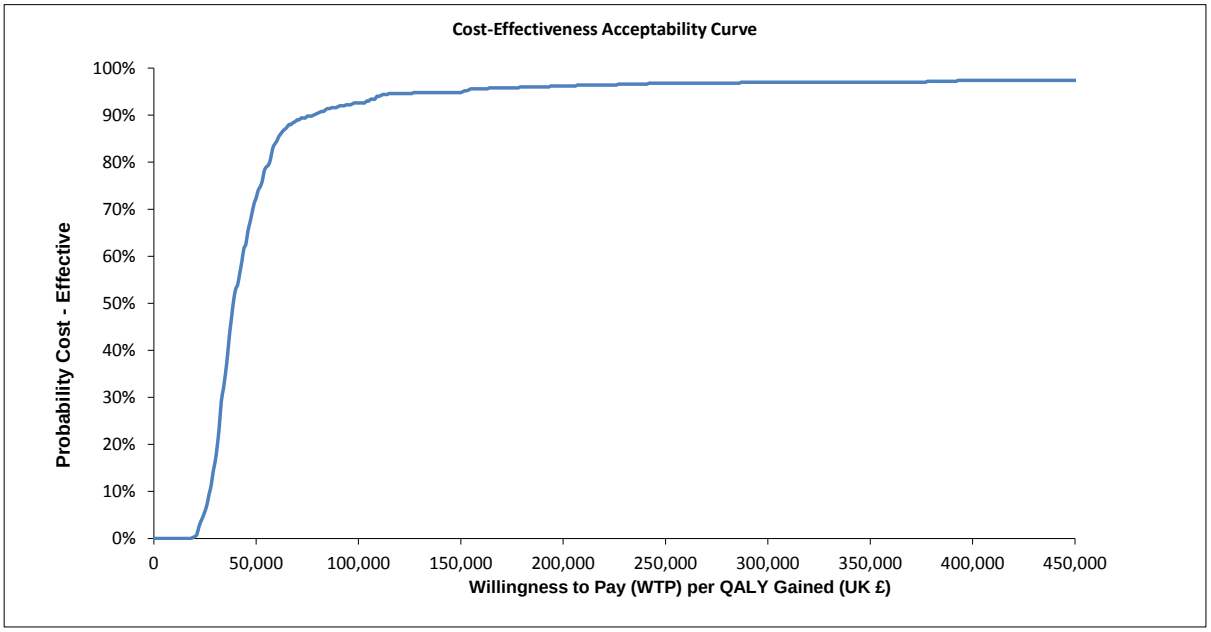
CI, confidence interval; CV, cardiovascular; ICER, incremental cost-effectiveness ratio

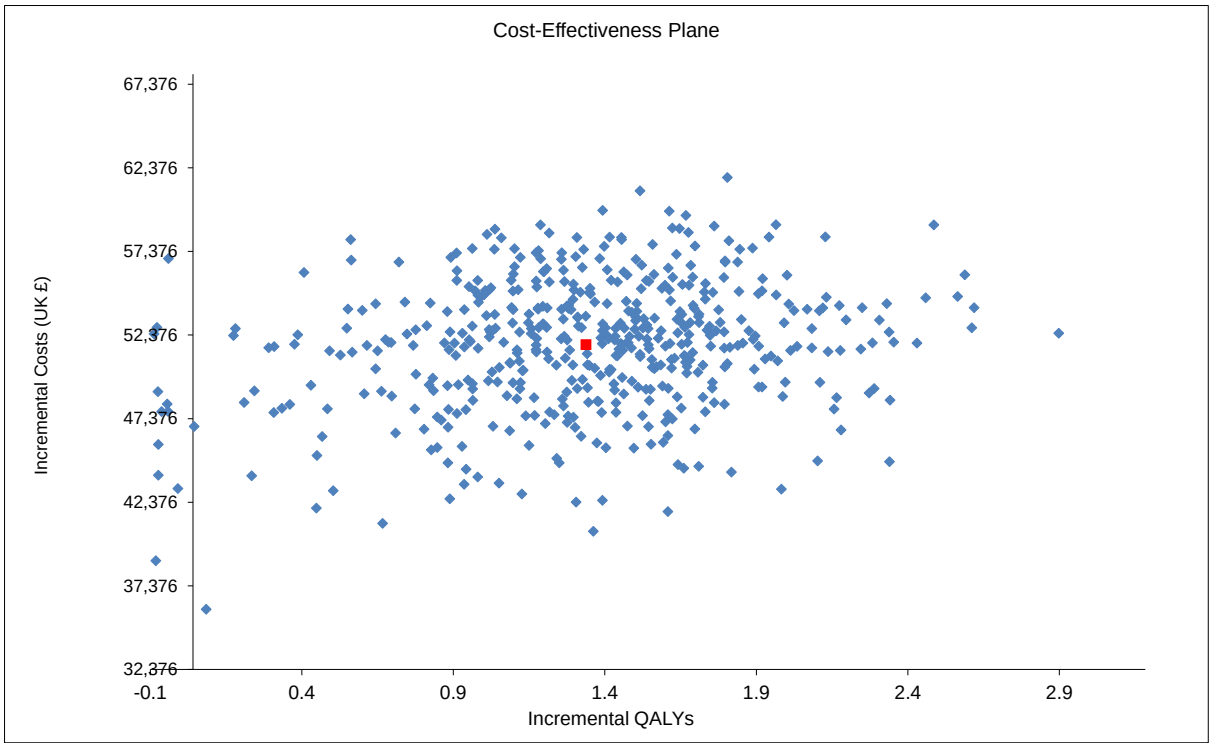
4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Response

HeFH primary prevention, Alirocumab + statins + ezetimibe versus statins + ezetimibe

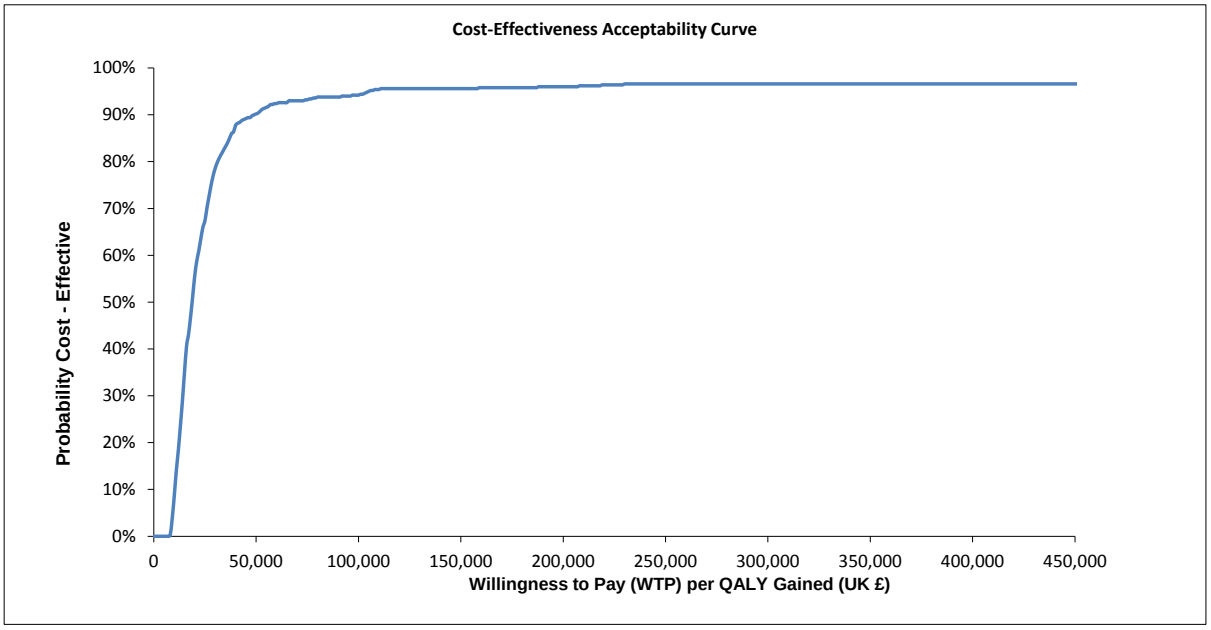
Figure 1 HeFH primary prevention, Scatter plot and CEAC
(Submission Figure 31, page 248)

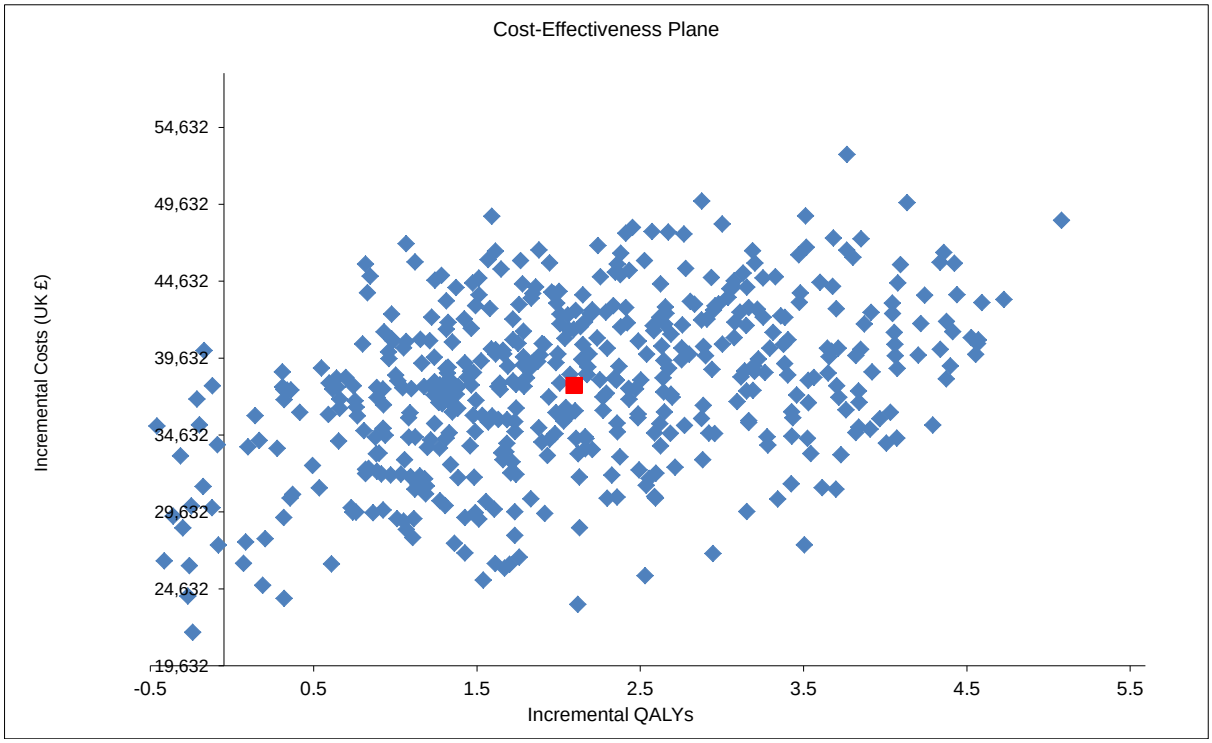




HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe

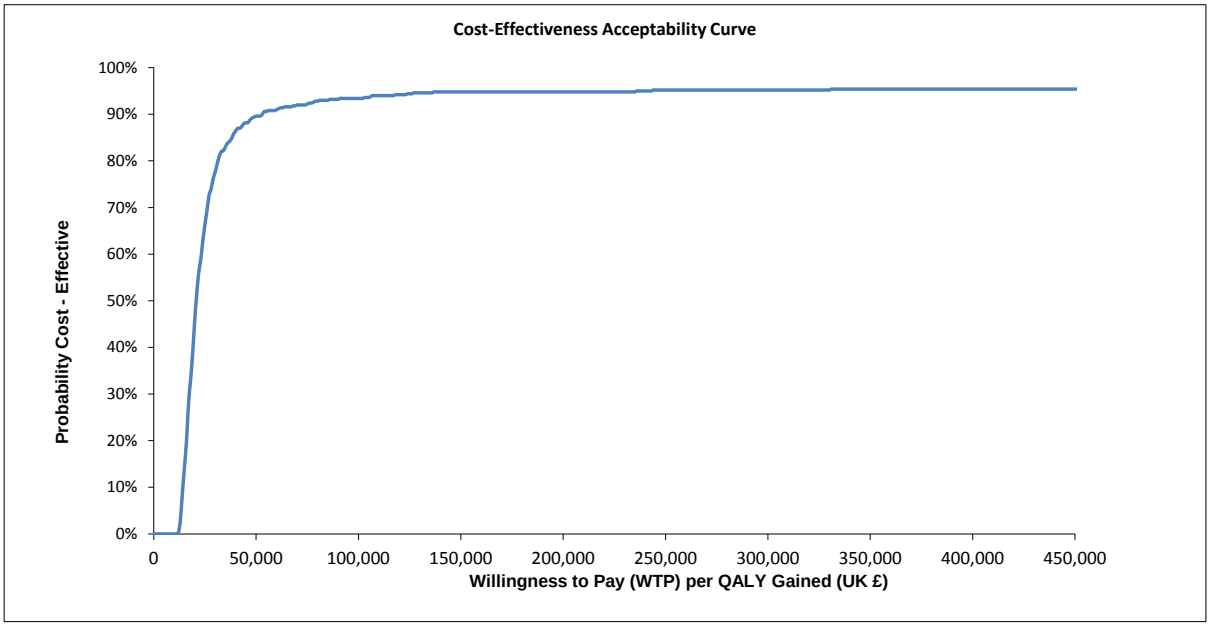
Figure 2 HeFH secondary prevention, Scatter plot and CEAC
(Submission Figure 32, page 249)

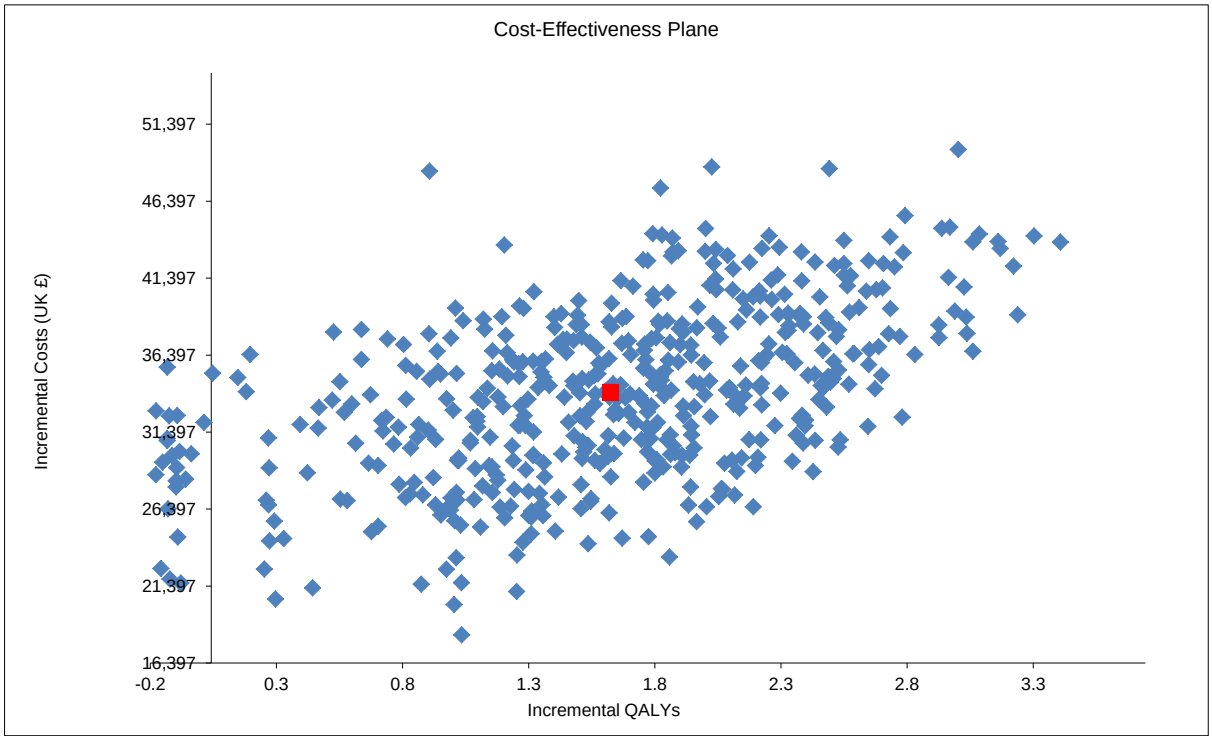




High risk CVD, alirocumab + statins versus statins

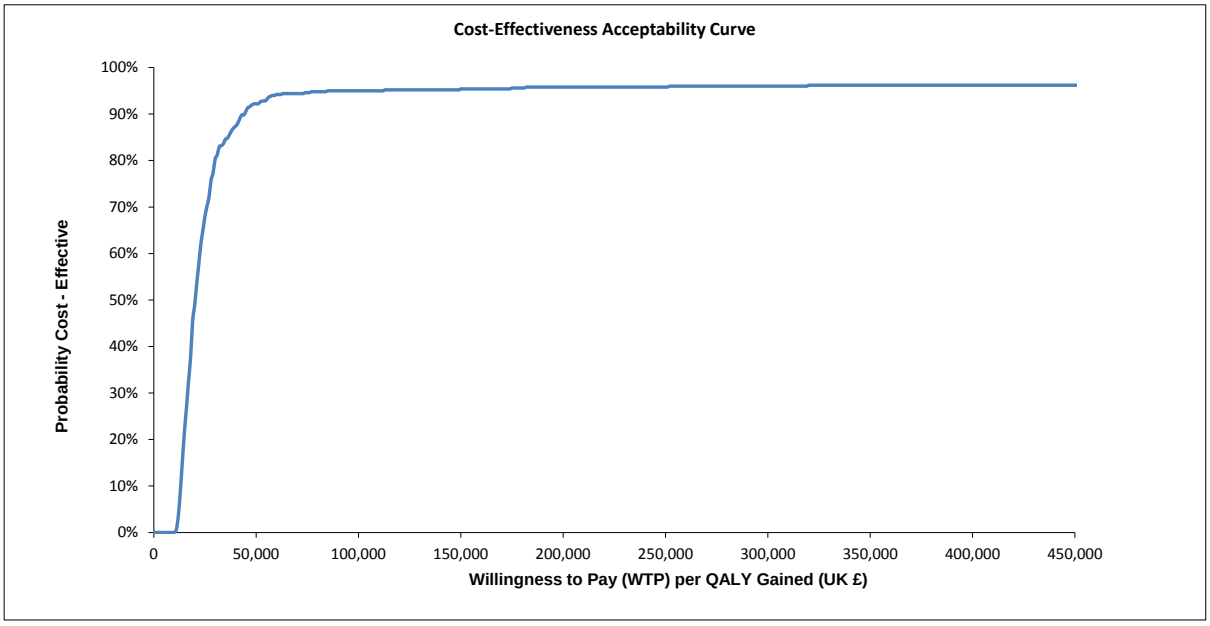
Figure 3 High Risk CVD, scatter plot and CEAC
(Submission Figure 33, page 250)

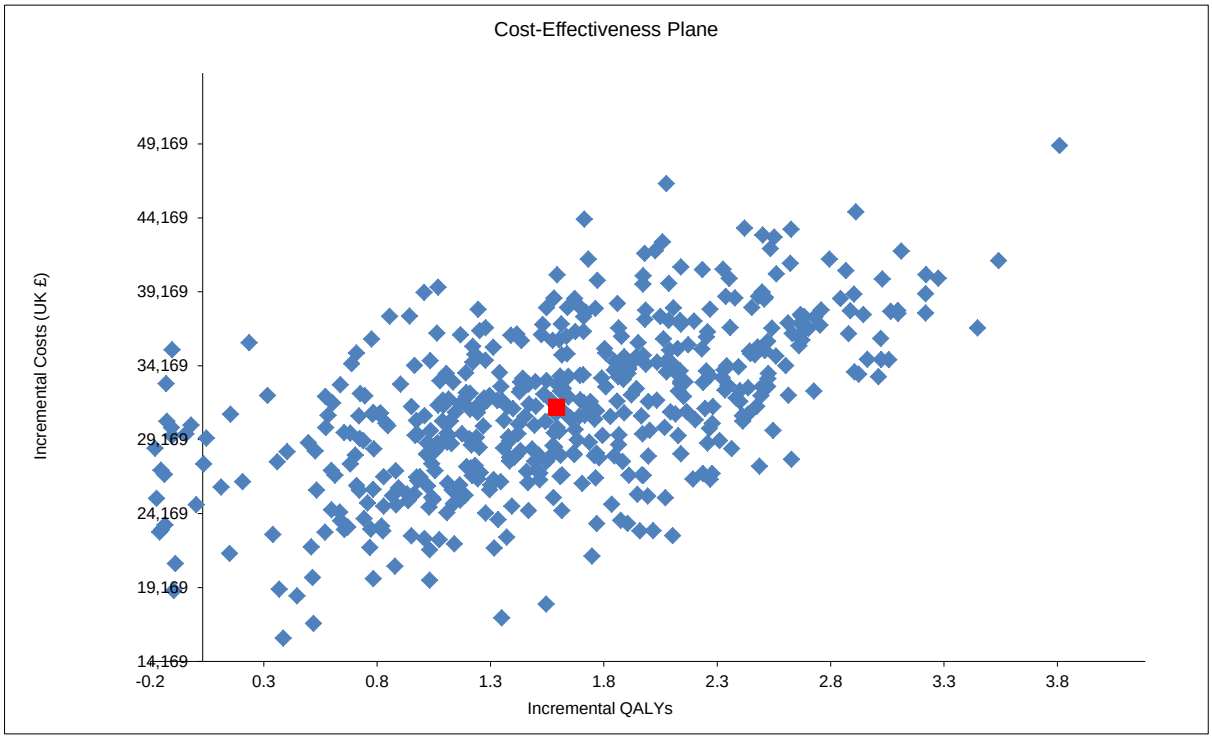




Recurrent events/ Polyvascular disease, alirocumab + statins versus statins

Figure 4 Polyvascular, scatter plot and CEAC
(Submission Figure 34, page 251)





Probability of cost-effectiveness by Willingness to Pay for key patient groups – with Patient Access Scheme
(Submission Table 79 page 251)

	HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	High-risk CVD (baseline LDL-C ≥3.36 mmol/L) – alirocumab + statins versus statins	Recurrent events/ polyvascular disease (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins versus statins
Willingness to pay	**Probability of cost-effectiveness**			
20,000/QALY	15%	56%	46%	49%
30,000/QALY	36%	79%	78%	80%
40,000/QALY	51%	88%	86%	87%

CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; 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.

Response

HeFH primary prevention - alirocumab plus statins plus ezetimibe versus statins plus ezetimibe

Table 7 HeFH primary prevention, Scenario analyses
(Submission Table 86 page 258)

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with PAS**			**36,793**
Discontinuation rate	0%	3%	38,168
		8%	41,852
Cost and benefit discount rates	3.50%	0%	24,821
		5%	43,533
Treatment duration	Lifetime	1 year	50,197
		5 years	47,326
Model time horizon	Lifetime	5 years	398,895
		10 years	197,133
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	60,736
		LONG TERM study	40,929
		Pooled phase III vs placebo	52,476
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	37,592
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	28,679
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	39,235
		100% use of 150 mg	35,954

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non fatal; QALY, quality-adjusted life-year

HeFH secondary prevention- alirocumab plus statins plus ezetimibe versus statins plus ezetimibe

Table 8 HeFH secondary prevention – Scenario analyses
(Submission Table 87 page 258-9)

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			**16,896**
Baseline risk data	As per Morschladt 2004	As per THIN	19,060
Discontinuation rate	0%	3%	17,264
		8%	17,949
Cost and benefit discount rates	3.5%	0%	13,984
		5%	18,306
Treatment duration	Lifetime	1 year	18,863
		5 years	18,102
Model time horizon	Lifetime	5 years	64,199
		10 years	36,856
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	32,937
		LONG TERM study	19,294
		Pooled phase III vs placebo	25,741
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	16,734
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	13,347
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	18,259
		100% use of 150 mg	16,348

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; HSE; Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non-fatal

High risk CVD - alirocumab plus statins versus statins

Table 9 High Risk CVD – Scenario analyses
(Submission Table 88 page 259-60)

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			19,751
Discontinuation rate	0%	3%	19,979
		8%	20,601
Cost and benefit discount rates	3.5%	0%	16,181
		5%	21,472
Treatment duration	Lifetime	1 year	20,148
		5 years	20,660
Model time horizon	Lifetime	5 years	85,694
		10 years	44,495
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	41,431
		LONG TERM study	22,578
		Pooled phase III vs placebo	30,218
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	19,654
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	15,761
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	21,571
		100% use of 150 mg	18,781

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; CVD, cardiovascular disease; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P-NF, post-non-fatal

Recurrent events/ Polyvascular Disease - alirocumab plus statins versus statins

Table 10 Recurrent events/ polyvascular disease – Scenario analyses
(Submission Table 89 page 260)

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			**19,447**
Discontinuation rate	0%	3%	19,738
		8%	20,353
Cost and benefit discount rates	3.5%	0%	16,317
		5%	20,931
Treatment duration	Lifetime	1 year	20,869
		5 years	20,222
Model time horizon	Lifetime	5 years	72,896
		10 years	38,468
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	44,154
		LONG TERM study	22,651
		Pooled phase III vs placebo	31,181
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	19,336
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	15,968
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	20,969
		100% use of 150 mg	17,915

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P -NF, post-non-fatal

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.

Response
N/A

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. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 11 Results showing the impact of patient access scheme on ICERs

	ICERs							
	HeFH Primary Prevention Alirocumab + statins + ezetimibe versus statins + ezetimibe		HeFH Secondary Prevention Alirocumab + statins + ezetimibe versus statins + ezetimibe		High Risk CVD Alirocumab + statins + versus statins + ezetimibe		Recurrent events/ polyvascular disease Alirocumab + statins + versus statins + ezetimibe	
	Without PAS	With PAS	Without PAS	With PAS	Without PAS	With PAS	Without PAS	With PAS
Basecases	[redacted]	£36,793	[redacted]	£16,896	[redacted]	£19,751	[redacted]	£19,447

PAS: patient access scheme.

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.

Response

N/A

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.

Response

N/A – simple discount only

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.

Response

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.

Response

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).

Response

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.

Response

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.

Response

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.

Response

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.

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.

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Produced by Aberdeen HTA Group

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Date completed 2 December 2015

Version 1

Source of funding: This report was commissioned by the NIHR HTA Programme as project number **14/206/03**.

Declared competing interests of the authors

None.

Acknowledgements

The authors are grateful to Lara Kemp for her secretarial support.

Rider on responsibility for report

The view 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:

Scotland G, Neilson A, Javanbakht M, Fielding S, Cruickshank M, Sharma P, Fraser C, Simpson W, Brazzelli M. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Aberdeen HTA Group, 2015.

Contribution of authors

Graham Scotland, Aileen Neilson and Mehdi Javanbakht acted as health economists; critiqued and reviewed the cost-effectiveness evidence presented in the submission, checked and re-analysed the economic model, and carried out further sensitivity analyses. Shona Fielding acted as statistician; critiqued the statistical methods presented in the submission, checked the numerical results, tables, and figures related to the review of the clinical effectiveness evidence. Moira Cruickshank and Pawana Sharma acted as systematic reviewers; critiqued the clinical effectiveness methods. Cynthia Fraser acted as information scientist; critiqued the methods used for identifying relevant studies in the literature and conducted additional searches. William Simpson acted as clinical expert; provided clinical advice and general guidance. Miriam Brazzelli acted as project lead for this appraisal; contributed to the critique and review of the clinical effectiveness methods, and supervised the work throughout the project. All authors contributed to the writing of the report and approved its final version.

Table of contents

List of tables

List of figures

List of abbreviations

ACS	Acute coronary syndrome
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
Apo B	Apolipoprotein B
BMI	Body mass index
CAD	Coronary artery disease
CEAC	Cost-effectiveness acceptability curve
CFB	Change from baseline
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CRD	Centre for Reviews and Dissemination
CTT	Cholesterol Treatment Trialists' collaboration
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
EAS	European Atherosclerosis Society
EQ5D	EuroQol 5-dimensions
ERG	Evidence review group
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FH	Familial hypercholesterolaemia
HCHS	Hospital and community health services
HDL	High density lipoprotein
HeFH	Heterozygous familial hypercholesterolaemia
HMG-CoA	3-Hydroxy-3-Methyglutaryl Co-enzyme A
HoFH	Homozygous familial hypercholesterolaemia
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio

IDL	Intermediate density lipoprotein
IS	Ischaemic stroke
JBS	Joint British societies
LDL-C	Low density lipoprotein cholesterol
LMT	Lipid modifying therapy
LY	Life years
MD	Mean difference
MI	Myocardial infarction
NCEP	National Cholesterol Education Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ONS	Office for national statistics
OR	Odds ratio
PAD	Peripheral artery disease
PAS	Patient access scheme
PCSK9	Proprotein convertase subtilisin/kextin type 9
PSS	Personal social services
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QALY	Quality adjusted life years
QD	Every day
QM	Every 4 weeks
QoL	Quality of life
RCT	Randomised controlled trial
RR	Risk ratio
SAE	Serious adverse event
SD	Standard deviation
SI	Statin intolerance
SmPC	Summary of product characteristics
TA	Technology assessment
TC	Total cholesterol

TEAE	Treatment emergent adverse event
TG	Triglycerides
TIA	Transient ischaemic attack
TTO	Time trade off
ULN	Upper limit of normal
VLDL	Very low density lipoprotein
WHO	World Health Organisation

1 Summary

Primary hypercholesterolaemia is a form of dyslipidaemia characterised by abnormalities of lipoprotein transport associated with high concentrations of cholesterol in the blood. Primary hypercholesterolaemia can be caused by a single genetic defect (*monogenic familial*) or by the interaction of a genetic predisposition and other environmental factors such as smoking, diet, or physical inactivity (*polygenic or non-familial*). In familial hypercholesterolaemia (FH), people inherit an abnormal (mutant) gene that affects the rate at which cholesterol is cleared from the blood. A mutant gene can be inherited from either one parent (heterozygous FH) or both parents (homozygous FH). In Europe, prevalence of heterozygous FH is commonly estimated at 1 in 500, and prevalence of homozygous FH at 1 in 1,000,000. Non-familial hypercholesterolaemia is the most common form of primary hypercholesterolaemia, with an estimated prevalence of 42 in 1000.

Dyslipidaemia is a key, but modifiable, risk factor for development of atherosclerosis, the accumulation and hardening of fatty deposits in the arteries. Atherosclerosis is the cause of cardiovascular disease events such as coronary heart disease, transient ischaemic attack and stroke. Dyslipidaemia refers to a broad spectrum of health conditions, including hypercholesterolaemia and mixed dyslipidaemia.

Mixed dyslipidaemia is characterised by raised levels of LDL-C and triglycerides, commonly with concomitant decreased concentration of HDL-C. The risk of cardiovascular disease is significantly increased in people with mixed dyslipidaemia due to a cluster of lipid disorders and thrombogenic abnormalities. The estimated prevalence of mixed dyslipidaemia in the UK is 10%.

1.1 Critique of the decision problem in the company's submission

The NICE scope considered the clinical and cost-effectiveness of alirocumab (Praluent®, Sanofi-Aventis Groupe, Paris, France) within its licensed indication for the management of primary hypercholesterolaemia (heterozygous and non-familial) and mixed dyslipidaemia in adults for whom lipid modifying therapies, in line with current NICE guidance, would be considered. Alirocumab is a fully human

monoclonal antibody that specifically binds proprotein convertase subtilisin/kextin type 9 (PCSK9), a down regulator of LDL receptors in the liver, thereby increasing its ability to bind LDL-C, which reduces levels of LDL-C in the blood. According to the current marketing authorisation, alirocumab is indicated "*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*.".

The NICE final scope specified the intervention for this appraisal as alirocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe. In contrast, the decision problem addressed by the company specified maximal tolerated dose of statins in combination with alirocumab with or without ezetimibe, or alirocumab on a background of no statins, with or without ezetimibe. The company's justification for the deviation from the scope was based on current NHS usage of ezetimibe. The ERG was in agreement that these changes were appropriate.

The decision problem addressed in the submission deviated from the NICE final scope in that the company did not consider evolocumab, an alternative PCSK9 inhibitor, as a comparator. The company's rationale for this omission was that guidance on evolocumab had not yet been issued by NICE and that at present the use of evolocumab it is not standard of care within the NHS. In addition, in cases where statins were contraindicated or not tolerated, the company specified no active comparator while the NICE scope specified ezetimibe, evolocumab or both. The ERG agreed with the company's choice.

The company maintained that the outcomes reported in the submission were in line with final NICE scope. However, the ERG noted that outcomes relating to requirement of procedures including LDL apheresis and revascularisation were not reported by the company.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted two systematic reviews of clinical evidence, with slightly different inclusion criteria. The first review considered people at high risk of CVD and identified a total of 32 studies. The second review considered people at moderate or high CVD risk and identified 20 studies. Nonetheless, for the assessment of the clinical effectiveness of alirocumab the company decided to focus exclusively on 10 phase III multicentre RCTs from the ODYSSEY programme, which was sponsored by the manufacturers of alirocumab. The trials involved comparison of alirocumab with placebo (n=5), ezetimibe (n=2) or ezetimibe and a statin (n=3). Eight studies evaluated alirocumab at a dose of 75 mg every two weeks with up-titration to 150 mg according to pre-defined criteria. The remaining two studies evaluated alirocumab at 150 mg every two weeks. There were three trials involving people with heterozygous familial hypercholesterolaemia (HeFH), five in people with high CV risk, one in people at moderate to very high CV risk and one in people at moderate CV risk and no history of CV disease. The primary outcome reported by all 10 trials was percentage change in LDL-C from baseline to 24 weeks. A total of 3188 people were randomised to alirocumab, 1175 to placebo, 620 to ezetimibe and 313 to statins (giving an overall total of 5296 people randomised). In general, mean baseline LDL-C levels were balanced within individual trials but there was some variation between trials. Trials including people with HeFH had higher mean LDL-C at baseline.

The company presented the results for each trial for the primary efficacy endpoint (percentage reduction in LDL-C at 24 weeks) and secondary endpoints (Total-C, non-HDL-C, ApoB, Lp(a), Fasting TG, HDL-C, Apo-A1). Results showed clear evidence of a significantly greater percentage reduction on LDL-C at 24 weeks for alirocumab versus placebo, ezetimibe or statins. Compared with placebo, the mean change in LDL-C was between -39.1% and -61.9% greater reduction; compared with ezetimibe between -23.6% and -36.2%; and compared with statin between -20.4% and -49.2%.

The positive effect of alirocumab over its comparators was also clear for a range of lipid parameters across all trials, i.e. Total-C, non-HDL-C, Apo-B, Lp(a). There was some evidence of an effect of alirocumab on Fasting TG, HDL-C and Apo-A1, but not across all trials. The proportions of patients reaching the LDL-C targets of 1.81

mmol/L or 2.59 mmol/L were significantly higher for alirocumab versus all comparators.

The treatment effect of alirocumab versus the specified comparators (lowering LDL-C) was broadly consistent across a range of patient subgroups (HeFH, High/very high risk CVD, statin intolerance, LDL-C level). The company conducted pre-specified pooled analyses and the results were consistent with the treatment effect shown in the individual studies.

Results from phase II and phase III trials submitted by the company as part of the EMA filing were used to assess the safety profile of alirocumab. The combined phase II/III database comprised a cohort of 5234 patients of whom 3340 were treated with alirocumab. In general, the rate of TEAEs and serious TEAEs leading to permanent treatment discontinuation were similar between alirocumab and the control interventions. The most common adverse reaction leading to treatment discontinuation was local injection site reactions (0.2% in alirocumab versus 0.3% in control groups).

No differences were observed between the two alirocumab doses (75 mg and 150 mg administered every two weeks). There were no drug-drug interactions that could have impacted on the safety profile.

The mortality rate was similar between alirocumab and the control interventions.

In the pooled analysis of the phase III trials, major adverse cardiovascular events (MACE) (i.e. death from coronary heart disease, nonfatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation) were comparable for alirocumab versus placebo (1.5% versus 2.3%, respectively) and slightly lower for alirocumab versus ezetimibe (2% versus 10%, respectively). In the post hoc analysis of the longest clinical trial, which assessed long term CV events (LONG TERM), the rate of MACE was lower for alirocumab than for placebo (1.7% versus 3.3%, respectively; HR = 0.52, 95% CI 0.31 to 0.90).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The inclusion and exclusion criteria reported by the company appear to be both comprehensive and appropriate and seem to have been applied consistently during the systematic review process. However, the company proceeded to include only the ODYSSEY programme trials in subsequent analyses, stating at clarification that these trials provided sufficient information to demonstrate the clinical effectiveness of alirocumab. The ERG was unable to comment upon whether this was actually the case, in the absence of relevant information from the omitted trials.

The results provided by the company for the 10 phase III clinical trials from the ODYSSEY programme were relevant and presented appropriately. However, evolocumab, an alternative PCSK9 inhibitor, was not included as a comparator since it was still under NICE assessment. Since the company submission, NICE has issued a preliminary guidance on the use of evolocumab in this clinical population in November 2015. It is worth pointing out, however, that no head to head trials exist so any comparison would have been through an indirect comparison/meta-analysis.

No long term data on the effect of alirocumab on CV events were available, but the ERG note that the CVOT ongoing trial (reporting in January 2018) should provide this information.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a de novo Markov model with annual cycle, simulating the occurrence of acute coronary syndrome (ACS) events (non-fatal MI, unstable angina), elective revascularisation, ischaemic stroke, CV death, and death from other causes. The model was used to assess the cost-effectiveness of alirocumab as an adjunctive treatment in four high risk patient populations with baseline LDL-C levels remaining above pre-specified thresholds on current maximally tolerated lipid modifying therapy:

- HeFH (primary prevention) - mean age 50, 50% male
- HeFH (secondary prevention) - mean age 60, 50% male

- Patients at high CV risk due to a history of CVD (MI, unstable angina, history of revascularisation or other evidence of CHD, ischaemic stroke, peripheral arterial disease (PAD)) - mean age 65, 60% male
- A subgroup of the above patients with existing CV disease at even higher risk, namely patients with recurrent CV events/ polyvascular disease – mean age 65, 60% male

For the HeFH populations and the subgroup with recurrent CV events/polyvascular disease, an LDL-C threshold of ≥ 2.59 mmol/L on current maximally tolerated lipid therapy was applied. For the high risk CV population as a whole, a higher treatment threshold of ≥ 3.36 mmol/L was applied. Mean baseline LDL-C levels for patients above these thresholds were estimated using data for the respective populations from a large UK primary care database (THIN database). In the base case alirocumab was modelled as an adjunct to maximally tolerated statin therapy (+/- ezetimibe) for those able to tolerate a statin. For those intolerant to statins, it was modelled as adjunct to ezetimibe alone. Further subgroup analyses were conducted for alternative LDL-C thresholds (≥ 1.81, ≥ 2.59 and ≥ 3.36 mmol/L) in each population – each threshold having its own associated mean baseline LDL-C level for each population.

Transition probabilities in the model were informed by Kaplan Maier time-to-event analysis of the relevant patient populations identified in the THIN database. These estimated event rates were then adjusted to the mean baseline LDL-C level and age being applied for each modelled cohort. Risks of events were modelled to increase with age over time, and with the occurrence of recurrent CV events. Post CV event states were split into three, to reflect time since the event (0-1, 1-2, and ≥ 2 years). This allowed cost, utilities and subsequent event probabilities to be modified by time following the event. Costs and utilities were incorporated in the model based on existing published literature.

The effects of alirocumab treatment were modelled by applying pooled estimates of percentage reductions from mean baseline LDL-C levels (to estimate absolute reductions in LDL-C (mmol/L)); and then linking these reductions with relative reductions in CV event rates using published evidence. In the base case analysis,

hazard ratios from a published meta-analysis of 24 trials of PCSK9 inhibitors were applied for alirocumab (Navarese et al.); 0.49 (0.26-0.93) for MI and other non-fatal CV events and 0.49 (0.23-1.07) for CV death. These were scaled per 1 mmol/L reduction in LDL-C, assuming a linear/log-linear relationship between LDL-C reductions and proportional reductions in CV events, yielding rate ratios of 0.64 per 1 mmol/L reduction in LDL-C for both MI and CV death. In the model, these rate ratios are then rescaled to the size of the absolute reduction in LDL-C being modelled (again assuming a liner/log-linear relationship). As an alternative more conservative approach, the company presented scenarios where the effects of alirocumab were modelled similarly but using a well-established linear/log-linear relationship between LDL-C reductions with statins and rate ratios for CV events (CTT meta-analysis). The company's base case approach assumes LDL-C reductions mediated through PCSK9 inhibitors have a steeper log-linear relationship with CV event rates as compared to statins; i.e. they achieve greater reductions in the CV event rates compared with statins for equivalent reductions in LDL-C.

In the base case, treatment continuation and compliance were assumed to be 100% over the cohort's lifetime (maximum 99 years). Costs and QALYs were discounted at 3.5% per year in line with reference case.

The company's base case ICERs for alirocumab (with agreed PAS) as an adjunctive to maximally tolerated statin therapy were: £36,793 (incremental cost=£52,256; incremental QALY = 1.42) for HeFH primary prevention; £16,896 (incremental cost=£39,306; incremental QALY = 2.33) for HeFH secondary prevention; £19,751 (incremental cost=£34,684; incremental QALY = 1.76) for high risk CVD; £19,447 (incremental cost=£31,953; incremental QALY = 1.64) for recurrent CVD / polyvascular disease. For those intolerant to statins, the company provided with PAS ICERs for the high risk CVD and recurrent CVD/polyvascular disease populations. These were £17,256 (incremental cost = £35,146; incremental QALY = 2.04) for high risk CVD and £15,853 (incremental cost = £32,719; incremental QALY = 2.06) for recurrent CVD/polyvascular disease.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the submitted model to be of good quality and the structure is generally appropriate. Significant effort has gone into informing the model with real world risk data for relevant UK populations. Based on comparing survival from the model with published survival data for UK cohorts, there is good agreement with medium term survival expectations for the high risk CVD and recurrent CV events cohort, and particularly ACS cohorts. The utility weights incorporated in the model were coherent, from a single UK population based source. Appropriate age adjustment was conducted. The ERG has a number of concerns with some of the parameter estimates and base case assumptions applied in the model as detailed below:

- The model structure uses a composite event states for ACS which includes MI and stable angina (UA). This makes it impossible to model different effects for MI and UA (see below)
- Two options were presented by the company for the secondary prevention HeFH analysis; one using CV risks estimated from analysis of THIN data, and the other using CV risk estimated from a previous published study. The composite annual baseline CV risk using the latter approach is more than twice as high. The ERG has been unable to verify which is more appropriate.
- Costs for the stroke and post-stroke health states appeared low and inconsistent with estimates based on UK population data and values applied in previous technology appraisals.
- Also related to the application of post-CV event costs, it appeared inconsistent with previous technology appraisals, that these should only be applied to 2 years following a CV event (as they were in the company's analysis), particularly for stroke which may result in long-term social care costs.
- The LDL-C threshold applied for the high risk CV cohort in the base case analysis appeared very restrictive, particularly given that statin + ezetimibe is a valid comparator in this population. The base case results for this cohort apply only to those with LDL-C $\geq$ 3.36 mmol/L on maximally tolerated statin. The ERG suspects that a very low proportion of patients in the wider high risk CVD population would meet these criteria. This raises a question over the relevance of the base case analysis for the high risk CVD population. Moreover, if alirocumab is being positioned as an adjunct to statin alone in

this population, then based on NICE guidance the comparator for this analysis should be statin + ezetimibe.

- The mean LDL-C levels above the specified thresholds applied for alirocumab treatment in the model are also uncertain, as these were informed by analysis of THIN data for patients with CVD or probable HeFH, who were not necessarily on optimal statin therapy. Thus, it is uncertain whether these mean values are applicable to those remaining above specified thresholds on optimal statin therapy (+/- ezetimibe).
- The modelled effects of alirocumab on CV outcomes were based on pooled hazard ratios from a meta-analysis of all phase II and III trials of PCSK9 inhibitors - scaled to the modelled size of LDL-C reductions and assuming a linear/log-linear relationship between LDL-C reductions and relative reductions in CV event rates. However, the majority of trials included in the pooled analyses were ≤ 52 weeks and none were designed to assess CV outcomes. Therefore, the observed number of CV events in the pooled analyses were very small, and consequently the confidence intervals are wide for the pooled estimates of the hazard ratios. Indeed the hazard ratio for CV death is not significantly different from 1. Thus the ERG questioned the company's justification for the base case assumption that LDL-C reductions mediated through alirocumab have a greater expected impact on CV events than those estimated for equivalent reductions in LDL-C mediated through statin therapy. There is currently limited data available to accurately inform the relationship between LDL-C reduction with PCSK9 inhibitors and CV event rates.
- In order to rescale reported hazard ratios for the effects of alirocumab on CV events - to a 1 mmol/L reduction LDL-C - the company used a weighted average of the LDL-C reductions across all the trials included in the review by Navarese et al, rather than only using those informing the estimated hazard ratios applied in the model. The resulting rate ratios were 0.64 per 1 mmol/L reduction in LDL-C for both MI and CV death. In response to the ERGs request for clarification, the company provided estimates of the mean LDL-C reductions based only on the trials informing the pooled hazard ratios for each specific event. This rescaling resulted in a rate ratio of 0.58 per 1 mmol/L

reduction in LDL-C for CV death, and 0.67 per 1mmol/L reduction in LDL-C for MI.

- In the absence of available evidence for the effect of PCSK9 inhibitors on stroke and revascularisation, the company applied the estimated hazard ratio for MI to these events. They also applied the same HR to unstable angina (as part of the composite ACS state in the model), although Navarese et al. reported a separate much more uncertain estimate for this effect (HR = 0.51; 95%CI: 0.05-4.86). The application of the MI hazard ratio to stroke seems particularly unjustified, given that the current estimates from the CTT meta-analysis suggest that the effect of LDL-C lowering on ischaemic stroke may not be as great as that observed for ischaemic heart disease events.
- In the base case analysis, the company assumed 100% compliance and 0% discontinuation. This seems unrealistic in light of the discontinuation rates reported in the available trials, which suggested a discontinuation rate of 8% per year or more may be more appropriate.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

In general, the methods used in the clinical effectiveness and cost-effectiveness sections of the company's submission were appropriate. The economic model was adequately structured and informed using real world data on CV risks.

1.6.2 Weaknesses and areas of uncertainty

- The rationale for conducting two systematic reviews of the literature with very similar inclusion criteria was unclear.
- Lack of consistency and transparency in the way studies were selected for inclusion or consideration in the clinical effectiveness section of the submission:
    - selective inclusion of studies;
    - unclear reasons for exclusion of trials that met the original inclusion criteria;

    - lack of information on how some studies were identified (for example the trials within the PROFICIO clinical programme and the three recently published meta-analyses of PCSK9 inhibitors).
- No recording of some lipid parameters when they were actually reported in the clinical study reports.
- Uncertainty regarding the way in which the effects of alirocumab have been modelled in the cost-effectiveness analysis, through reductions in LDL-C linked with reductions in CV event rates using a published meta-analysis of phase II and III trials
- The potential lack of relevance of the modelled base case LDL-C threshold for the population with high risk CVD (≥ 3.36 mmol/L)
- Uncertainty surrounding the mean LDL-C levels above the specified LDL-C thresholds for the specified patient populations
- Uncertainty surrounding the baseline CV event risks for the HeFH populations

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Given the above uncertainties outlined above, the ERG applied several changes to the company's base case model: 1) updated stroke and post stoke costs; 2) applied post CV event costs in perpetuity throughout the model; 3) for scenarios using effect estimates from Navarese et al., hazard ratios for the effects of alirocumab on CV events were scaled per 1 mmol/L reduction in LDL-C using the weighted average reductions from only those trials informing the specific hazard ratios; 4) the effects of alirocumab on stroke were modelled using the CTT meta-analysis (in the absence of a direct estimate of effect for this event); 5) an annual discontinuation rate of 8% per year was applied; and 6) for direct head-to-head comparisons with ezetimibe, effects of ezetimibe on LDL-C reductions were linked to effects on CV events using the relationship from the CTT meta-analysis.

Following incorporation of the above changes, all the company's base case comparisons were replicated. Then, given the uncertainty surrounding the use and scaling of direct effect estimates from Navarese et al., we also present additional scenarios for each comparison using the more conservative CTT meta-analysis approach to model all the effects of alirocumab on all CV event rates.

Based on the ERGs updated base case assumptions (with effects for ACS, CV death and revasularisation still modelled using the scaled Navarese hazard ratios), the ICERs remain very similar to the company's base case ICERs. As an add-on to maximally tolerated lipid lowering therapy, these are below £20,000 per QALY in the HeFH secondary prevention, high risk CVD and polyvascular disease populations, but slightly greater than £40,000 per QALY in the HeFH primary prevention cohort. For those intolerant to statins, the ICERs are also below £20,000. We also produce very similar results to the company's subgroup analysis (by LDL-C thresholds) using our updated base case model, and for probabilistic and deterministic sensitivity analysis. Modelling the effects of alirocumab using the more conservative effectiveness scenario (effects from the CTT meta-analysis), the ICERs for alirocumab as an add-on to maximally tolerated lipid lowering therapy rise above £30,000 in all the patient populations at the base case LDL-C thresholds (ranging from ~£33,000 to £67,215). They also rise slightly above £30,000 for people intolerant to statins.

From repeating the subgroup analysis using the CTT to model effects of alirocumab, the ICERs fall below £30,000 in the highest risks groups (HeFH secondary prevention and polyvascular disease) at the highest LDL-C threshold applied ≥ 4.13 mmol/L on maximally tolerated lipid modifying therapy.

Thus the cost-effectiveness results do appear particularly sensitive to the rate ratios (per mmol/L reduction in LDL-C) used to model the relationship between LDL-C reductions with alirocumab and reductions in CV events.

From further one-way sensitivity analysis with the more conservative model, results are also shown to be quite sensitive (in the HeFH secondary prevention cohort) to the baseline CV risks and the mean baseline LDL-C levels applied. For example, from a base case ICER of £33,339, a 10% increase in the baseline mean LDL-C level decreased the ICER to £28,527, whereas a 10% decrease increased the ICER to £39,420.

2 Background

Primary hypercholesterolaemia is a form of dyslipidaemia characterised by abnormalities of lipoprotein transport associated with high concentrations of cholesterol in the blood. The five major classes of lipoproteins include high density lipoprotein (HDL), low density lipoprotein cholesterol (LDL-C), intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL), and chylomicrons. LDL-C typically constitutes around 60-70% of total serum cholesterol. Non HDL-C (calculated as total-C minus HDL-C) is the total of cholesterol carried by all potentially atherogenic lipoproteins such as LDL-C, IDL, Lipoprotein (a), VLDL, chylomicron particles.[1-3] Primary hypercholesterolaemia can be caused by a single genetic defect (*monogenic familial*) or by the interaction of a genetic predisposition and other environmental factors such as smoking, diet, or physical inactivity (*polygenic or non-familial*).[4] The term secondary hypercholesterolaemia refers to hypercholesterolaemia caused by concomitant clinical conditions or by drug therapies.[5] Secondary hypercholesterolaemia is not relevant to the scope of this appraisal.

In familial hypercholesterolaemia (FH), people inherit an abnormal (mutant) gene that affects the rate at which cholesterol is cleared from the blood, resulting in a high level of cholesterol in the bloodstream. A mutant gene can be inherited from either one parent (heterozygous FH) or both parents (homozygous FH or compound heterozygous FH). In Europe, prevalence of heterozygous FH is commonly estimated at 1 in 500, and prevalence of homozygous FH at 1 in 1,000,000.[6 7] However, recent estimates suggest prevalence of 1 in 200 for heterozygous FH[8] and 1 in 640,000 for homozygous FH.[9] Polygenic (non-familial) hypercholesterolaemia is the most common form of primary hypercholesterolaemia, with an estimated prevalence of 42 in 1000.[5]

Dyslipidaemia refers to a broad spectrum of lipid abnormalities that lead to changes in plasma lipoprotein function and/or levels. Dyslipidaemia is a key hereditary risk factor, by itself and in conjunction with other cardiovascular risk factors, for development of atherosclerosis. Dyslipidaemia is modifiable and is, therefore, a major

focus for prevention and treatment of coronary artery disease.[10 11] The term dyslipidaemia subsumes a number of conditions, including hypercholesterolaemia and mixed dyslipidaemia.

Mixed dyslipidaemia is characterised by raised levels of LDL-C and triglycerides, commonly with concomitant decreased concentration of HDL-C. The risk of cardiovascular disease is significantly increased in people with mixed dyslipidaemia due to a cluster of lipid disorders and thrombogenic abnormalities. The estimated prevalence of mixed dyslipidaemia in the UK is 10%.[12] Mixed dyslipidaemia may originate in childhood.[13] Mixed dyslipidaemia is the most common lipid disorder in people experiencing myocardial infarction before the age of 60.[14]

High serum cholesterol is regarded as the key risk factor for atherosclerosis,[1 15] which is the accumulation and hardening of fatty deposits in the arteries.[16] Any level of LDL-C above 100 mg/dL (2.59 mmol/L) appears to be atherogenic.[1] Atherosclerosis is the cause of cardiovascular disease (CVD) events such as coronary heart disease, transient ischaemic attack (TIA) and stroke, and peripheral arterial diseases. There is robust and consistent evidence that reduction in LDL- C can reduce the risk of atherosclerotic CVD, and, therefore, reduction in LDL-C has become the primary focus of many therapeutic studies.[10 17] However, the importance of non-HDL-C and its relation to the risk of atherosclerotic CVD has also been recently acknowledged and supported by various guidelines.[2 18 19]

There are no fixed normal ranges for blood lipids due to differences in biological, methodological, genetic and environmental factors.[20 21] In general, at the population level, average plasma cholesterol concentration of more than 5 mmol/L (equivalent to LDL-C of 3 mmol/L) is considered to be unhealthy.[12] The World Health Organisation (WHO) specifies a level.[22] A mean of total cholesterol of 5.6 mmol/L for adults in the general population in England has been reported.[23] The average cholesterol level within a population is a key explanatory factor of that population's risk of coronary heart disease (CHD).[24]

Cardiovascular disease accounts for more than a quarter of all deaths in the UK, amounting to around 160,000 deaths each year. Recent statistics suggest that about 7

million people are living with CVD in the UK and the total cost of premature death, lost productivity, hospital treatment and prescriptions related to CVD is an estimated £19 billion annually.[25] CVD is the major cause of death, disability and reduced quality of life in Europe and costs approximately €196 billion annually to the European Union.[26] The American Heart Association has estimated that 83.6 million people are living with CVD in the USA (15.4 million with atherosclerotic CVD) which contributes to around one third of deaths.[27]

Current guidelines for target lipid levels for people at risk of, or with, CVD include The Joint British Societies guidelines, which recommend non-HDL-c of <2.5 mmol/L and/or LDL-c of <1.8 mmol/L (page ii34).[19] The ESC/EAS guidelines for the management of dyslipidaemias (2011) recommend LDL-C targets of < 1.8 mmol/L or a ≥ 50% reduction from baseline LDL-C for people with a very high CV risk and < 2.5 mmol/L in people at high CV risk.[10] It is estimated that over half of adults in the UK have cholesterol levels of 5 mmol/l or above[5 23 25] with around one quarter (27%) having a level of at least 6.5 mmol/L.[5]

The management of hypercholesterolaemia is continually progressing.[5] The main objective of treatment is prevention of CVD, which involves reducing the coronary heart disease (CHD) risk by modifying lifestyle factors and management of other modifiable risk factors such as smoking, hypertension and diabetes (Isles 2000). In general, intensity of preventive interventions should reflect the total CV risk.[10]

Lifestyle modification, for example, diet, exercise, smoking, body weight, remains a key factor of health promotion and CVD risk reduction, before and alongside cholesterol-lowering drug treatments.[28] If modification of these factors is not effective in achieving the target lipid levels, or the CVD risk is high, then more aggressive treatment, such as drug therapy, is recommended.

Statins are generally the first choice of drugs for modification of the lipid profile to reduce CV events. Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have been used in humans since 1980.[29]Statins act by inhibiting HMG CoA reductase, an enzyme responsible for cholesterol synthesis in the body. As

a result, the concentration of LDL-C levels reduces due to the slower production of cholesterol and thereby increasing the liver's ability to clear LDL-C from the blood.[30]

A recent meta-analysis of individual participant data from randomised trials that assessed the effects of statins has shown that statin therapy can significantly reduce the incidence of major coronary events, coronary revascularisation, and stroke by about one fifth per mmol/L reduction in LDL-C.[31 32]

At present, statins that have received approval from both the FDA and the European Medicine Agency are atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin. The NICE guideline on lipid modification does not, however, recommend the use of rosuvastatin due to the lack of evidence of its relative efficacy compared with atorvastatin.[29] Statins should only be started after an informed discussion between the clinician and patient about the risks and benefits of statin treatment, taking account of factors such as benefits from lifestyle modifications, co-morbidities, general frailty and life expectancy.[33]

Alirocumab (praluent®, Sanofi-Aventis Groupe, Paris, France) is a fully human monoclonal antibody that specifically binds proprotein convertase subtilisin/kextin type 9 (PCSK9), a down regulator of LDL receptors in the liver. The liver's ability to bind LDL-C is thus increased and levels of LDL-C in the blood are reduced.[34]

Alirocumab was granted European marketing authorisation on 23rd September 2015. The current approved indication is "*for 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*."

Alirocumab has also received approval from the FDA in the USA (on 24th July 2015) for use in clinical practice as an adjunct to diet and to the maximum tolerated statin dose for the treatment of adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C.

Other lipid-modifying therapy includes fibrates, nicotinic acid, bile acid sequestrants, and omega-3 fatty acids.

2.1 Critique of company's description of underlying health problems

The company's description of primary hypercholesterolaemia and mixed dyslipidaemia appears accurate and appropriate to the decision problem.

2.2 Critique of company's overview of current service provision

There are currently two sets of NICE clinical guidelines, one NICE Technology Appraisal and one NICE Quality Standard relating to lipid disorders and CVD prevention, which are relevant to the purpose of this assessment:

1. **CG181**[29] Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease; published in July 2014 and updates and replaces the previous guideline on lipid modification (CG67, published September 2008)
2. **CG71**[18] Identification and management of familial hypercholesterolaemia; published in August 2008 and is due to be updated in September 2016.
3. **TA132**[35] Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia; published November 2007 and an update is currently in progress.
4. **Quality Standard 41**[36] Familial hypercholesterolaemia; published August 2013

The company adequately refers to CG181, CG71 and TA132 in their submission.

In general terms, NICE CG181 recommends that statin treatment should be offered to patients for whom lifestyle modification is ineffective or inappropriate. Atorvastatin 20 mg is advised for the primary prevention of CVD to people who have a 10% or

greater 10-year risk of developing CVD (estimated using the QRISK2 assessment tool).(www.qrisk.org) For secondary prevention, in people with established CVD, statin treatment with atorvastatin 80 mg should be started. Recommended follow up is at 3 months after initiation of statin treatment and a reduction in non-HDL cholesterol greater than 40% should be expected. If such a reduction in non-HDL cholesterol is not achieved, an increase in the dosage of atorvastatin (if started on less than 80mg) should be considered. NICE CG 71 recommends a high-intensity statin for consideration in people with FH, to achieve a reduction in LDL-C of greater than 50% from baseline. Ezetimibe is recommended as a possible option by both NICE CG181 and CG71 for adults with primary hypercholesterolaemia (familial and non-familial) who are either contraindicated or are intolerant to statins. Alternatively, ezetimibe can be co-administered with statins if LDL-C is not appropriately controlled. These recommendations are consistent with NICE TA132. Fibrates, nicotinic acid, bile acid sequestrants and omega-3 fatty acid compounds are not recommended by NICE CG181 in the populations considered in this appraisal.

The company also appropriately refers to the Joint British Societies consensus recommendations for the prevention of cardiovascular disease[19] and the ESC/EAS.[10]

Hospital Episode Statistics data for England show that there were 555 finished consultant episodes for "pure hypercholesterolaemia" (code E78.0) for the year April 2013 to March 2014. There were 524 admissions, 63 as emergencies, with a median length of stay of 1 day. There were 437 day cases. For "mixed hyperlipidaemia" (code E78.2), there were 15 finished consultant episodes and 12 admissions, with 2 of these being emergencies. Median length of stay was 7 days. There were 9 day cases. For "hyperlipidaemia, unspecified" (code 78.5), there were 70 finished consultant episodes, 58 admissions and 32 emergencies, with a median length of stay of 2 days. There were also 20 day cases. In addition, there were 822 finished consultant episodes and 820 admissions for "low-density lipoprotein apheresis" (code X47.1), with mean length of stay of 0.3 days. There were 817 day cases.

Figure 1 presents a modified version of the NICE clinical pathway of care for lipid modification therapy for preventing cardiovascular disease [33]. The clinical pathway

has been adapted by the ERG to include the likely position of statins, ezetimibe and alirocumab.

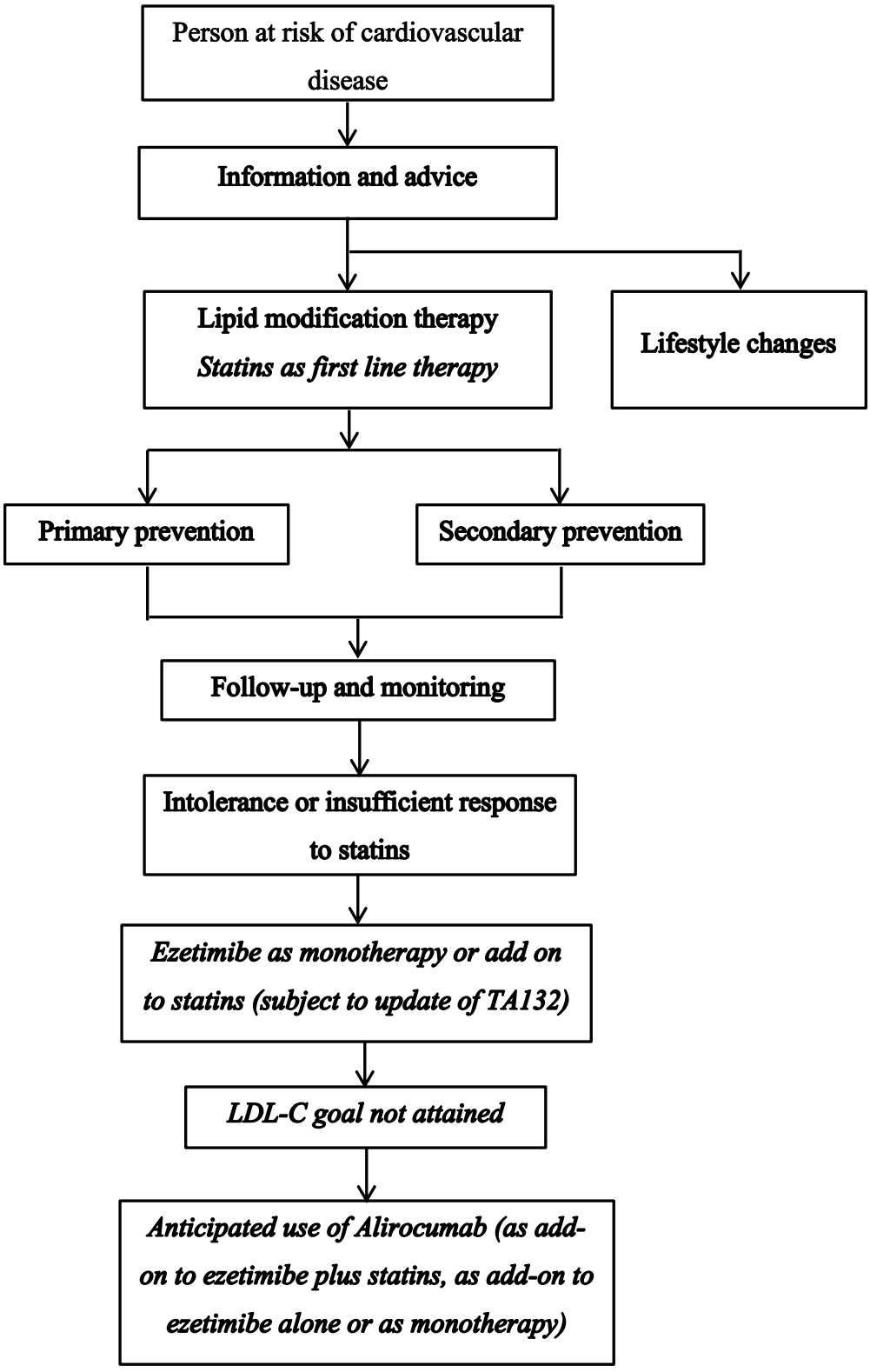


Figure 1 Pathway of clinical care for lipid modification therapy for the prevention of cardiovascular diseases (adapted from Cardiovascular disease prevention. NICE Pathway. London: National Institute for Health and Care Excellence, 2014[33])

3 Critique of company's definition of decision problem

3.1 Population

Both the NICE final scope and the company's submission specify the relevant population for this appraisal as "*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*". This definition would preclude the inclusion of people with homozygous familial hypercholesterolaemia (HoFH). However, the ERG noted that two studies included in the company's systematic review did, in fact, include people with HoFH.[37 38] At clarification, the company explained that their initial systematic review considered patients at high CV risk, including people with both heterozygous and homozygous familial hypercholesterolaemia. It is worth noting, however, that the decision problem addressed by the company did not cover people with HoFH.

3.2 Intervention

Alirocumab (Praluent®, Sanofi-Aventis Groupe, Paris, France) is a fully human monoclonal antibody targeting proprotein convertase subtilisin/kexin type 9 (PCSK9), which is a negative regulator of LDL receptors in the liver. PCSK9 decreases the liver's ability to remove LDL-C from the blood. Alirocumab inhibits PCSK9-mediated degradation of LDL receptors, and increases the expression of LDL receptors on the surface of the liver, thereby improving its capacity to bind LDL-C.[34]

Alirocumab has received marketing authorisation in the UK for the treatment of adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia. In particular, alirocumab is indicated "*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*."

Alirocumab is given by subcutaneous injection into the thigh, abdomen or upper arm.

According to the Summary of Product Characteristics the usual starting dose for alirocumab (Praluent) is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg administered subcutaneously once every 2 weeks. The dose can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response.

Lipid levels can be assessed four weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dose adjusted accordingly (up-titration or down-titration). Patients should be treated with the lowest dose necessary to achieve the desired LDL-C reduction.

In people with HeFH, it is anticipated that alirocumab will be used continuously once initiated.

Most common adverse reactions with alirocumab include local injection site reactions, upper respiratory tract signs and symptoms, and pruritus.Generic allergic reactions include pruritus, as well as rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis. If signs or symptoms of serious allergic reactions occur, treatment with alirocumab must be discontinued and appropriate symptomatic treatment initiated. Full details of adverse reactions and contraindications are given in the Summary of Product Characteristics.

The list price acquisition cost is £168 per one-pen pack and £336 per two two-pen pack (Table 5 of the company's submission). The company has recently agreed a patient access scheme with the Department of Health.

3.3 Comparators

The NICE final scope specified optimised statin therapy as a comparator, without any further qualifying criteria in terms of previous or current treatment or its effectiveness. The company did not consider this specific configuration of comparator. However, optimised statin therapy was one of two comparators specified by the company for people whose LDL-C was not adequately controlled with optimised (maximum tolerated dose) statin therapy. Both the NICE final scope and the company's

submission specified optimised statin therapy plus ezetimibe for this subgroup. The other relevant comparator specified in the NICE final scope was evolocumab plus optimised statin therapy.

Evolocumab, an alternative PCSK9 inhibitor, was not considered by the company for this appraisal. In the decision problem table (Table 4 of the original company's submission), the company stated that they did not conduct a formal comparison versus evolocumab (as opposed to versus ezetimibe) as NICE had not yet issued clinical guidance and the use of evolocumab cannot be considered standard care. The ERG agree that at the time the company's submission was finalised this was the case. A preliminary NICE guidance regarding evolocumab for this population was issued in November 2015.

The company did include nine evolocumab studies in its systematic literature reviews (YUKAWA II, RUTHERFORD-2, TESLA part B, DESCARTES, LAPLACE-TIMI-57, LAPLACE-2, GAUSS, GAUSS-2, OSLER). These trials were not included in any of the quantitative analyses carried out by the company, who did present only a narrative, qualitative, comparison of the ODYSSEY and PROFICIO programmes of trials.

For people in whom LDL-C is not adequately controlled with optimised statin therapy in combination with ezetimibe, the NICE scope specified the comparator as evolocumab plus ezetimibe and a statin. The company specified the comparator as "optimised statin therapy plus ezetimibe (i.e. no additional comparator)". The meaning of "no additional comparator" was unclear to the ERG as ezetimibe would appear to be an additional comparator. In addition, "no additional comparator" was earlier specified by the company alongside optimised statin therapy alone, which is logical in that context.

Where statins are contraindicated or not tolerated, the NICE final scope specified ezetimibe, evolocumab or a combination of the two. In contrast, the company specified no additional therapy on a background of ezetimibe. The company explained that their choice of no active comparator was based on the notion that alirocumab was considered as an adjunctive agent to maximum tolerated statin dose with or without

ezetimibe, or a background of statins with or without statins. The ERG considered this choice appropriate.

3.4 Outcomes

The outcomes considered by the company were percentage reduction in LDL-C at 24 weeks; non-HDL-C; apolipoprotein B; lipoprotein(a); triglycerides; apolipoprotein A1; HDL-C; non-fatal CV events; all-cause mortality; CV-related mortality; intervention-related deaths; serious adverse events; treatment-emergent adverse events; EQ-5D.

The outcomes specified in the NICE final scope were plasma lipid and lipoprotein levels, including LDL-C, non-HDL-C, apolipoprotein B and lipoprotein(a); requirement of procedures including LDL apheresis and revascularisation; fatal and non-fatal cardiovascular events; mortality; adverse effects of treatment; health-related quality of life.

The company stated that the outcomes considered in the submission were as per the final NICE scope. However, the ERG was unable to identify outcomes relating to requirement of procedures including LDL apheresis and revascularisation in the submission. Moreover, the ERG also noted some discrepancies between the data reported in the company's submission and those available in the CSRs. For example, while the submission states that 52-week data for some lipid parameters (i.e. Total-C, non-HDL-C, Apo B, Lp(a), Fasting TG, HDL-C and Apo A1) were "not recorded" (see Tables 19 to 24 of the company's submission), they appear to be available in the CSRs.

3.5 Other relevant factors

The decision problem addressed by the company for the economic analysis was consistent with the NICE final scope.

Subgroups specified in the NICE final scope were presence or risk of CV disease, people with HeFH, people with statin intolerance, and severity of hypercholesterolaemia. For the economic analysis, the company's submission considered the following subgroups: people with HeFH (with and without existing

CVD), people with existing CVD, a higher risk subgroup of people with CVD (i.e. people with recurrent events/polyvascular disease, and severity of hypercholesterolaemia by variation of LDL-C levels. The company did not consider people with statin intolerance as a separate group. Instead, the company modelled subsets of the high risk groups, varying the background therapy and baseline LDL-C levels. The ERG considered these strategies appropriate for the economic analysis.

The company also conducted subgroup analyses of the primary efficacy endpoint within each included study which were described as pre-specified, albeit they were absent from the specification of the decision problem (Table 4 of the company's submission). The subgroups were: demographic (BMI, gender, region, age, race, ethnicity), other baseline characteristics (prior history of MI or IS, diabetes at randomisation, baseline total PCSK9 level, baseline free PCSK9 level), lipids at baseline (baseline LDL-C, baseline HDL-C, baseline fasting TG, baseline lipoprotein(a) and statins, and other LMTs at randomisation (statins at randomisation, LMTs at randomisation). The ERG considered these groups to be clinically appropriate.

The decision problem addressed by the company differs from the NICE final scope but is considered appropriate and clinically relevant by the ERG.

Table 1 illustrates the discrepancies between the NICE final scope and the decision problem addressed by the company and includes for clarity the company as well as the ERG's comments.

Table 1 Comparison of NICE final scope and decision problem addressed by company

	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	• People with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom LMTs, in line with current NICE guidance, would be considered	The company stated that the population addressed in the submission was as per the final scope	The ERG agreed with the company's comments
Intervention	• Alirocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe	• **Alirocumab in combination with maximal tolerated dose of statins, with or without ezetimibe, or alirocumab on a background of no statins, with or without ezetimibe**	The company stated that the intervention addressed in the submission was in line with the scope but adjusted to reflect current NHS usage of ezetimibe	The ERG noted that the intervention addressed differed from the final scope but agreed that the company's specification of the intervention was appropriate and clinically relevant

Comparators	• Optimised statin therapy
	• When LDL-C is not adequately controlled with optimised statin therapy:
	  ○ Ezetimibe in combination with optimised statin therapy
		• When LDL-C is not adequately controlled with optimised (maximum tolerated dose) statin therapy:
		  ○ **Optimised statin therapy alone (i.e. no**
			The company stated that they anticipated that alirocumab will be used in patients who are not adequately controlled on all maximally used existing therapy and that this issue would be discussed in further detail in the submission	The ERG noted that the company did not include evolocumab as a comparator because it is still under NICE assessment and it is not standard of care within the NHS.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
	○ Evolocumab in combination with optimised statin therapy (subject to NICE guidance) • When LDL-C is not adequately controlled with optimised statin therapy in combination with ezetimibe: ○ Evolocumab in combination with ezetimibe and a statin (subject to NICE guidance) • When statins are contraindicated or not tolerated: ○ Ezetimibe ○ Evolocumab (subject to NICE guidance) ○ Evolocumab in combination with ezetimibe (subject to NICE guidance)	**additional comparator)** ○ **Optimised statin therapy plus ezetimibe** • When LDL-C is not adequately controlled with optimised statin therapy in combination with ezetimibe: ○ **Optimised statin therapy plus ezetimibe (i.e. no additional comparator)** • When statins are contraindicated or not tolerated: ○ **No additional therapy (on background of ezetimibe)** As base case, the company		

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
		considered Alirocumab as an adjunctive agent to current maximal therapy (maximal tolerated dose statins with or without ezetimibe, or a background of no statins with or without ezetimibe). The comparison is therefore versus no active comparator. The company presented scenario comparisons versus ezetimibe The company did not conduct a formal economic comparison versus evolocumab as NICE have not yet issued guidance and it is not NHS standard of care		
Outcomes	• Plasma lipid and lipoprotein levels, including LDL-C, non-HDL-C, apo B and lipoprotein a • Requirement of procedures including LDL apheresis	• LDL-C • Non-HDL-C • Apo B • Lipoprotein a • TG	As per the final scope	The ERG agreed that the outcomes addressed in the company's submission were in line with the NICE final scope

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
	and revascularisation • Fatal and non-fatal cardiovascular events • Mortality • Adverse effects of treatment • HRQoL	• Apo A1 • HDL-C • Non-fatal CV events • All-cause mortality • CV-related mortality • Intervention-related deaths • SAEs • TEAEs • EQ-5D		
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	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	As per the final scope	The ERG agreed that the economic analysis addressed in the company's submission were in line with the NICE final scope

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Subgroups	• Presence or risk of cardiovascular disease • People with HeFH • People with statin tolerance • Severity of hypercholesterolaemia	• People with existing CVD • People with HeFH (with and without existing CVD) • Analysis is also conducted by severity of hypercholesterolaemia by variation of LDL-C levels • **A higher risk subgroup of people with CVD, namely people with recurrent events/ polyvascular disease** (Above subgroups evaluated in the economic analysis only)	People with statin intolerance are not considered as one separate group but are modelled as subsets of the above high risk groups, differing in terms of the background therapy and in terms of baseline LDL-C levels	The ERG noted the differences in subgroups specified in the NICE final scope and those addressed in the company's submission, which were considered to be clinically appropriate. The company also conducted subgroup analyses on the primary efficacy outcomes, in terms of demographics, other baseline characteristics, lipids at baseline, statins and LMTs at baseline.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company's submission provides full details of the searches that were undertaken to identify the included studies for the literature reviews of clinical effectiveness. The MEDLINE (Ovid), EMBASE (Ovid) and CENTRAL (Cochrane Library) electronic databases were searched on 15th May 2015 for publications written in English and published from 1980 onwards. In addition, conference proceedings of five major cardiovascular associations for 2013 and 2014 were searched.

The search strategies are documented in full in Appendix 8.2.1 of the company's original submission and are reproducible. The MEDLINE and EMBASE searches combine three search facets using the Boolean operator AND: alirocumab and the comparator drugs (evolocumab, PCSK9 inhibitors and ezetimibe), hypercholesterolaemia; and RCTs. The search in the Cochrane Library for CENTRAL excluded the RCT facet, which was appropriate. A comprehensive range of terms was included in the search strategies in the title and abstract fields. However, no MeSH or Emtree terms were included for the hypercholesterolaemia facet in any of the searches. Exploding the MeSH term *Hyperlipidemias* or the broader term *Dyslipidemias* and the Emtree terms *Hyperlipidemia* or *Disorders of lipid and lipoprotein metabolism* should have been included to ensure a highly sensitive search. Furthermore, searching of the Registry Number/Name of Substance fields for the drugs facet should also have been undertaken. The MEDLINE search did not use the currently recommended Cochrane sensitive maximising RCT strategy. The term drug therapy.fs is the most notable omission. Overall, these omissions may have affected the overall sensitivity of the search strategies, however, given the extensive range of text terms included in the hypercholesterolaemia facet, the ERG considers that the searches were fit-for purpose.

The company state that a separate search was undertaken on May 15th for PCSK9 only trials to inform a separate systematic review. These strategies are reproduced in

Appendix 8.2.4 of the company's submission and are a repetition of the original searches with the exclusion of only one search line related to ezetimibe. Therefore, the reports screened for this second literature review were basically a subset of those retrieved for the original literature review. The number of records retrieved, however, was considerably smaller than that of the original search and this, presumably, facilitated the screening process. The ERG cannot see other explanations for undertaking an additional separate literature search.

In section 4.9.1 of the submission, the company discusses three recently published meta-analyses of PCSK9 inhibitors, which showed significant reduction in LDL-C and other lipid parameters with no significant differences in adverse events, but gives no indication as to how these were identified in the literature.

4.1.2 Inclusion criteria

The company conducted two systematic reviews to assess the clinical effects of alirocumab: Alirocumab was considered:

1. as "add on therapy" in people whose LDL-C was not adequately controlled with maximum tolerated dose of statin or non-statin (niacin, fibrates, bile acid sequestrants), or
2. as "monotherapy" for people in whom statins are not appropriate or not tolerated or whose LDL-C was not adequately controlled with non-statin lipid modifying therapies (i.e. niacin, fibrate, bile acid sequestrants).

The first literature review focused on patients at *high risk of CVD* (**Review 1)**. According to the NICE final scope, the relevant population for this assessment were people with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies (LMT) would be indicated. Review 1 considered a broader definition, by including a population with high CV risk. The company defined 'high risk of CVD' as patients with FH, recent ACS (i.e. MI or unstable angina with inpatient hospitalisation during the past 0–12 months), CHD (i.e. patients with a history of ACS or non-invasive diagnosis of CHD) or history of ischaemic stroke, peripheral arterial disease, diabetes or as defined by study authors. The ERG considered these groups to be clinically appropriate.

However, the ERG noted that Review 1 inclusion criteria did not specifically define the FH population as 'heterozygous' and/or 'homozygous'. At clarification, the company explained that the high CV risk population included patients with both homozygous and heterozygous familial hypercholesterolaemia. Moreover, the company stated that there are no trials evaluating alirocumab in people with HoFH, which the current alirocumab license does not cover, so studies in this population are not considered relevant to the decision problem addressed in the submission. The ERG is of the opinion that studies enrolling patients with HoFH should have been considered within the exclusion criteria of the company's systematic reviews.

The company's submission stated that "some PCSK9 trials were conducted in patient populations that also included individuals at moderate CVD risk, and these were excluded from the original systematic review." For this reason, a separate modified review, **Review 2**, of PCSK9 inhibitor trials was conducted to assess patients at *moderate or high CVD risk*, with moderate risk defined as patients with LDL-C ≥75 mg/dL (1.9 mmol/L).

Review 1 and Review 2 included only RCTs published in English from 1980 to May 2015. The interventions considered in Review 1 were alirocumab, evolocumab, other PCSK9 inhibitors and ezetimibe; comparators were any active agent and placebo (with background therapy e.g. statin). The intervention and comparator considered in Review 2 were alirocumab and evolocumab. The inclusion criteria applied in Review 1 and Review 2 are presented in Table 2.

Table 2 Comparison of inclusion criteria used in the two systematic reviews of clinical effectiveness conducted by the company (reproduced from Table 6 and 7 of the company's submission).

Criteria	Review 1	Review 2
Population	Adults (>18 years of age) at **high CVD risk** • who are unable to achieve desired LDL-C levels, on a statin, or a statin in combination with a non-statin LMT (i.e. niacin, fibrate, bile acid sequestrants) • for whom statins are not appropriate or are not tolerated and who are unable to achieve LDL-C levels on non-statin LMT (i.e. niacin, fibrate, bile acid sequestrants)	Adults (>18 years of age) at **moderate or high CVD risk** • who are unable to achieve desired LDL-C levels, on a statin, or a statin in combination with a non-statin LMT (i.e. niacin, fibrate, bile acid sequestrants) • for whom statins are not appropriate or are not tolerated and who are unable to achieve LDL-C levels on non-statin LMT (i.e. niacin, fibrate, bile acid sequestrants)
	Where high risk is defined as patients with: • FH • Recent ACS (i.e. MI or unstable angina with inpatient hospitalisation during the past 0–12 months) • CHD (i.e. patients with a history of ACS or non-invasive diagnosis of CHD) • History of ischaemic stroke, peripheral arterial disease, diabetes or as defined by study authors And moderate risk is defined as patients with: • LDL-C ≥75 mg/dL (1.9 mmol/L)	

Criteria	Review 1	Review 2
Intervention	• Alirocumab • Evolocumab • Other PCSK9 inhibitors • Ezetimibe	• Alirocumab • Evolocumab
Comparators	• Any active agent • Placebo (with background therapy)	• Alirocumab • Evolocumab
Outcomes	**Efficacy** • Definition of target LDL-C level • Number and proportion (%) of patients reaching target LDL-C • Mean change from baseline – absolute and % for LDL-C, HDL-C, non-HDL-C, lipoprotein(a), triglycerides, apolipoprotein A1, apolipoprotein B • Non-fatal CV events including MI, unstable angina with hospitalisation, coronary revascularisation, ischaemic stroke • All-cause mortality • CV-related mortality	**Efficacy** • Proportion (%) of patients reaching target LDL-C • Mean % change from baseline for LDL-C, HDL-C, non-HDL-C, lipoprotein(a), triglycerides, apolipoprotein A1, apolipoprotein B, total cholesterol • Non-fatal CV events including MI, unstable angina with hospitalisation, coronary revascularisation, ischaemic stroke • All-cause mortality • CV-related mortality

Criteria	Review 1	Review 2
	Safety • Death related to the intervention • Discontinuation due to an adverse events • Any serious adverse events • Treatment emergent adverse events including myalgias (without creatinine kinase elevation), creatinine kinase elevation, myositis, rhabdomyolysis, transaminase elevation (alanine aminotransferase or aspartate transaminase), new onset of diabetes, cancer incidence, neurocognitive disorder, haemorrhagic stroke, injection site reaction	**Safety** • Death related to the intervention • Discontinuation due to an adverse events • Any serious adverse events • Treatment emergent adverse events including myalgias (without creatinine kinase elevation), creatinine kinase elevation, myositis, rhabdomyolysis, transaminase elevation (alanine aminotransferase or aspartate transaminase), new onset of diabetes, cancer incidence, neurocognitive disorder, haemorrhagic stroke, injection site reaction
Study design	RCTs (defined as trials in which an active intervention is included in the control arm of the trial, e.g. control arm is statin plus placebo) • Outcome measurements at ≥10 weeks	RCTs
Time horizon	1980 to date of executing search strategy (Jan 14th, 2015 and updated May 15th, 2015)	Between 1980 and date of executing search strategy, (May 15th 2015)

ACS, Acute coronary syndrome; CHD, Coronary heart disease; CVD, Cardiovascular disease; FH, Familial hypercholesterolaemia; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; LMTs, Lipid-lowering therapies; MI, Myocardial infarction.

4.1.3 Identified studies

The company's submission identified relevant clinical evidence from two systematic reviews. **Review 1**, which focused on patients at *high risk of CVD*, included a total of 32 studies from 30 papers (two articles each described two studies). Of the 32 included studies, 10 were alirocumab trials (HIGH FH, FH I, FH II, LONG TERM, OPTION I, OPTION II, COMBO I, COMBO II, Stein 2012, McKenney 2012)[39-46] six were evolocumab trials,[38 47-51] 16 were ezetimibe trials.[52-67] The company's submission stated that "none of these trials were conducted in patients who were intolerant to statins or for whom statins are inappropriate".

Review 2, which considered patients at *moderate or high CVD risk*, included 20 studies from 18 papers (two articles each described two studies). Of the 20 included studies, 11 were alirocumab trials (HIGH FH, FH I, FH II, LONG TERM, OPTION I, OPTION II, COMBO I, COMBO II, ALTERNATIVE, MONO, Teramoto 2014)[39-43 68-71] and nine were evolocumab trials[38 45 49 51 72-76] The ERG further noted that Tables 40-45 of the company's submission, which provide qualitative summaries of the evolocumab trials, included also the MENDEL-2,[77] FOURIER (reference not provided) and the OSLER[78] studies. It is not clear to the ERG how these trials were identified for inclusion as they were excluded from Review 1 and /or 2.

Despite the results of the two systematic reviews, the company decided to focus on 10 phase III clinical trials from the ODYSSEY (alirocumab) programme, to provide clinical effectiveness evidence relevant to the purpose of this assessment. Table 8 in the company's submission further lists five phase II trials (DFI11565, CL-1003, DFI11566, CL-1018, DFI12361)[44 46 79] and three phase III trials (not submitted to support marketing authorisation) (CHOICE I, CHOICE II, EFC13672) that were identified (references not provided), but not included, in the clinical effectiveness assessment.

At clarification, the company described the ODYSSEY programme as "*the pivotal trial programme [that] provides sufficient evidence to address the relative effectiveness of alirocumab*" and added that "*the additional trials of ezetimibe plus statins captured in the systematic review are not necessary to inform the decision problem."* The adoption of such subjective criteria for the selection of relevant studies

seems to contravene the core principles of the systematic review process and may potentially introduce biases.[80]

In total, 118 and 20 articles were excluded from **Review 1** and **Review 2,** respectively during full-text assessment. Common reasons for exclusion of full text articles from **Review 2** are reported in Appendix 8.2.5.3 of the company's submission: study design (11 articles), population (2 articles), duplicate publication (already included in previous review) (6 articles) and other reasons (1 article). Reasons for exclusion of full text articles from Review 1 are not reported in the company's submission.

4.1.4 Characteristics of identified studies

Characteristics of ten included trials from ODYSSEY programme

Detailed comparative summaries of the trials' methods are shown in Tables 10 and 11 of the company's submission. Table 3, below, presents a summary of the main characteristics of each of the 10 included trials.

The 10 phase III clinical trials in the ODYSSEY programme evaluated alirocumab either as add on therapy in people whose LDL-C was not adequately controlled with maximum tolerated dose of statin or non-statin LMTs (High FH, FH I, FH II, COMBO I, COMBO II, OPTION I, OPTION II, LONG TERM) or as monotherapy for those in whom statins were not tolerated (ALTERNATIVE, MONO). In five of these trials, the comparator was placebo (HIGH FH, FH I, FH II, COMBO I, LONG TERM). The five remaining trials compared alirocumab with either ezetimibe only (MONO, COMBO II) or with ezetimibe and/or high intensity statins (OPTION I, OPTION II, ALTERNATIVE).

In eight trials, participants randomised to alirocumab started with 75 mg every 2 weeks (Q2W). If the LDL-C level was ≥70mg/dL (1.8mmol/L) at week 8 dosing was increased to 150 mg Q2W at week 12 (MONO, ALTERNATIVE, FH I, FH II, COMBO I, COMBO II, OPTION I, OPTION II). In the remaining two trials, participants in the alirocumab arm received 150 mg Q2W throughout the duration of the trial (LONG TERM, HIGH FH).

Nine of the 10 trials were multicentre and multinational. The remaining trial (COMBO I) was conducted in 80 study centres, all within the USA. The active treatment duration was 24 weeks in four trials (OPTION I, OPTION II, ALTERNATIVE, MONO), 52 weeks in two (COMBO I, COMBO II) and 78 weeks in four (HIGH FH, FH I, FH II, LONG TERM). The primary efficacy endpoint was percent change in calculated LDL-C from baseline to week 24 in all 10 trials. All 10 trials in the ODYSSEY clinical programme were supported by Sanofi and Regeneron pharmaceuticals, the joint manufacturers of alirocumab.

Appendix 5 of the company's submission reports the baseline demographics of the participants from the individual trials of the ODYSSEY clinical programme. In general, mean baseline LDL-C levels were balanced within individual trials but there was some variation between trials. In the alirocumab versus placebo trials, mean values in the alirocumab groups ranged from 2.595 (SD 0.764) mmol/L (COMBO I) to 5.083 (SD 1.495) mmol/L (HIGH FH) while in the placebo groups, mean values were between 2.746 (SD 0.915) mmol/L (COMBO I) and 5.205 (SD 1.125) mmol/L (HIGH FH). In the alirocumab versus ezetimibe/statin trials, mean LDL-C values in the alirocumab groups ranged from 2.812 (SD 0.945) mmol/L (COMBO II) to 4.951 (SD 1.883) mmol/L (ALTERNATIVE). In the ezetimibe groups, mean values ranged from 2.710 (SD 0.884) mmol/L (COMBO II) to 5.011 (SD 1.837) mmol/L (ALTERNATIVE) and in the statins groups values were between 2.740 (SD 0.914) mmol/L (OPTION I) and 4.850 (SD 1.540) mmol/L (ALTERNATIVE). Trials that exclusively enrolled participants with HeFH (HIGH FH, FH I, FH II) or some participants with HeFH (LONG TERM) had higher mean LDL-C at baseline. Only one of the 10 trials included exclusively participants with moderate CV risk. (MONO)

Characteristics of trials identified in the review but not included in the clinical assessment

Evolocumab trials and phase II alirocumab trials that were identified in the company's submission but not included in the quantitative analysis of clinical effectiveness evidence are summarised in Appendix 1 of the ERG report.

Table 3 Characteristics of relevant alirocumab trials included in the clinical effectiveness assessment (reproduced from Table 15, 16 and Appendix 8.2.5.1 of the company's submission)

Study ID (trial acronym)	Intervention	Number of patients	Study population (LDL-C in mmol/L)	Primary outcomes	Treatment duration	Funders
Alirocumab vs placebo						
Ginsberg 2014[41] (HIGH FH)	Alirocumab 150 mg (Q2W)	72	Not adequately controlled with statin and/or other LMTs; LDL-C≥ 4.138 (160 mg/dL) *Mean LDL-C*: 5.123 (SD 1.382) HeFH: 100% *Mean age:* 50.6 (SD 13.3) (range 18-80) *White race*: 94 (87.9%) *CHD:* 53 (49.5%) *CHD risk equivalents:* 18 (16.8%)	% change in calculated LDL-C from baseline to week 24	78 weeks	Sanofi and Regeneron
	Placebo	35				
Kastelein 2015[42] (FH I)	Alirocumab 75-150 mg (Q2W)	323	Not adequately controlled with statin and/or other LMTs; LDL-C>1.8 (70 mg/dL) (history of CVD), LDL-C>2.6 (100 mg/dL) (no history of CVD)	% change in calculated LDL-C from baseline to	78 weeks	Sanofi and Regeneron

Study ID (trial acronym)	**Intervention**	**Number of patients**	**Study population (**LDL-C in mmol/L)	**Primary outcomes**	**Treatment duration**	**Funders**
	Placebo	163	*Mean LDL-C*: 3.746 (SD 1.287) *HeFH:* 100% *Mean age:* 51.9 (SD12.7) (range 20-87) *White race*: 444 (91.4%) *CHD:* 225 (46.3%) *CHD risk equivalents:* 79 (16.3%)	week 24		
Kastelein 2015[42] (FH II)	Alirocumab 75-150 mg (Q2W)	167	Not adequately controlled with statin and/or other LMTs; LDL-C>1.8 (70 mg/dL) (history of CVD), LDL-C>2.6 (100 mg/dL) (no history of CVD *Mean LDL-C*: 3.480 (SD 1.065) *HeFH*: 100% *Mean age:* 53.2 (SD 12.8) (range 22-85) *White race*: 244 (98%) *CHD:* 88 (35.3%) *CHD risk equivalents:* 9 (7.6%)	% change in calculated LDL-C from baseline to week 24	78 weeks	Sanofi and Regeneron
	Placebo	82				
Keriakes 2015[43] (COMBO I)	Alirocumab 75-150 mg (Q2W)	209	Not adequately controlled with statin and/or other LMTs; LDL-C≥1.8 (70 mg/dL) and established CVD or LDL-C≥2.6 (100 mg/dL)with CHD risk equivalents stable	% change in calculated LDL-C from baseline to week 24	52 weeks	Sanofi and Regeneron

Study ID (trial acronym)	**Intervention**	**Number of patients**	**Study population (**LDL-C in mmol/L)	**Primary outcomes**	**Treatment duration**	**Funders**
	Placebo	107	*Mean LDL-C*: 2.646 (SD 0.820) *HeFH*: not reported *Mean age:* 63 (SD 9.3) *White race*: 258 (81.6%) *CHD:* 247 (78.2%) *CHD risk equivalents:* 136 (43.0%)			
Robinson 2015[69] (LONG TERM)	Alirocumab 75-150 mg (Q2W)	1553	LDL-C≥1.8 (70 mg/dL) with or without established CHD or CHD risk equivalents *Mean LDL-C*: 3.171(SD 1.092) *HeFH*: 415 (17.7%) *Mean age:* 60.5 (SD 10.4) (range 18-89) *White race*: 2171 (92.7%) *CHD:* 1607 (68.6%) *CHD risk equivalent:* 962 (41.1%)	% change in calculated LDL-C from baseline to week 24	78 weeks	Sanofi and Regeneron
	Placebo	788				
Alirocumab vs active agent						
Bays 2014 [39] (OPTIONS I)	Alirocumab 75-150 mg Q2W plus atorvastatin 20 mg QD	57	Prior CVD with LDL-C=1.8 (70 mg/dL) or CVD risk factors with LDL-C=2.6 (100 mg/dL); stable atorvastatin 20 or 40 mg/day *Mean LDL-C*: 2.723 (SD 0.884)	% change in calculated LDL-C from baseline to week 24	24 weeks	Sanofi and Regeneron
	Alirocumab 75-150 mg Q2W plus atorvastatin 40 mg QD	47				
	Ezetimibe 10 mg QD plus	55				

Study ID (trial acronym)	**Intervention**	**Number of patients**	**Study population** (LDL-C in mmol/L)	**Primary outcomes**	**Treatment duration**	**Funders**
	atorvastatin 20 mg QD		*HeFH*: 32 (9.0%) *Mean age*: 62.9 (SD 10.2) (range 30-85) *White race*: 306 (86.2%) *CHD*: 200 (56.3%) *CHD risk equivalent*: 100 (28.2%)			
	Ezetimibe 10 mg QD plus atorvastatin 40 mg QD	47				
	Atorvastatin 40 mg QD	57				
	Atorvastatin 80 mg QD	47				
	Rosuvastatin 40 mg QD	45				
Bays 2014 [39] (OPTIONS II)	Alirocumab 75-150 mg Q2W plus rosuvastatin 10 mg QD	49	Prior CVD with LDL-C=1.8 (70 mg/dL) or CVD risk factors with LDL-C=2.6 (100 mg/dL); stable rosuvastatin 20 or 40 mg/day *Mean LDL-C*: 2.882 (SD 1.009) *HeFH*: 41 (13.4%) *Mean age*: 60.9 (SD 10.4) (range 27-87) *White race*: 256 (83.9%) *CHD*: 177 (58.0%) *CHD risk equivalent*: 79 (25.9%)	% change in calculated LDL-C from baseline to week 24	24 weeks	Sanofi and Regeneron
	Alirocumab 75-150 mg Q2W plus rosuvastatin 20 mg QD	54				
	Ezetimibe 10 mg QD plus rosuvastatin 10 mg QD	48				
	Ezetimibe 10 mg QD plus rosuvastatin 20 mg QD	53				
	Rosuvastatin 20 mg QD	48				
	Rosuvastatin 40 mg QD	53				

Study ID (trial acronym)	**Intervention**	**Number of patients**	**Study population** (LDL-C in mmol/L)	**Primary outcomes**	**Treatment duration**	**Funders**
Cannon 2015 [40] (COMBO II)	Alirocumab 75-150 mg (Q2W)	479	Hypercholesterolaemia and established CHD or CHD risk equivalents; not adequately controlled with maximum tolerated statin dose; LDL-C>1.8 (70 mg/dL) (history of CVD), LDL-C>2.6 (100 mg/dL) (no history of CVD) *Mean LDL-C*: 2.778 (SD 0.926) *HeFH*: 0 *Mean age*: 61.6 (SD 9.3) (range 29-88) *White race*: 610 (84.7%) *CHD*: 649 (90.1%) CHD risk equivalents: 223 (31.0%)	% change in calculated LDL-C from baseline to week 24	52 weeks	Sanofi and Regeneron
	Ezetimibe 10 mg QD	241				
Moriarty 2014[68] (ALTERNATIVE)	Alirocumab 75-150 mg Q2W	126	With history of SI due to muscle symptoms; inability to tolerate statins at lowest approved starting dose and with CHD/other CV risk factors *Mean LDL-C*: 4.954 (SD 1.796) *HeFH*: 47 (15.0%)	% change in calculated LDL-C from baseline to week 24	24 weeks	Sanofi and Regeneron
	Ezetimibe 10 mg QD	125				

Study ID (trial acronym)	**Intervention**	**Number of patients**	**Study population** (LDL-C in mmol/L)	**Primary outcomes**	**Treatment duration**	**Funders**
	Atorvastatin 20 mg QD	63	*Mean age*: 63.4 (SD 9.5) (range 31-88) *White race*: 295 (93.9%) *CHD*: 146 (46.5%) *CHD risk equivalent*: 73 (23.2%)			
Roth 2014[70] (MONO)	Alirocumab 75 mg or 150 mg Q2W	52	Hypercholesterolaemia and moderate CV risk (10 years risk of fatal CV events of ≥1% and 5%, based on the European Systematic Coronary Risk Estimation); not receiving statin or any other LMT *Mean LDL-C*: 3.619 (SD 0.668) *HeFH*: not reported *Mean age*: 60.2 (SD 5.0) (range 45-72) *White race*: 93 (90.3%) *CHD*: not reported *CHD risk equivalent*: not reported	% change in calculated LDL-C from baseline to week 24	24 weeks	Sanofi and Regeneron
	Ezetimibe 10 mg QD	51				

4.1.5 Critique of data extraction

The ERG considers the methods described in company's submission to be appropriate. Two reviewers independently selected studies and extracted data with any discrepancies resolved by discussion between the two reviewers. Any unresolved issues were adjudicated by a third reviewer.

4.1.6 Quality assessment

The quality of the relevant studies was assessed according to the Cochrane Collaboration's tool for assessing risk of bias of RCTs. The criteria involved assessment of selection bias, performance bias, detection bias, attrition bias, reporting bias and other potential biases. The number of reviewers involved in the quality assessment of the selected studies was not detailed in the submission.

The ERG conducted a broad assessment of the methods used by the company for the systematic review of clinical effectiveness evidence using the CRD criteria. Results are shown in Table 4.

Table 4 Quality assessment of the company's systematic review

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	No
2. Is there evidence of a substantial effort to search for all of the relevant research?	No
3. Is the validity of included studies adequately assessed?	No
4. Are sufficient details of the individual studies presented?	No*
5. Are the primary studies summarised appropriately?	No

*Only details of the 10 trials from the ODYSSEY programme are provided but not those of all studies identified by the literature searches

Inclusion/exclusion criteria relating to the primary studies which address the review question are clearly described in Appendix 6 of the company's submission. As highlighted in section 4.1.2, two systematic reviews - with two different sets of inclusion criteria - were conducted by the company: **Review 1** focused on patients at *high risk of CVD* and Review 2 focused on patients *at moderate to high risk of CVD*.

The decision of the company to restrict their assessment (and quantitative analyses) to the 10 alirocumab phase III trials from the ODYSSEY programme on the basis that this programme provides sufficient evidence to address the relative effectiveness of alirocumab is not considered entirely justifiable by the ERG. The ERG also noted some inconsistencies in the studies selection process. For example, MENDEL-2[77] FOURIER (reference not provided) and OSLER[78] are presented for the first time in Table 40 amongst the evolocumab trials but it is unclear how these trials were identified for inclusion.

Only the 10 trials from the ODYSSEY programme which were considered relevant by the company were assessed for their methodological validity. Full details of the risk of bias assessments of these 10 trials are reported in Appendix 6 of the company's submission. A check by the ERG of the risk of bias assessment revealed some inconsistencies.

The company assessed the LONG TERM trial to be at 'low risk of detection bias' and the justification provided for this judgment is that *'active drug and placebo were identically packaged to protect blinding. Injections could be performed at home by the patient or a designated caregiver. Training for the person performing the injection was provided during screening'.* As this explanation does not mention blinding of outcome assessor, the ERG considered that unclear risk of bias would be a more appropriate assessment. According to the company's submission, only two trials, LONG TERM and MONO, were judged at 'low risk of selection bias' due to adequate sequence generation in both trials and concealed allocation of the participants in one of them (LONG TERM). All 10 trials were judged to be at low risk of performance bias (i.e. participants and personnel blinded), attrition bias (i.e. low attrition rates) and reporting bias (i.e. comprehensively reported safety and efficacy). In all but one trial (HIGH FH) intervention groups were balanced at baseline.

The company's submission provided sufficient details of the 10 alirocumab phase III trials from the ODYSSEY programme. Only brief details of phase II trials identified by the search strategies (DFI11565, CL-1003, DFI11566, CL-1018, DFI12361) were given. The company also attempted to present a qualitative comparison of the main characteristics (but not outcomes) of six evolocumab trials from the PROFICIO

clinical programme with those of relevant alirocumab trials from the ODYSSEY programme, which had similar patient population (Tables 41 to 46 of the company's submission).

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The clinical effectiveness for alirocumab was based on the 10 clinical trials from the ODYSSEY programme. This programme was a series of randomised, double-blind, parallel group, multicentre, multinational trials designed to assess the efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia (HeFH) and non-familial hypercholesterolaemia including patients with mixed dyslipidaemia. Alirocumab was evaluated as a monotherapy (or add-on to non-statin LMT) in ALTERNATIVE (statin intolerant) and MONO. In all other studies alirocumab was evaluated as an add-on to statins with or without LMT:

- 5 compared alirocumab to placebo (FH I, FH II, HIGH FH, COMBO I, LONG TERM)
- 2 compared alirocumab to ezetimibe (COMBO II, MONO)
- 3 compared alirocumab to ezetimibe and to a statin (OPTIONS I, OPTIONS II, ALTERNATIVE)

Eight of these studies evaluated alirocumab at a dose of 75 mg every two weeks with up-titration to 150 mg according to pre-defined criteria. In HIGH FH and LONG TERM alirocumab was evaluated as 150 mg every two weeks. Three trials (FH I, FH II and HIGH FH) were in patients with HeFH, while COMBO I and COMBO II evaluated alirocumab in high CV risk patients (excluding familial hypercholesterolemia), and LONG TERM evaluated high risk patients, which could include FH. Two trials (OPTIONS I and OPTIONS II) evaluated alirocumab in comparison to modulation of existing statin therapy in high risk CV patients. ALTERNATIVE included patients at moderate, high and very high risk of CV (including FH), while MONO recruited those with moderate CV risk and no history of CV disease.

The ITT population for each trial was defined as all randomised patients who had an evaluable primary outcome which required the availability of a baseline calculated LDL-C value and the availability of at least one calculated LDL-C value within the analysis window up to week 24. The primary endpoint was change in LDL-C from baseline to 24 weeks as a percentage of baseline values. All trials used a mixed effect model with repeated measurements (MMRM) which accounted for missing data using the missing at random assumption. This model included fixed effects for treatment, randomisation strata, time point, and treatment by time point interaction, strata by time point interaction, baseline LDL-C value and baseline LDL-C by time point interaction. SAS PROC MIXED was used with appropriate options to generate the estimates required. The sample sizes used within the trials were sufficient to achieve the 90% or 95% power desired. The ERG considered this approach to be appropriate.

Table 5 Number of patients (UK patients) randomised by trial and treatment

	Alirocumab	Placebo	Ezetimibe	Statins
FH I	323 (16)	163 (7)	-	-
FH II	167 (17)	82 (8)	-	-
HIGH FH	72	35	-	-
COMBO I	209	107	-	-
COMBO II	479	-	241	-
LONGTERM	1553 (317)	788 (167)	-	-
OPTIONS I	104 (3)	-	102 (0)	149 (4)
OPTIONS II	103 (4)	-	101 (3)	101 (4)
ALTERNATIVE	126 (8)	-	125 (8)	63 (3)
MONO	52	-	51	-
	3188	1175	620	313

The 10 phase III trials presented within the ODYSSEY programme were conducted in 30 countries worldwide including 36 UK NHS centres within 6 of the trials (FH I, FH II, LONG TERM, OPTIONS I, OPTIONS II, ALTERNATIVE). In total, these trials randomised 5296 patients, with 3188 to alirocumab, 1175 to placebo, 620 to ezetimibe and 313 to statins. The breakdown within the trials is shown in Table 5. In total 569/5296 (10.7%) randomised were patients from the UK.

The populations showed a variety of baseline characteristics (see Table 6), FH I, FH II, HIGH FH tended to involve younger participants with mean age in early 50s while the mean age of participants in the other trials was early 60s. All trials had a higher proportion of males than females with COMBO II approaching three quarters male. ALTERNATIVE and HIGH FH had mean baseline LDL-C around 5 mmol/L while the other trials were between 2.6 and 3.7 mmol/L. Eight trials contained 100% high or very high CV risk patients, ALTERNATIVE had 82% of participants with high CV risk and MONO was entirely in moderate CV risk patients. There were 100% patients with familial hypercholesterolemia in three trials (FH I, FH II and HIGH FH), between 9% and 13% for four trials (OPTIONS I, OPTIONS II, ALTERNATIVE and LONG TERM) while three trials had no patients with FH (COMBO I, COMBO II, MONO).

The company presented the results of each of the 10 trials in turn for the primary outcome (% change from baseline in LDL-C at 24 weeks), and various secondary outcomes relating to other key lipid parameters (non-HDL-C, ApoB, ApoA-1, Lp(a) and HDL-C). In addition, the proportion of patients reaching pre-defined treatment goals was provided. Data were provided for 12 weeks, 24 weeks and 52 weeks, where applicable. The ERG report focuses on 24 weeks as the primary endpoint. Table 7 shows the mean percentage change from baseline for the treatment groups along with the mean difference and 95% confidence interval between the groups for the primary LDL-C outcome, where available. Tables 8–16 show the results for each of the secondary outcomes.

Table 6 ODYSSEY programme trial populations at baseline (source Table 15 of the company's submission)

Study	Age (mean [SD])	Males (%)	Mean calculated LDL-C, mmol/L	High CV risk patients (%)	Very high CV risk patients (%)	High/very high CV risk patients (%)	Treatment with high-intensity statin (%)	Treatment with ezetimibe (%)	Proportion of patients with FH (%)
EFC12492 FH I	51.9 (12.7)	56.4	3.746	48.8	51.2	100	81.5	57.0	100
CL1112 FH II	53.2 (12.8)	52.6	3.480	61.4	38.6	100	86.3	66.3	100
EFC12732 HIGH FH	50.6 (13.3)	53.3	5.123	43.0	57.0	100	72.9	24.3	100
EFC11568 COMBO I	63.0 (9.3)	65.8	2.646	0	100	100	57.6	8.2	0
EFC11569 COMBO II	61.6 (9.3)	73.6	2.778	0	100	100	66.7	N/A	0
LTS11717 LONG TERM	60.5 (10.4)	62.2	3.171	8.5	91.5	100	44.1	14.3	17.7
CL1110 OPTIONS I	62.9 (10.2)	65.1	2.723	39.7	60.3	100	N/A	N/A	9.0
CL1118 OPTIONS II	60.9 (10.4)	61.3	2.882	37.0	63.0	100	N/A	N/A	13.4
CL1119 ALTERNATIVE	63.4 (9.5)	54.8	4.954	28.3	54.1	82.4	N/A	N/A	15.0
EFC11716 MONO	60.2 (5.0)	53.4	3.619	0	0	0	N/A	N/A	0

Table 7 Primary efficacy endpoint for ITT analysis

	Mean % change from baseline to 24 weeks LDL-C		LS difference vs comparator		
	Alirocumab	Placebo	Difference	95% CI	p-value
FH I	-48.8	9.1	-57.9	(-63.3, -52.6)	<0.0001
FH II	-48.7	2.8	-51.4	(-58.1, -44.9)	<0.0001
HIGH FH	-45.7	-6.6	-39.1	(-51.1, -27.1)	<0.0001
COMBO I	-48.2	-2.3	-45.9	(-52.5, -39.3)	<0.0001
LONGTERM	-61.0	0.8	-61.9	(-64.3, -59.4)	<0.0001
	Alirocumab	Ezetimibe	Difference	95% CI	p-value
COMBO II	-50.6	-20.7	-29.8	(-34.4, -25.3)	<0.0001
OPTIONS I on baseline atorvastatin 20mg	-44.1	-20.5	-23.6	(-40.7, -6.5)	<0.0001
OPTIONS I on baseline atorvastatin 40mg	-54.0	-22.6	-31.4	(-47.4, -15.4)	<0.0001
OPTIONS II on baseline rosuvastatin 10mg	-50.6	-14.4	-36.1	98.75% CI (-51.5, -20.7)	<0.0001
OPTIONS II on baseline rosuvastatin 20mg	-36.3	-11.0	-25.3	98.75% CI (-50.9, 0.3)	0.0136
ALTERNATIVE	-45.0	-14.6	-30.4	(36.6, -24.2)	<0.0001
MONO	-47.2	-15.6	-31.6	(-40.2, -23.0)	<0.0001
	Alirocumab	Statins	Difference	95% CI	p-value
OPTIONS I on baseline atorvastatin 20mg: vs atorvastatin 40mg	-44.1	-5.0	-39.1	(-55.9, -22.2)	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs atorvastatin 80mg	-54.0	-4.8	-49.2	(-65.0, -33.5)	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs rosuvastatin 40mg	-54.0	-21.4	-32.6	(-48.4, -16.9)	<0.0001
OPTIONS II on baseline rosuvastatin 10mg vs rosuvastatin 20mg	-50.6	-16.3	-34.3	98.75% CI (-49.2, -19.3)	<0.0001
OPTIONS II on baseline rosuvastatin 20mg vs rosuvastatin 40mg	-36.3	-15.9	-20.4	98.75% CI (-45.8, 5.1)	0.0453

Table 8 Secondary endpoint: Total-C

	Mean % change from baseline to 24 weeks TOTAL-C		LS difference vs comparator		
	Alirocumab	Placebo	Difference	95% CI	p-value
FH I	-31.4	7.3	-38.7	Not given	<0.0001
FH II	-30.6	2.1	-32.7	Not given	<0.0001
HIGH FH	-41.9	-6.2	-35.7	Not given	<0.0001
COMBO I	-27.9	-2.9	-25.0	Not given	<0.0001
LONGTERM	-37.7	-0.3	-37.4	Not given	<0.0001
	Alirocumab	Ezetimibe	Difference	95% CI	p-value
COMBO II	-29.3	-14.6	-14.7	Not given	<0.0001
OPTIONS I on baseline atorvastatin 20mg	-27.1	-11.2	-15.9	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg	-33.6	-15.2	-18.4	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 10mg	-28.9	-8.7	-20.2	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 20mg	-20.6	-12.4	-8.2	Not given	<0.0001
ALTERNATIVE	-31.8	-10.9	-20.9	Not given	<0.0001
MONO	-29.6	-10.9	-18.7	Not given	<0.0001
	Alirocumab	Statins	Difference	95% CI	p-value
OPTIONS I on baseline atorvastatin 20mg: vs atorvastatin 40mg	-27.1	-4.0	-23.1	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs atorvastatin 80mg	-33.6	-4.8	-28.8	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs rosuvastatin 40mg	-33.6	-11.7	-21.9	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 10mg vs rosuvastatin 20mg	-28.9	-8.3	-20.6	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 20mg vs rosuvastatin 40mg	-20.6	-8.5	-12.1	Not given	<0.0001

Table 9 Secondary endpoint: Non HDL-C

	Mean % change from baseline to 24 weeks Non HDL-C		LS difference vs comparator		
	Alirocumab	Placebo	Difference	95% CI	p-value
FH I	-42.8	9.6	-52.4	Not given	<0.0001
FH II	-42.6	3.1	-45.7	Not given	<0.0001
HIGH FH	-41.9	-6.2	-35.7	Not given	<0.0001
COMBO I	-39.1	-1.6	-37.5	Not given	<0.0001
LONGTERM	-51.6	0.7	-52.3	Not given	<0.0001
	Alirocumab	Ezetimibe	Difference	95% CI	p-value
COMBO II	-42.1	-19.2	-22.9	Not given	<0.0001
OPTIONS I on baseline atorvastatin 20mg	-36.7	-15.1	-21.6	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg	-47.6	-21.0	-26.6	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 10mg	-42.7	-13.4	-29.3	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 20mg	-31.4	-12.9	-18.5	Not given	<0.0001
ALTERNATIVE	-40.2	-14.6	-25.6	Not given	<0.0001
MONO	-42.5	-16.7	-25.8	Not given	<0.0001
	Alirocumab	Statins	Difference	95% CI	p-value
OPTIONS I on baseline atorvastatin 20mg: vs atorvastatin 40mg	-36.7	-6.3	-30.4	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs atorvastatin 80mg	-47.6	-6.5	-41.1	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs rosuvastatin 40mg	-47.6	-17.4	-30.2	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 10mg vs rosuvastatin 20mg	-42.7	-11.3	-31.4	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 20mg vs rosuvastatin 40mg	-31.4	-11.2	-20.2	Not given	<0.0001

Table 10 Secondary endpoint: Apo-B

	Mean % change from baseline to 24 weeks Apo-B		LS difference vs comparator		
	Alirocumab	Placebo	Difference	95% CI	p-value
FH I	-41.1	4.7	-45.8	Not given	<0.0001
FH II	-42.8	-3.5	-39.3	Not given	<0.0001
HIGH FH	-39	-8.7	-30.3	Not given	<0.0001
COMBO I	-36.7	-0.9	-35.8	Not given	<0.0001
LONGTERM	-52.8	1.2	-54	Not given	<0.0001
	Alirocumab	Ezetimibe	Difference	95% CI	p-value
COMBO II	-40.7	-18.3	-22.4	Not given	<0.0001
OPTIONS I on baseline atorvastatin 20mg	-33.7	-10.1	-23.6	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg	-41.9	-14.3	-27.6	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 10mg	-36.5	-9.7	-26.8	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 20mg	-28.3	-22.7	-5.6	Not given	0.0057
ALTERNATIVE	-36.3	-11.2	-25.1	Not given	<0.0001
MONO	-36.7	-11	-25.7	Not given	<0.0001
	Alirocumab	Statins	Difference	95% CI	p-value
OPTIONS I on baseline atorvastatin 20mg: vs atorvastatin 40mg	-33.7	-4.4	-29.3	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs atorvastatin 80mg	-41.9	-3.5	-38.4	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs rosuvastatin 40mg	-41.9	-10.9	-31	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 10mg vs rosuvastatin 20mg	-36.5	-7.3	-29.2	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 20mg vs rosuvastatin 40mg	-28.3	-9.8	-18.5	Not given	0.0024

Table 11 Secondary endpoint: Lp(a)

	Mean % change from baseline to 24 weeks Lp(a)		LS difference vs comparator		
	Alirocumab	Placebo	Difference	95% CI	p-value
FH I	-25.2	-7.5	-17.7	Not given	<0.0001
FH II	-30.3	-10	-20.3	Not given	<0.0001
HIGH FH	-23.5	-8.7	-14.8	Not given	<0.0001
COMBO I	-20.5	-5.9	-14.6	Not given	<0.0001
LONGTERM	-29.3	-3.7	-25.6	Not given	<0.0001
	Alirocumab	Ezetimibe	Difference	95% CI	p-value
COMBO II	-27.8	-6.1	-21.7	Not given	0.0294
OPTIONS I on baseline atorvastatin 20mg	-23.6	-10.6	-13	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg	-30.8	0.2	-31	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 10mg	-27.9	-4.3	-23.6	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 20mg	-22.7	-5.8	-16.9	Not given	0.0131
ALTERNATIVE	-25.9	-7.3	-18.6	Not given	<0.0001
MONO	-16.7	-12.3	-4.4	Not given	0.4013
	Alirocumab	Statins	Difference	95% CI	p-value
OPTIONS I on baseline atorvastatin 20mg: vs atorvastatin 40mg	-23.6	-20.2	-3.4	Not given	0.0004
OPTIONS I on baseline atorvastatin 40mg: vs atorvastatin 80mg	-30.8	-9.7	-21.1	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs rosuvastatin 40mg	-30.8	-4.9	-25.9	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 10mg vs rosuvastatin 20mg	-27.9	-4	-23.9	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 20mg vs rosuvastatin 40mg	-22.7	-5.2	-17.5	Not given	0.0123

Table 12 Secondary endpoint: Fasting TG

	Mean % change from baseline to 24 weeks Fasting TG		LS difference vs comparator		
	Alirocumab	Placebo	Difference	95% CI	p-value
FH I	-9.6	6.3	-15.9	Not given	<0.0001
FH II	-10.4	0.5	-10.9	Not given	0.0012
HIGH FH	-10.5	-1.9	-8.6	Not given	0.1386
COMBO I	-6.0	-5.4	-0.6	Not given	0.8699
LONGTERM	-15.6	1.8	-17.4	Not given	<0.0001
	Alirocumab	Ezetimibe	Difference	95% CI	p-value
COMBO II	-13	-12.8	-0.2	Not given	0.9117
OPTIONS I on baseline atorvastatin 20mg	-12	-3.3	-8.7	Not given	0.1116
OPTIONS I on baseline atorvastatin 40mg	-19.1	-13.9	-5.2	Not given	0.3652
OPTIONS II on baseline rosuvastatin 10mg	-11.2	-8.3	-2.9	Not given	0.1491
OPTIONS II on baseline rosuvastatin 20mg	-8.7	-11.1	2.4	Not given	0.7135
ALTERNATIVE	-9.3	-3.6	-5.7	Not given	0.1426
MONO	-11.9	-10.8	-1.1	Not given	0.8433
	Alirocumab	Statins	Difference	95% CI	p-value
OPTIONS I on baseline atorvastatin 20mg: vs atorvastatin 40mg	-12	-6.7	-5.3	Not given	0.3054
OPTIONS I on baseline atorvastatin 40mg: vs atorvastatin 80mg	-19.1	-7.3	-11.8	Not given	0.0403
OPTIONS I on baseline atorvastatin 40mg: vs rosuvastatin 40mg	-19.1	-0.5	-18.6	Not given	0.0011
OPTIONS II on baseline rosuvastatin 10mg vs rosuvastatin 20mg	-11.2	-1.8	-9.4	Not given	0.1454
OPTIONS II on baseline rosuvastatin 20mg vs rosuvastatin 40mg	-8.7	-9.9	1.2	Not given	0.8088

Table 13 Secondary endpoint: HDL-C

	Mean % change from baseline to 24 weeks HDL-C		LS difference vs comparator		
	Alirocumab	Placebo	Difference	95% CI	p-value
FH I	8.8	0.8	8.0	Not given	<0.0001
FH II	6.0	-0.8	6.8	Not given	0.0009
HIGH FH	7.5	3.9	3.6	Not given	0.2745
COMBO I	3.5	-3.8	7.3	Not given	<0.0001
LONGTERM	4.0	-0.6	4.6	Not given	<0.0001
	Alirocumab	Ezetimibe	Difference	95% CI	p-value
COMBO II	8.6	0.5	8.1	Not given	0.0294
OPTIONS I on baseline atorvastatin 20mg	4.8	-0.1	4.9	Not given	0.3152
OPTIONS I on baseline atorvastatin 40mg	7.7	2.0	5.7	Not given	0.1426
OPTIONS II on baseline rosuvastatin 10mg	9.1	1.7	7.4	Not given	0.1491
OPTIONS II on baseline rosuvastatin 20mg	7.2	-1.8	9.0	Not given	0.0072
ALTERNATIVE	7.7	6.8	0.9	Not given	0.6997
MONO	6	1.6	4.4	Not given	0.1116
	Alirocumab	Statins	Difference	95% CI	p-value
OPTIONS I on baseline atorvastatin 20mg: vs atorvastatin 40mg	4.8	1.9	2.9	Not given	0.0973
OPTIONS I on baseline atorvastatin 40mg: vs atorvastatin 80mg	7.7	4.7	3.0	Not given	0.4456
OPTIONS I on baseline atorvastatin 40mg: vs rosuvastatin 40mg	7.7	5.7	2.0	Not given	0.6086
OPTIONS II on baseline rosuvastatin 10mg vs rosuvastatin 20mg	9.1	1.7	7.4	Not given	0.0311
OPTIONS II on baseline rosuvastatin 20mg vs rosuvastatin 40mg	7.2	1.5	5.7	Not given	0.0866

Table 14 Secondary endpoint: Apo-Al

	Mean % change from baseline to 24 weeks Apo-A1		LS difference vs comparator		
	Alirocumab	Placebo	Difference	95% CI	p-value
FH I	5.0	0.3	4.7	Not given	0.0002
FH II	2.8	-1.6	4.4	Not given	0.0062
HIGH FH	5.6	2	3.6	Not given	0.1715
COMBO I	3.3	-2.5	5.8	Not given	0.0002
LONGTERM	4	1.2	2.8	Not given	<0.0001
	Alirocumab	Ezetimibe	Difference	95% CI	p-value
COMBO II	5.0	-1.3	6.3	Not given	0.0294
OPTIONS I on baseline atorvastatin 20mg	7.6	1.0	6.6	Not given	0.0029
OPTIONS I on baseline atorvastatin 40mg	5.8	-1.8	7.6	Not given	0.0066
OPTIONS II on baseline rosuvastatin 10mg	6.7	5	1.7	Not given	0.5484
OPTIONS II on baseline rosuvastatin 20mg	6.7	-0.9	7.6	Not given	0.0063
ALTERNATIVE	4.8	2.9	1.9	Not given	0.2768
MONO	4.7	-0.6	5.3	Not given	0.0196
	Alirocumab	Statins	Difference	95% CI	p-value
OPTIONS I on baseline atorvastatin 20mg: vs atorvastatin 40mg	7.6	1.2	6.4	Not given	0.0034
OPTIONS I on baseline atorvastatin 40mg: vs atorvastatin 80mg	5.8	2.2	3.6	Not given	0.1986
OPTIONS I on baseline atorvastatin 40mg: vs rosuvastatin 40mg	5.8	4.7	1.1	Not given	0.6745
OPTIONS II on baseline rosuvastatin 10mg vs rosuvastatin 20mg	6.7	5.4	1.3	Not given	0.6271
OPTIONS II on baseline rosuvastatin 20mg vs rosuvastatin 40mg	6.7	2.9	3.8	Not given	0.1651

Table 15 Secondary endpoint: proportion of patients reaching LDL target < 1.81 mmol/L

	Proportion of patients reaching LDL target < 1.81 mmol/L at 24 weeks		LS difference vs comparator		
	Alirocumab	Placebo	Difference	95% CI	p-value
FH I	59.8	0.8	59	Not given	<0.0001
FH II	68.2	1.2	67	Not given	<0.0001
HIGH FH	32.4	2.9	29.5	Not given	0.0082
COMBO I	75	9	66	Not given	<0.0001
LONGTERM	79.3	8	71.3	Not given	<0.0001
	Alirocumab	Ezetimibe	Difference	95% CI	p-value
COMBO II	77.0	45.6	31.4	Not given	<0.0001
OPTIONS I on baseline atorvastatin 20mg	79.2	50.3	28.9	Not given	0.0018
OPTIONS I on baseline atorvastatin 40mg	74.5	52.0	22.5	Not given	0.0002
OPTIONS II on baseline rosuvastatin 10mg	77.8	43.1	34.7	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 20mg	60.1	43.6	16.5	Not given	0.0657
ALTERNATIVE	32.5	0.8	31.7	Not given	<0.0001
MONO	59.4	2.4	57	Not given	<0.0001
	Alirocumab	Statins	Difference	95% CI	p-value
OPTIONS I on baseline atorvastatin 20mg: vs atorvastatin 40mg	79.2	16.0	63.2	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs atorvastatin 80mg	74.5	24.6	49.9	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs rosuvastatin 40mg	74.5	45.6	28.9	Not given	0.0002
OPTIONS II on baseline rosuvastatin 10mg vs rosuvastatin 20mg	77.8	31.3	46.5	Not given	<0.0001
OPTIONS II on baseline rosuvastatin 20mg vs rosuvastatin 40mg	60.1	29.9	30.2	Not given	0.0006

Table 16 Secondary endpoint: proportion of patients reaching LDL target < 2.59 mmol/L

	Proportion of patients reaching LDL target < 2.59 mmol/L at 24 weeks		LS difference vs comparator		
	Alirocumab	Placebo	Difference	95% CI	p-value
FH I	83.7	11.6	72.1	Not given	<0.0001
FH II	85.4	18.7	66.7	Not given	<0.0001
HIGH FH	57	11.4	45.6	Not given	<0.0001
COMBO I	93.8	64.1	29.7	Not given	<0.0001
LONGTERM	90.3	35.5	54.8	Not given	<0.0001
	Alirocumab	Ezetimibe	Difference	95% CI	p-value
COMBO II	91.0	76.4	14.6	Not given	<0.0001
OPTIONS I on baseline atorvastatin 20mg	89.9	84.2	5.7	Not given	0.2543
OPTIONS I on baseline atorvastatin 40mg	90.1	80.7	9.4	Not given	0.0074
OPTIONS II on baseline rosuvastatin 10mg	91.4	71.3	20.1	Not given	0.0047
OPTIONS II on baseline rosuvastatin 20mg	74.6	64.8	9.8	Not given	0.3185
ALTERNATIVE	61	10	51	Not given	<0.0001
MONO	88.1	32.2	55.9	Not given	<0.0001
	Alirocumab	Statins	Difference	95% CI	p-value
OPTIONS I on baseline atorvastatin 20mg: vs atorvastatin 40mg	89.9	67.0	22.9	Not given	0.003
OPTIONS I on baseline atorvastatin 40mg: vs atorvastatin 80mg	90.1	61.4	28.7	Not given	<0.0001
OPTIONS I on baseline atorvastatin 40mg: vs rosuvastatin 40mg	90.1	71.1	19	Not given	0.0025
OPTIONS II on baseline rosuvastatin 10mg vs rosuvastatin 20mg	91.4	79.4	12	Not given	0.1809
OPTIONS II on baseline rosuvastatin 20mg vs rosuvastatin 40mg	74.6	69.1	5.5	Not given	0.3736

Within these 10 trials, there is clear evidence of an effect on LDL-C at 24 weeks for alirocumab versus placebo, alirocumab versus ezetimibe and alirocumab versus statins with alirocumab showing significantly greater percentage LDL-C reductions from baseline to 24 weeks (see Table 7). Differences in percentage reduction ranged from 39.1% to 61.9% against placebo, 23.6% to 36.1% against ezetimibe and 20.4% to 49.2% against statins.

Evidence of an effect of alirocumab over its comparators for the secondary endpoints was also clear for lipid parameters Total-C, non-HDL-C, Apo-B, Lp(a). Some trials showed an effect on Fasting TG, HDL-C and Apo-A1, but others didn't (Tables 12-14). The proportion of patients reaching their LDL-C target of 1.81 mmol/L was also significantly higher for alirocumab versus its comparators (Table 15), as was the target of 2.59 mmol/L (Table 16).

A number of subgroup analyses were implemented by the company and presented in either their main submission or in the appendices:

- BMI (< 30, ≥30kg/m^2)
- Region: various depending on trial (see Table 32, CS)
- Age: various depending on trial (see Table 32, CS)
- Race: White, black por African American, other
- Ethnicity: Hispanic or Latino, not Hispanic or Latino
- Statin treatment (high dose, low/modoerate dose)
- Dose of atovarstatin at randomisation (10mg, 20mg, 40mg, 80mg)
- Dose of rosuvastatin at randomisation (5mg, 10mg, 20mg, 40mg)
- Dose of simvastatin at randomisation (10mg, 20mg, 40mg, 80mg)
- LMT other than statins at randomisation (yes/no)
- Prior history of myocardial infarction (MI) or ischaemic stroke (IS) (yes/no)
- Diabetes mellitus (DM) (yes/no)
- Moderate chronic kidney disease (CKD) (yes/no)
- HeFH (yes/no)
- Baseline LDL-C: various depending on trial (see Table 32, CS)
- Baseline HDL-C: < 1.04 mmol/L , ≥1.04 mmol/L
- Baseline fasting triglycerides: < 1.7 mmol/L , ≥1.7 mmol/L

- Baseline Lp(a): various depending on trial (see Table 32, CS)
- Baseline total PCSK9 level: <median, ≥median
- Baseline free PCSK9 level: <median, ≥median

In general, the effect of alirocumab versus its comparators was consistent between subgroups. No further details are provided by the ERG.

Pooled-analysis

The company indicated they undertook some pre-specified pooled analysis for the following trials' populations:

- FH I and FH II for HeFH patients
- ALTERNATIVE and MONO for efficacy versus ezetimibe in patients not receiving statins
- OPTIONS I and OPTIONS II for alirocumab as add on to statin, ezetimibe as add on to statin and statin up titration.

The company indicated that each pooled analysis used individual patient data and results were presented for the primary endpoint and for key secondary efficacy endpoints.

In addition, the company undertook pooled analysis to look at two dosing regimens:

- Alirocumab 75 mg 2QW as initiation dose with potential up titration to 150 mg Q2W (FH I, FH I, COMBO I in combination with statins vs placebo; ALTERNATIVE, MONO without statins vs ezetimibe; COMBO II, OPTIONS I, OPTIONS II in combination with statins vs ezetimibe)
- Alirocumab 150 mg 2QW as initiation dose (LONG TERM, HIGH FH in combination with statins vs placebo).

The results of these various pooled analyses are shown in Table 17 for comparisons at 24 weeks. No confidence intervals were provided by the company.

Table 17 Mean % change from baseline in LDL-C in pooled analysis

	Mean % change from baseline to 24 weeks LDL-C		
	Alirocumab + background statin	Placebo + background statin	Difference (SE)
75/150 mg (up titrations, pooling FH I, FH II)	-49.3 (1.2)	6.8 (1.7)	-56.1 (2.1)
75/150 mg (up titrations, pooling FH I, FH II, COMBO I)	-49.7 (1.0)	4.4 (1.5)	-54.1 (1.8)
150 mg (pooling LONG TERM and HIGH FH)	-62.1 (0.7)	0.4 (1.0)	-62.5 (1.2)
	Alirocumab	Ezetimibe	
75/150 mg up titration studies (ALTERNATIVE)	-52.2 (2.0)	-17.1 (2.0)	not given
	Alirocumab+statin	Ezetimibe + statin	
75/150 mg up titration studies (COMBO II, OPTIONS I, OPTIONS II)	-51.6 (1.3)	-21.6 (1.6)	not given

The pooled analyses findings are similar to the results of the individual trials and show a clear reduction in LDL-C for alirocumab over its comparators.

Published meta-analyses

The company summarised the results of three published meta-analyses of PCSK9 inhibitors.[81-83] Some of the trials included in these meta-analyses overlapped with the company's submission but each of them included additional trials for alirocumab and additional trials for evolocumab. In particular, Navarese et al.[82] conducted a systematic review and meta-analyses of phase II and phase III trials assessing the efficacy and safety of PCSK9 inhibitors (alirocumab and evolocumab) compared with no anti-PCSK9 treatment in adults with hypercholesterolaemia. They assessed a total of 24 RCTs with 10,159 participants. Duration of included trials ranged from 8 weeks to 104 weeks. All trials were multicentre and funded by industry. Compared with no anti-PCSK9 treatment, use of PCSK9 inhibitors reduced LDL-C level by almost 50% (mean difference, -47.49%, 95% CI, -69.64% to -25.35%; P <0.001) and total cholesterol by 31% (mean difference -31.49%, 95% CI -46.35% to -16.64%; P <

0.001). Treatment with PCSK9 inhibitors reduced all-cause mortality (OR 0.45, 95% CI 0.23 to 0.86; P = 0.015; heterogeneity P = 0.63; I^2 = 0%) and cardiovascular mortality (OR 0.50, 95% CI 0.23 to 1.10; P = 0.084; heterogeneity P = 0.78; I^2 = 0%) compared to control. Treatment with PCSK9 significantly reduced the rate of myocardial infarction (OR 0.49, 95% CI 0.26 to 0.93; P = 0.030; heterogeneity P = 0.45; I^2 = 0%). The rates of unstable angina were, however, similar between intervention groups (OR 0.61, 95% CI 0.06 to 6.14; P = 0.676; heterogeneity P = 0.34; I^2 = 0%). There was statistically significant reduction in increase serum creatinine kinase level in those treated with PCSK9 antibodies (OR 0.72, 95% CI 0.54 to 0.96; P = 0.026; heterogeneity P = 0.65; I^2 = 0%) compared to control group. There was no evidence of increase in serious adverse events with the use of PCSK9 inhibitors. The authors concluded that treatment with PCSK9 inhibitors in adults with hypercholesterolaemia appeared to be safe and effective. However, amongst the limitations of their study, they acknowledged the fact that results were derived from study-level data rather than individual patient data, that clinical event outcomes were derived from a small number of events and therefore had to be interpreted with caution and that the majority of trials (17/24) were less than 6 months in duration.

The results of the Navarese et al.'s meta-analysis[82] were utilised in the cost-effectiveness section of the company's submission and are further discussed in Chapter 5 of this report.

Adverse events

The company's submission of safety data was based on both phase II and phase III trials submitted as part of the EMA filing. These data include the findings of the 10 ODYSSEY trials used to assess the clinical effectiveness of alirocumab. In total 5234 patients with hypercholesterolaemia were included in the safety analyses, among whom 3340 received alirocumab (75 mg or 150 mg once every two weeks). Treatment duration was up to 18 months, leading to an overall exposure of 3451 patient-years in the alirocumab group.

Table 18 Adverse event profile

	Placebo controlled pool		Ezetimibe controlled pool	
	Placebo (n = 1276)	Alirocumab (n = 2476)	Ezetimibe (n = 618)	Alirocumab (n = 864)
Patients with any TEAE	975 (76.4%)	1876 (75.8%)	421 (68.1%)	607 (70.3%)
Patients with any treatment emergent SAE	182 (14.3%)	340 (13.7%)	69 (11.2%)	113 (13.1%)
Patients with any TEAE leading to death	11 (0.9%)	13 (0.5%)	7 (1.1%)	2 (0.2%)
Patients with any TEAE leading to permanent treatment discontinuation	65 (5.1%)	131 (5.3%)	60 (9.7%)	76 (8.8%)

The adverse event profile is presented in Table 18 and shows that the proportion of patients experiencing at least one TEAE and those with any TEAE leading to permanent treatment discontinuation are similar between the alirocumab and control groups. The most common adverse reaction leading to treatment discontinuation was local injection site reactions (0.2% in alirocumab versus 0.3% in control groups).
In both placebo controlled trials and ezetimibe-controlled trials no differences between alirocumab and controls were identified with regard to neurological and neurocognitive events, musculoskeletal-related events, diabetes mellitus, hepatic disorders, ophthalmological events and haemolytic anaemia.

No differences were observed between the two alirocumab doses (75 mg and 150 mg administered every two weeks). There were no drug-drug interactions that could have impacted on the safety profile.

In the pooled analysis of the phase III studies, all-cause mortality was 0.6% (20/3182) in the alirocumab group and 0.9% (17/1792) in the control groups. Table 19 shows the summary of mortality information and cause of death. There were no deaths in the phase II studies included in the safety submission. The profile of deaths was similar between alirocumab and controls.

Table 19 Summary of deaths- safety population (source Table 50, CS)

Primary cause of death as per adjudication, n (%)	Control (n=1792)	Alirocumab (n=3182)
Death on study	17 (0.9%)	20 (0.6%)
CHD death	9 (0.5%)	12 (0.4%)
Any CV	11 (0.6%)	15 (0.5%)
Acute MI	0	4 (0.1%)
CV haemmorhage	1 (<0.1%)	2 (<0.1%)
CV procedure	1 (<0.1%)	1 (<0.1%)
Heart failure or cardiogenic shock	1 (<0.1%)	1 (<0.1%)
Stroke – haemmorhagic	0	1 (<0.1%)
Sudden cardiac death	8 (0.4%)	6 (0.2%)
Any non-CV	6 (0.3%)	4 (0.1%)
Accidental	1 (<0.1%)	1 (<0.1%)
Pancreatic	1 (<0.1%)	1 (<0.1%)
Pulmonary	2 (0.1%)	2 (<0.1%)
Suicide	1 (<0.1%)	0
Other non-CV	1 (<0.1%)	0
Non-CV: infection	1 (<0.1%)	0
Non-CV: malignant	2 (0.1%)	2 (<0.1%)
New malignancy	1 (<0.1%)	1 (<0.1%)
Worsening prior malignancy	1 (<0.1%)	1 (<0.1%)
Not adjudicated	0	1 (<0.1%)

Major adverse cardiac events (MACE) which comprised death from coronary heart disease (CHD), non-fatal myocardial infarction (MI), fatal or non-fatal ischaemic stroke and unstable angina requiring hospitalisation, were recorded for the pooled phase III trials. In the placebo controlled trials, 35/2318 (1.5%) of patients who received alirocumab had treatment emergent MACE compared with 27/1174 (2.3%) of those who received placebo. In the ezetimibe controlled trials, 17/864 (2.0%) of patients treated with alirocumab and 6/618 (10%) of patients treated with ezetimibe had treatment emergent MACE.

A post hoc analysis of the largest trial assessing CV events that occurred in the TEAE period (LONG TERM) was undertaken by the company. The rate of MACE was 48% lower for alirocumab than placebo (27/1550 (1.7%) versus 26/788 (3.3%), respectively; HR = 0.52 (95% CI 0.31 to 0.90, p =0.02).

The effect of alirocumab on cardiovascular mortality and morbidity is currently being fully evaluated in the CVOT ongoing trial with the primary endpoint being MACE. Findings will be reported in 2018.

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

No indirect comparisons were undertaken by the company as there was direct evidence between alirocumab and relevant comparators (placebo, statins, and ezetimibe). However, the company did provide a descriptive comparison in terms of study design of the ODYSSEY and the PROFICIO clinical programmes, which assessed the effects of evolocumab (Tables 41-46 of the company's submission). No results of the PROFICIO programme were provided.

In brief, the ODYSSEY and PROFICIO programmes investigated broadly similar populations. The PROFICIO programme assessed evolocumab versus relevant comparators. A number of differences were observed between programmes: 10/12-week assessment was used as the primary endpoint for evolocumab compared with the 24-week assessment for alirocumab; most of the ODYSSEY trials were in high risk patients while the PROFICIO trials enrolled low risk populations; PROFICIO did not include dose titration and used four weekly dosing compared with two weekly dosing of alirocumab. It is worth pointing out that the PROFICIO trials programme did not contribute to the company's decision problem as evolocumab was not included as relevant comparator.

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

No indirect comparisons were undertaken by the company.

4.5 Additional work on clinical effectiveness undertaken by the ERG

None.

4.6 Conclusions of the clinical effectiveness section

The clinical effectiveness submitted was based on 10 phase III trials within the ODYSSEY clinical programme. The statistical analyses showed that alirocumab provided significant LDL-C reductions compared with controls (placebo, ezetimibe, or statins) in the magnitude of 39-62% reduction. The effect was rapid and persisted throughout the follow up. The observed effects were consistent across a range of subgroups and on top of background maximal tolerated statins with or without other lipid lowering drugs. Alirocumab also showed an impact on other lipid parameters. Alirocumab was shown to have a similar safety profile to the control groups (placebo or ezetimibe) The data submitted provides strong evidence that alirocumab is clinically effective, however, the ERG suggest this should be weighed up against the following issues.

The 10 included trials were phase III trials from the ODYSSEY programme. Additional phase II trials were relevant and included within the safety submission, but not clinical effectiveness. The ERG considers exclusion of these trials to be reasonable since there are available phase III trials and the follow-up points of the phase II studies tended to be shorter, with fewer patients.

Evolocumab, an alternative PCSK9 inhibitor, was not included as a relevant comparator. The reason given by the company is that evolocumab is currently under assessment and definitive NICE guidance for use in this population has yet to be finalised. While the ERG recognise this is correct, evolocumab trials do provide evidence relevant to the decision problem for this assessment. However, it is worth pointing out that there are no head to head trials of alirocumab versus evolocumab so any comparison would have been through an indirect comparison/network meta-analysis. The company did provide a qualitative description of evolocumab trials within the PROFICIO programme but provided no results. The meta-analysis results from Navarese et al. utilised in the economic evaluation used data from both alirocumab and evolocumab trials. The ERG clinical opinion is that the clinical effectiveness of evolocumab and alirocumab is likely to be similar.

Effectiveness data for CV events was available for the LONG TERM trial only. The company presented a *post-hoc* analysis of major adverse cardiac events (MACE)

comprising CHD death, non-fatal MI, fatal or non-fatal ischaemic stroke and unstable angina requiring hospitalisation. The rate of MACE was 48% lower for alirocumab as compared with placebo (HR = 0.52, 95% CI 0.31 to 0.90). The ERG was concerned that no other long term data for CV event risk was available. Nonetheless, the ERG noted that the CVOT ongoing trial (due to be reported in January 2018) should provide this information in the future.

5 Cost effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

A review of studies assessing the cost-effectiveness of alirocumab or ezetimibe, used alone or in combination with statins or other lipid-lowering therapies in individuals with hyercholesterolaemia at high-risk of CV events including those with familial hypercholesterolaemia as per the NICE scope.

Reports of cost effectiveness were sought by searching MEDLINE (Ovid), EMBASE (Ovid), NHS Economics Evaluation Database (NHS EED) and EconLit in December 2014/January 2015 for economic evaluations published from 2004 in English. In addition recent relevant conference proceedings were searched in EMBASE in January 2015. The search strategies are documented in full in Appendix 8.10.2 of the submission. A broad range of interventions were included in the search strategy. In addition to alirocumab and the relevant clinical comparators, statins, fibrates, nicotinic acid and sequestrants were considered. Appropriate MeSH and text terms were used. However, where MeSH or Emtree were not available, searching in the Registry Number/Name of Substance field may have been beneficial. No MeSH or Emtree terms were used for the hypercholesterolaemia facet in the MEDLINE, Embase and NHS EED search strategies and this may have potentially affected the sensitivity of the search. The SIGN economic study filters were used for MEDLINE and Embase searches and was appropriate.

5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate.

Articles considered suitable for inclusion were any cost-effectiveness or cost-utility studies of populations on LMT (ezetimibe + statin; ezetimibe +/- other LMT; Alirocumab +/- statin; Alirocumab +/- LMT), where the intervention was either

Alirocumab +/- statin or Alirocumab +/- LMT, and the comparators were either ezetimibe + statin; ezetimibe +/- other LMT. The criteria seem appropriate to the decision problem.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies.

The results of the search identified a total of eight economic evaluations of potential relevance.[5 84-90] None of these included alirocumab or any other PCSK9 inhibitor. Therefore the company reported and quality assessed the identified studies (using the checklist adapted by Drummond and colleague)[91] in Appendix 10 of their submission (8.10.4).

A scoping search carried out by the ERG did not find any relevant studies evaluating the use of alirocumab in hypercholesterolaemia but identified a draft health technology assessment report that had been made public after the date of the company search, so would not have been available to the company.[92] The assessment focused on the evidence for the comparative effectiveness and value of alirocumab and evolocumab for use in patients with familial hypercholesterolaemia, established CV disease or elevated risk of CV disease.

In summarising the existing clinical evidence, the report noted that PCSK9 treatment improved intermediate risk factors for CV (for all of the included patient subpopulations), and there was high certainty that they lead to superior reductions in LDL-C levels compared to both placebo and ezetimibe. The potential net benefit from this level of LDL-C reduction will be greater among subpopulations of patients at higher CV risk. They cited the meta-analysis conducted by Navarese et al. of 24 PCSK9 trials which reported a 55% reduction in all-cause mortality a ~50% reduction in MI, and a similar magnitude but non-significant reduction in CV death.[82] The review team did note the short duration of included trials (many of less than 6 months follow-up) and the current lack of long-term follow-up data from trials designed to assess the effect of PCSK9 inhibitors on hard clinical endpoints.

The review team undertook their own *de-novo* cost-effectiveness analysis using a previously validated computer simulation discrete-state Markov model of CHD and stroke incidence, prevalence, mortality and, costs in the adult population (aged 35 years) in the United States.[93-95] The analytic horizon was 20 years (2015-2034). The model assessed the costs and effects (QALYs) of PCSK9 inhibitors (as a class) when used alone or in combination with statins. Effects of alirocumab, statins and ezetimibe on CV events were modelled through the reduction in LDL-C achieved; with the relative risk per unit reduction in LDL-C assumed to be equal for all drugs. All drug costs where based on US wholesale prices. All drug costs where based on US wholesale prices. All costs and benefits were discounted at a rate of 3.0% per year and the perspective was that of the health system. The base case ICERs for adding PCSK9 inhibitors to current treatment for each sub-population were:

- Patients with familial hypercholesterolaemia (comparator maximum tolerated statin therapy + ezetimibe) = $681,000 per QALY
- Secondary prevention in patients with a prior history of CVD and intolerant of statins (comparator ezetimibe monotherapy) = $506,000 per QALY
- Secondary prevention in patients with a prior history of CVD and LDL-C ≥70 mg/dL on statin therapy (comparator maximum tolerated statin therapy + ezetimibe) = $557,000 per QALY

Over the 20 year model time horizon, the cost-effectiveness analysis suggested that PCSK9 inhibitors may generate substantial reductions in terms of CV events (non-fatal MIs, non-fatal strokes, and CV deaths). However, the ICERs with PCSK9 inhibitors were reported to exceed commonly accepted thresholds such as $100,000/ QALY.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

The company's review of the published cost-effective literature (for the dates that were searched) did not identify any studies which evaluated alirocumab and so were not considered directly relevant to the decision problem. The ERG is in agreement with this statement. Whilst the above study suggested high ICERs in a US setting,

these are not transferable to the UK setting where prices may be considerably different.

5.2 Summary and critique of company's submitted economic evaluation by the ERG Suggested research priorities

5.2.1 NICE reference case checklist (table only)

Table 20 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes, base case comparators are: **maximal tolerated dose of statins plus ezetimibe** for those people with heterozygous familial hypercholesterolaemia whose condition is not appropriately controlled with current treatment; **maximal tolerated dose of statins** for patients with high risk CVD and patients with recurrent CV events/ polyvascular disease; and **ezetimibe monotherapy** for patients with familial hypercholesterolemia, high risk CVD, and recurrent CV events/ polyvascular disease in whom a statin is considered inappropriate or is not tolerated. Note, **maximally tolerated dose of statin plus ezetimibe** is a recommended combination for patients with high risk CVD who are not appropriately controlled on

		statin alone, but is not included as a comparator for these cohorts.
Patient group	As per NICE scope. *"People with hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia:* • *whose condition is not appropriately controlled with maximal tolerated dose of statins, with or without ezetimibe* • *in whom a statin is considered inappropriate or is not tolerated"*	Yes, but the focus of the company's submission is on four specific high risk sub populations: • Patients with HeFH (both primary and secondary prevention) • Patients with high risk CVD • Patients with recurrent CV events or disease in multiple vascular beds (i.e. polyvascular disease)
Perspective costs	NHS & Personal Social Services	Yes, but some costs associated with personal social services may have been omitted.
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Yes, a cost-utility analysis is performed.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	The effects of alirocumab in combination with maximal tolerated dose of statins, with or without ezetimibe, or alirocumab on a background of no statins, with or without ezetimibe (in terms of % reduction in LDL-C) are derived from a group of trials conducted within the ODYSSEY programme. Systematic searches are used to inform health state utilities and costs in the model. Baseline CV event rates are

		derived from an analysis of UK primary care data (THIN database), and are adjusted where necessary for modelled age and baseline LDL-C levels. The effects of LDL-C reductions achieved by alirocumab are derived from a recently conducted systematic review of PCSK9 inhibitors.[82]
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes, health states defined by CV events (first year, second year and subsequent years following events)
Benefit valuation	Time-trade off or standard gamble	Yes, benefit is estimated based on EQ-5D responses of appropriate UK populations, scored using the UK time trade-off tariff.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes. Health utilities for relevant CV health states are derived from UK Health Survey for England (HSE) data and ODYSSEY.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Probabilistic modelling	Probabilistic modelling	Yes, the base cases were modelled deterministically and probabilistically.
Sensitivity analysis		Yes, the impact of varying a number of parameters is assessed

		through probabilistic and deterministic sensitivity analysis and results presented as scatter plots on the incremental cost-effectiveness plane, cost-effectiveness acceptability curves (CEACs) and tornado diagrams. A number of scenario analyses were also performed.

5.2.2 Model structure

The company constructed a *de-novo* model using a state-transition Markov framework to simulate the benefit and cost of alirocumab co-administration in patients with hypercholesterolaemia (at high risk of CV events) who have failed to reach their lipid goal (e.g. recommended (absolute) LDL-C target of 1.81 mmol/L according to ESC/EAS guidelines[10]) with their current maximally tolerated dose of statin (with/without other LMTs), or in patients who are statin intolerant or for whom a statin is contraindicated. The model uses a one-year cycle length and a lifetime time horizon (base case to age 99 years). Markov models are appropriate and commonly used for this type of analysis due to their ability to capture effects that occur over long time horizons and to extrapolate beyond shorter term trial data. The use of a Markov model is appropriate for (chronic) conditions such as hypercholesterolaemia which can lead to an increased cardiovascular risk profile and recurrent events over time.

The model includes 12 mutually exclusive discrete health states. 'Initial' (stable; 0-1 years following an ACS event; 1-2 years following an ACS event), 'post non-fatal ACS' (0-1 years; 1-2 years; stable CHD (i.e. >2years following ACS event), 'post non-fatal IS' (0-1 years; 1-2 years; stable IS (>2years following IS), 'stable elective revascularisation', 'CV death', and 'Non-CV death'. A diagram of the model, provided in the company's submission is shown in Figure 2. The model simulates the occurrence of CV events for a single cohort of patients (e.g. HeFH primary prevention and secondary prevention) or for a mixed cohort of patients (e.g. high-risk CVD).

The model allows annual transitions from one health state to another based on the predicted risks of CV events (fatal and nonfatal) and the risk of death from non-CV causes. Each health state is assigned a quality-of-life (utility) weight and an expected cost, allowing total survival time (expressed as life-years), quality-adjusted survival time (expressed as quality-adjusted life years) and lifetime costs to be calculated for alternative treatment strategies.

The baseline CV risks in the model are informed by data from the UK THIN database (a representative, large, well-validated electronic database),[96] which contains the electronic medical records of 11.1 million patients (3.7 million active patients) collected from 562 general practices in the UK, covering 6.2% of the UK population. Baseline CV risks are adjusted for age and baseline LDL-C levels in the model (detailed below), and the effect of alternative treatment strategies on CV events are modelled indirectly through their estimated effects on baseline LDL-C.

All patients begin the model in one of the 3 ‘Initial’ states and are assumed not at target LDL-C levels on existing maximal therapy. Patients receive alirocumab as an adjunct to existing therapy (i.e. as add-on to statin alone, statin plus ezetimibe, or ezetimibe alone). Treatment with alirocumab is initiated at 75 mg every 2 weeks with up-titration to 150 mg every 2 weeks in patients whose LDL-C measurement is not at target by Week 8 (as per the majority of ODYSSEY trials). Treatment effects and costs for alirocumab in year one are therefore calculated as weighted averages based on the estimated proportion of patients requiring to be up-titrated from the 75 mg to the 150 mg alirocumab dose. Treatment compliance is set at 100% over the lifetime of the cohort in the base case analysis, but the model has been constructed to allow treatment duration and discontinuation to be varied. The initial states are divided to reflect time since a prior ACS event, in order to accurately model the subsequent risks of further CV events, which are elevated in years 1 and 2 following an event.

From the initial states - ‘stable’, ‘0-1’ post-ACS and ‘1-2’ post-ACS - patients can experience fatal or non-fatal (NF) CV events and transition to post-event health states, or (in the absence of an event) transition through to, or stay in, the ‘Initial’ stable state. The included non-fatal post-CV event health states are: NF ACS (composite of non-fatal Myocardial Infarction (MI) and non-fatal unstable angina (UA) requiring

hospitalisation, but excluding stable angina), NF IS (non-fatal ischaemic stroke excluding TIA), and stable revascularisation (i.e. elective revascularisation undertaken in the absence of a new acute ACS event). The post-CV event health states also include a 0-1, 1-2 and > 2 years post-event state, mirroring the initial starting states. This allows subsequent state costs, and utility multipliers to vary by time since the event. Thus, in years 0-1, patients incur the costs of acute care and utility multipliers estimated for individuals who have experienced the CV event in question within one year. In years 1-2, post event costs and utility multipliers are applied, and beyond year two patients incur further utility multipliers but in the base case are not modelled to attract further post-event costs. From each of the post-CV event health states, patients can also experience another non-fatal CV event (ACS or IS) or CV death. Risks of subsequent CV events are similarly elevated in years 0-1 and 1-2 following an event, and are also further inflated for those modelled to experience recurrent ACS or IS events. The model does not explicitly incorporate risks for stable angina or TIA, although stable angina may to an extent be captured in the stable revascularisation state. The omission of risks for TIA and stable angina may be conservative in that greater reductions in LDL-C may also result in lower risks of these events.

The further event state included in the model is 'stable post-revascularization', which can be entered from the initial states prior to an acute event in the model. No transitions to the stable revascularization state are allowed from the NF-ACS and NF-IS states as this would unrealistically increase health state utility and alter subsequent risks, but the costs of elective revascularisation are applied to a proportion of patients in the stable post-ACS and stable post-IS health states.

Treatment effects of alirocumab are modelled as rate ratios for CV events (non-fatal MI, coronary revascularisation, ischaemic stroke, and vascular death) per 1.0 mmol/L reduction in LDL-C. The Navarese et al. meta-analysis of 24 PCSK9 trials provides the estimated rate ratios for MI and any vascular death, which are then scaled per 1 mmol/L reduction in LDL-C using the weighted average LDL-C reduction reported in the trials underlying the estimated ratios.[82]

The modelled transitions between health states occur between the model cycles (i.e. at the end of each cycle, before the next one starts). However, a half cycle correction is

appropriately applied to reflect the fact that, in reality, patients move continuously between states over time.

The ERG consider the company's model structure to be generally appropriate to the decision problem, and acknowledge the value of separating the post-event health states into three sub-states reflecting time since the event. One potential problem related to the use of a composite event state for ACS which includes MI and stable angina (UA). This makes it impossible to model different treatment effects for MI and UA, which is problematic because the primary source of effectiveness data suggests different degrees of uncertainty for these effects. There are also a few limiting structural assumptions which may be conservative. One relates to the omission of TIA and stable angina (although the latter may be partially captured by elective revascularization), and the other relates to the fact that the model has limited capacity to capture multiple CV event histories in terms of their cumulative impact on costs and quality of life (due to the memoryless property of Markov models). For example, patients in the post-stroke state who experience an ACS event, then go on to attract the event costs that reflect average values following the ACS event, and not the expected costs for patients with a history of stroke and ACS. It is possible that these assumptions may somewhat underestimate QALY gains and downstream cost savings associated with more effective treatments. One issue which has the potential to bias in favour of alirocumab is the omission of any treatment emergent adverse event (TEAE) states. The available safety data suggests no significant difference in the percentage of patients experiencing any TEAE, although it does indicate an incidence of injection site reactions of 6 per 100 patient years in the pooled alirocumab data (Table 48 of the company's submission). Whilst the severity of these was reported as generally mild and transient, it is unclear what the cost implications were. It is perhaps reasonable to assume that these would require at most a GP visit and so would be unlikely to have significant impact on cost-effectiveness. General allergic events were also more commonly reported for alirocumab (primarily pruritis), but pooled incidence was low (0.8-1.1%) and severity typically mild.

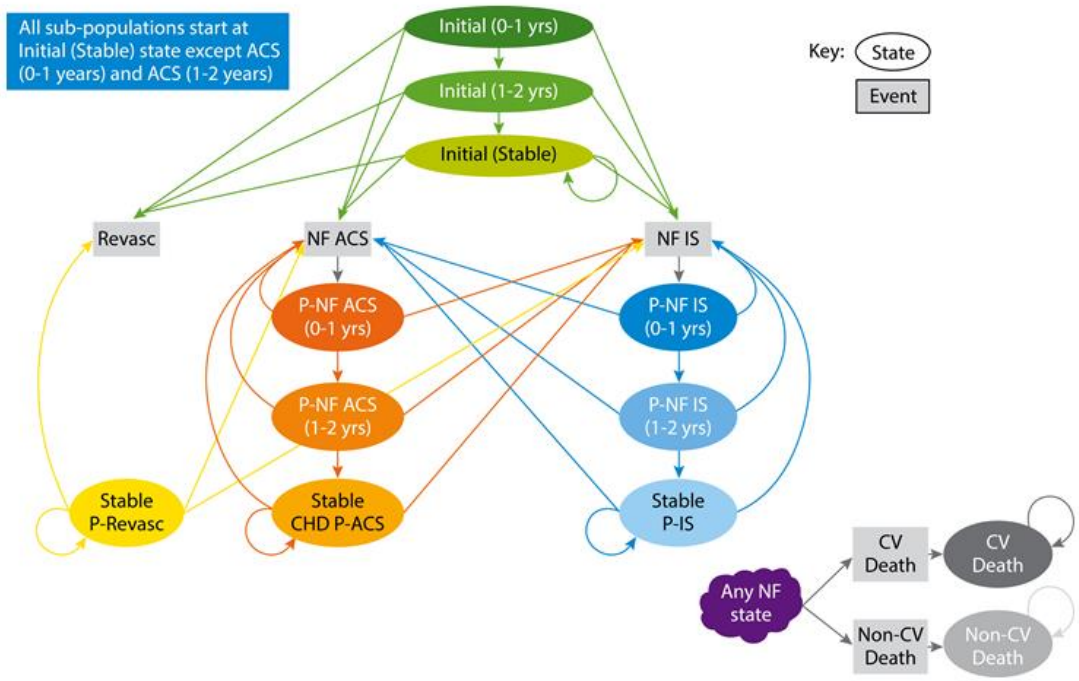


Figure 2 Model schematic (Source: Figure 30 of the company's submission)

ACS=acute coronary syndrome; IS=ischaemic stroke; CHD=Coronary heart disease; NF=non-fatal; P=post-; Revasc=elective revascularization.

5.2.3 Population

The NICE scope defined the population of interest as 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. The scope also stated that consideration should be given to the following subgroups:

- Presence or risk of cardiovascular disease
- Patients with heterozygous familial hypercholesterolaemia
- Patients with statin intolerance
- Severity of hypercholesterolaemia

The submission has focused on four specific high risk patient populations; 1) a HeFH primary prevention; 2) a HeFH secondary prevention; 3) a high-risk CVD; and 4) a higher risk CVD subgroup with recurrent CV events or polyvascular disease. The baseline characteristics of these four cohorts are informed by an analysis of routine primary care data from the UK THIN database. For the base case analysis the populations are defined as follows according to several variables associated with CV

risk: sex, age, diabetes prevalence, and baseline LDL-C level (on existing LMT prior to commencing alirocumab). Specific LDL-C thresholds for initiating alirocumab treatment are applied to each cohort in the model (varied in further sub-group analysis), and the mean LDL-C concentration for the corresponding patients above these thresholds in the THIN database are applied in the model:

1. Primary prevention HeFH: 50% male; mean age 50 years; 7% with diabetes; base case starting LDL-C threshold ≥2.59 mmol/L; mean baseline LDL-C = 4.82 mmol/L; annual composite CV event risk in first cycle of the model = [redacted]%.
2. Secondary prevention HeFH: 50% male; mean age 60 years; 2 options for percentage with diabetes - 26% using real-world data from the UK THIN database, or no split if using data from Morschladt, 2004; base case starting LDL-C threshold ≥2.59 mmol/L, mean baseline LDL-C = 4.56; annual composite CV event risk in first cycle of the model = [redacted]% using THIN data, or [redacted]% using Morschladt.[97]
3. High risk CVD population: history of ACS (MI or unstable angina requiring hospitalisation), coronary revascularisation, other arterial revascularisation procedures or other CHD, ischaemic stroke, or peripheral arterial disease (PAD); 60% male; mean age 65 years; 23% with diabetes; starting LDL-C threshold ≥3.36 mmol/L; mean baseline LDL-C = 4.03mmol/L; annual weighted composite CV event risk in first cycle of the model = [redacted]%.
4. Subgroup of the high risk CVD population with history of recurrent CV events or polyvascular disease: 60% male; mean age 65 years; 30% with diabetes; LDL-C threshold for alirocumab treatment ≥2.59 mmol/L; baseline LDL-C = 3.31 mmol/L; annual CV event risk in first cycle of the model = [redacted]%.

All of the above patient populations were included in the ODYSSEY trials. In addition to the chosen baseline LDL-C thresholds for alirocumab treatment, further subgroups for each of the four cohorts were defined for the alternative LDL-C thresholds. The company's Table, indicating the mean LDL-C concentration for each of the populations with LDL-C values above the different LDL-C thresholds, is replicated as Table 21. For patients intolerant to statins in each of the populations, the same baseline characteristics are applied, but higher baseline mean LDL-C values

(reflective of those for individuals on ezetimibe monotherapy) are derived from the ALTERNATIVE trial.

Table 21 Average LDL-C values by LDL-C cut-off (Source: Table 57 of the company's submission)

Cut-off threshold	≥1.81 mmol/L	≥2.59 mmol/L	≥3.36 mmol/L	≥4.14 mmol/L
HeFH (primary prevention)	4.50	4.82	5.28	5.59
HeFH (secondary prevention)	4.40	4.56	4.80	5.23
ACS (0-12 months)	2.60	3.31	4.11	4.83
ACS (13-24 months)	2.62	3.31	4.07	4.93
Ischaemic Stroke	2.65	3.27	4.00	4.67
Other CHD	2.67	3.30	4.02	4.73
PAD	2.79	3.36	4.03	4.73
Polyvascular	2.66	3.31	4.05	4.78
Statin intolerant patients on Ezetimibe monotherapy	3.74	4.00	4.55	5.07

ACS, acute coronary syndrome; CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral arterial disease

For the base case analyses, the model assumes an LDL-C treatment threshold on existing LLT of ≥2.59 for the HeFH and recurrent CV events/polyvascular disease populations, based on recognised guidelines[10] and following the segmentations used in the ODYSSEY trials. For the larger high risk CVD population, a LDL-C threshold ≥ 3.36 mmol/L is applied in the base case. The company noted in response to clarification that the American National Lipid Association guidelines suggests patients with LDL-C ≥ 2.58 mmol/L on maximally tolerated statin (+/- ezetimibe) are candidates for PCSK9 inhibitors in this population, but for mainly economic reasons the more conservative (higher) threshold of 3.36 was applied in the base case. In support, the company also cited a review of RCTs by O'Keefe et al.,[98] which showed that in patients with LDL-C ≥ 3.36 mmo/L, the risk of coronary events is three times

greater compared to those with LDL-C of 1.80 mmol/L (Figure 3). This illustrates the higher potential to benefit from treatment in this group.

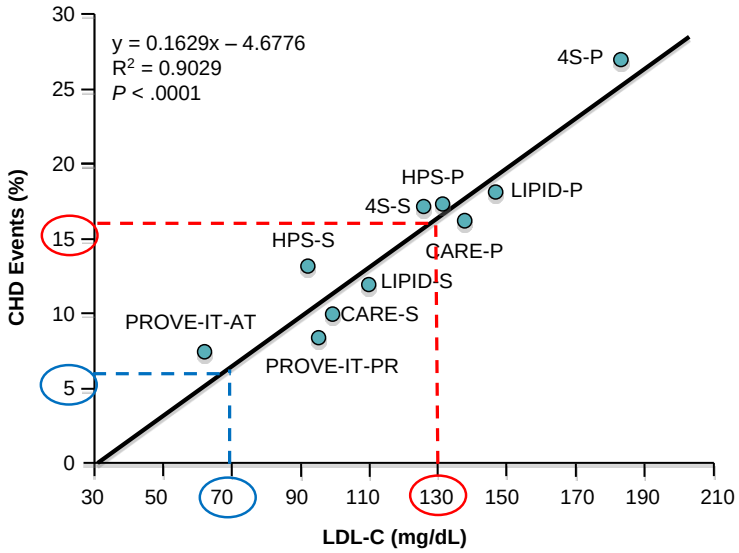


Figure 3 Relationship between LDL-C and CV event risk (Figure adapted from O'Keefe et al. 2004 - scale shown is in mg/dL; 70 mg/dL = 1.81mmol/L, 130 mg/dL = 3.36 mmol/L) (Source: Figure 29 of the company's submission)

The ERG accepts the reasoning behind the decision to focus on a threshold of 3.36 for the high risk CV cohort, but questions how applicable this analysis is to the high risk CVD population in the UK. Based on recent data reported by Jameson et al., the reported mean LDL-C (SD) in a UK primary care cohort with CVD, treated with atorvastatin, was 2.13 mmol/L (0.65). Assuming LDL-C is normally distributed, the proportion of patients above a threshold of 3.36 mmol/L would be ~2.5%. And this is without ezetimibe being co-administered. However, Jameson et al. did report that 25.5% of atorvastatin treated patients remained above a target threshold of 2.5 mmol/L. The base case thresholds applied for the HeFH cohorts are likely to be more inclusive for the respective populations at large, since, even with high-intensity statin treatment, mean LDL-C levels might reasonably be expected to be ≥ 2.59 or 3.36 mmol/L.[6]

The ERG also has some concerns relating to the fact that a substantial portion of the THIN cohort - used in the submission to inform the mean baseline LDL-C levels - are in fact not on optimised statin therapy. In response to clarification, the company

provided a breakdown of the LLTs that patients in the THIN dataset were on (Table 22). This shows that of those identified on LLT, a significant proportion were on low intensity statins. Thus the THIN subjects may represent a cohort that is not optimally treated on statin alone. This raises a question above whether the mean baseline LDL-C levels, for those above the specified LDL-C thresholds (Table 21), are applicable to patients on maximally tolerated statin (+/- ezetimibe). Overall, the ERG feels that the mean LDL-C values used for individuals above the given thresholds in the model (for the different populations on maximally tolerated therapy) are somewhat uncertain, but it is difficult to say which way any associated bias might go.

The company's submission also notes that the average age in THIN was ~ 70 years compared to participants in the ODYSSEY trials (~ 60 years). The company considers that alirocumab may be initiated in patients that are younger than average, and therefore, a series of assumptions for starting ages were made in the base case analyses: 65 years for the high risk CVD and recurrent CVD/ polyvascular disease populations; 50 years for HeFH primary prevention population; and 60 years for HeFH secondary prevention population. The ERG considers these assumptions reasonable, and note that these alterations to age are adjusted for in the model when incorporating the CV risks derived from the THIN data (section 5.2.6 below). The sex distribution was also informed by the THIN data, and is fixed over time in the model.

Table 22 Lipid-lowering therapies in THIN CV risk cohort (Source: Table 12, page 21 in the company's response to the ERG's points for clarification)

	Hierarchical Categorisation for Established CV Disease					Established CV Disease (N=148,051)	HeFH[1]	
	ACS ≤ 12 Months Prior to Index (N=4,717)	Ischaemic Stroke (N=15,835)	ACS 12-24 Months Prior to Index (N=4,107)	Other CHD (N=104,408)	PAD (N=18,984)		Primary Prevention (N=2,972)	Secondary Prevention[2] (N=1,421)
Currently on High-Intensity Statin	16.9%	3.3%	10.4%	4.4%	2.1%	4.6%	3.1%	13.3%
Monotherapy	14.3%	2.6%	8.9%	3.3%	1.5%	3.5%	1.9%	7.1%
+ Ezetimibe	0.7%	0.5%	0.8%	0.8%	0.4%	0.7%	1.0%	5.2%
+ Other LLT	1.9%	0.2%	0.7%	0.3%	0.2%	0.3%	0.2%	1.0%
Currently on Medium-Intensity Statin	16.3%	14.7%	18.5%	18.2%	12.5%	17.0%	10.7%	25.5%
Monotherapy	14.1%	13.1%	15.9%	15.9%	11.1%	14.9%	8.9%	19.8%
+ Ezetimibe	1.0%	1.0%	1.4%	1.5%	0.8%	1.3%	1.3%	4.4%
+ Other LLT	1.2%	0.6%	1.2%	0.9%	0.5%	0.8%	0.5%	1.4%
Currently on Low-Intensity Statin	52.3%	59.4%	57.5%	55.0%	51.1%	55.0%	33.0%	39.8%
Monotherapy	50.5%	57.6%	55.5%	52.9%	49.6%	53.0%	31.6%	36.0%
+ Ezetimibe	1.5%	1.5%	1.7%	1.7%	1.1%	1.6%	1.1%	3.7%
+ Other LLT	0.3%	0.3%	0.3%	0.4%	0.3%	0.4%	0.2%	0.1%
Currently on Non-Statin LLT	1.7%	2.2%	1.8%	2.4%	1.9%	2.3%	2.0%	3.9%
Ezetimibe Only	1.1%	1.5%	1.2%	1.5%	1.2%	1.4%	1.0%	2.2%
Other Non-Statin LLT Only	0.5%	0.7%	0.5%	0.8%	0.7%	0.7%	0.8%	1.3%
Ezetimibe + Other Non-Statin LLT	0.0%	0.1%	0.1%	0.1%	0.0%	0.1%	0.1%	0.5%
No Current Treatment with LLT	12.8%	20.3%	11.8%	20.0%	32.4%	21.2%	51.2%	17.5%

	Hierarchical Categorisation for Established CV Disease					Established CV Disease (N=148,051)	HeFH[1]	
	ACS ≤ 12 Months Prior to Index (N=4,717)	Ischaemic Stroke (N=15,835)	ACS 12-24 Months Prior to Index (N=4,107)	Other CHD (N=104,408)	PAD (N=18,984)		Primary Prevention (N=2,972)	Secondary Prevention[2] (N=1,421)
Previously on Statins	7.7%	11.5%	8.8%	11.7%	12.6%	11.6%	10.5%	12.9%
Previously on Non-statin LLT	0.1%	0.1%	0.0%	0.1%	0.2%	0.1%	0.1%	0.0%
No Treatment with LLT	5.0%	8.7%	3.0%	8.2%	19.6%	9.5%	40.5%	4.5%

The HeFH population consists of a single homogenous cohort in the model, while the high risk CVD population consists of a mixed cohort based on the distribution CV event histories observed in the THIN database. Table 23 presents the relevant proportional distribution. The effect of alirocumab treatment is assumed to be independent of patients' baseline characteristics in the model, i.e. homogenous treatment effects are applied.

Table 23 High risk CVD cohort proportions by patient types (Source: Table 59 of the company's submission)

ACS ≤12 months prior to index	3.28%
ACS 12–24 months prior to index	2.83%
Ischaemic Stroke	11.05%
Other CHD	68.55%
PAD	14.29%

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; IS, ischaemic stroke; PAD, peripheral arterial disease

5.2.4 Interventions and comparators

The intervention - alirocumab alone or in combination with a statin, with or without ezetimibe, or in combination with ezetimibe – is in line with the final scope. Alirocumab in the company's submission is considered in line with its marketing license - "*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 statin (when used as recommended by treatment guidelines); or alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated*" - for patients with primary hypercholesterolaemia who are failing to reach LDL-C goals. The company's submission states that it was assumed that in clinical practice alirocumab will only be prescribed in high risk, high unmet need patients, and will be supported by a homecare delivery service and patient support programme. In the main analyses, alirocumab is modelled as adjunctive treatment for those whose LDL-C is not adequately controlled on statin (+/-) ezetimibe, or ezetimibe alone in those who are intolerant to statins. However, in line with the scope, the company also presents an additional set of comparisons where alirocumab is compared directly against ezetimibe; i.e. as an alternative to ezetimibe

in patients not achieving LDL-C targets on optimised statin therapy alone, or in patients intolerant of statins. The company states that it does not consider this to be the best way of evaluating alirocumab.

The relevant treatment comparators in the NICE scope, when LDL-C is not adequately controlled with optimized statin therapy, include: ezetimibe in combination with optimised statin therapy; and evolocumab in combination with optimised statin therapy (subject to NICE guidance). Since no NICE guidance on the use of evolocumab has yet been issued, the ERG accepts that the appropriate comparator should be ezetimibe in combination with optimised statin therapy. This is the base case treatment comparator that has been modelled for the HeFH population in the company's submission. However, for the high risk CVD cohorts the company has modelled optimised statin therapy alone as the comparator. They justify this on grounds that there is wide variation in ezetimibe prescribing across the UK, and that it is prescribed more frequently for HeFH patients. However, if alirocumab is to be assessed as an adjunct to statin therapy alone in this population, then statin + ezetimibe may be the most relevant comparator according to NICE guidance. And since few patients may remain above an LDL-C threshold of 3.36 on maximally tolerated LMT (section 5.2.3), the ERG believes that alirocumab versus ezetimibe for those remaining above an LDL-C threshold of 2.59 mmol/L on statin alone may also be a relevant comparison here.

Where a statin is contraindicated or not tolerated, the comparator in the company's submission is ezetimibe monotherapy in all populations, which is in line with the NICE scope.

5.2.5 Perspective, time horizon and discounting

Costs have been considered from an NHS and Personal Social Services perspective and outcomes from the perspective of the health effects on individuals, both in accordance with the NICE reference case. The company's model uses a lifetime horizon (to age 99 years) with future costs and health benefits each discounted at 3.5% per year. The model has a cycle length of one-year and a half-cycle correction has been appropriately applied.

5.2.6 Treatment effectiveness and ***extrapolation***

The benefits of alirocumab treatment in terms of estimated QALY gains are modelled as a function of the baseline risk of CV events on existing maximally tolerated therapy (informed by analysis of THIN data), and the hazard ratios applied for the effects of alirocumab on CV events. Owing to the very limited direct evidence from the ODYSSEY trials for the effects of alirocumab on CV outcomes (i.e. the OYDSSEY cardiovascular outcomes trial (CVOT) is not due to report to 2018), pooled hazard ratios are taken from a meta-analysis of PCSK9 inhibitor trials.[82] The pooled estimates of the hazard ratios are then scaled and expressed per 1 mmol/L reduction in LDL-C, assuming a linear/log-linear relationship between LDL-C reductions (achieved with PCSK9 inhibitors) and the hazard ratios for CV events. The ERG feels that the general approach of scaling treatment effects to the estimated magnitude of reductions in LDL-C, rather than applying flat directly estimated relative risks, is justified given established relationships between absolute LDL-C reductions and CV event risks.[31 32 99 100] However, the ERG does have some concerns regarding the assumptions used to scale the estimated effects of alirocumab in the base case analyses. These are further discussed under extrapolation of treatment effects below.

Baseline CV risks

The company described how baseline risks of CV events and transition probabilities between the model health states were derived based on a retrospective analysis of observational data held on the THIN database. This was appropriately justified on the grounds that available risk estimators such as QRISK2 are not valid for the high CV-risk groups being modelled.

Using the 1st of January 2010 as the index date, patients with characteristics matching those included in the modelled populations were identified from their recorded CV history using READ codes (over a prior period of at least 24 months) and the Dutch Lipid Criteria to identify probable HeFH patients.[101]Included patients were grouped either hierarchically into mutually exclusive groups according to their CV history, or

alternatively according to their prevalent history (i.e. each patient could be included in more than one prevalent grouping). The hierarchical groupings were as follows:

- Established CVD:
    - ACS ≤12 months prior to the index date
    - Ischaemic stroke
    - ACS >12 to 24 months prior to the index date
    - Other coronary heart disease (CHD)
    - Peripheral arterial disease (PAD)

- HeFH (Dutch Lipid Criteria) and established CVD
- HeFH (Dutch Lipid Criteria) and no established CVD
- Diabetes (no established CVD) (NB not used in cost-effectiveness model)

The company noted that a key challenge in using the THIN data was to accurately identify those with HeFH. The ERG's clinical advisor agreed that the reliability of GP based systems like THIN for accurately identifying patients with HeFH – for primary prevention in particular - is well known to be very poor. After initial attempts to use READ codes to identify ("Familial Hypercholesterolaemia" and "Familial Hypercholesterolaemia according to Simon Broome criteria"[102]), this was found to produce counterintuitive clinical and demographic profiles. Therefore, the company resorted to using the Dutch Lipid criteria (described in Appendix 11 of the company's submission). The company acknowledged that this algorithm too has its limitations as it does not allow a definite judgement on the presence/absence of HeFH. However, it was considered a rational approach in the absence of better data recording. The company's submission reported that identification of primary prevention HeFH patients through Dutch Lipid Criteria had reasonably good face validity, with lower percentage rates for diabetes, and a younger mean age than other patient groups.

Details of the analysis are provided in Appendix 11 of the company's submission. It is the ERGs understanding that the analysis was conducted using data from those patients with a valid LDL-C measure in the preceding year or, if not available, one in 2010 so long as it preceded any CV event. This provided 148,051 patients with established CVD, 2,975 patients with probable HeFH but no CVD, and 1,424 patients

with probable HeFH and established CVD. Demographics of the wider THIN cohort and selected demographics of the cohort with a valid LDL-C measure used for the economic analysis are replicated from Appendix 11 of the company's submission in Tables 24 and 25 below.

It was noted in the company's submission that the characteristics of both cohorts were similar (Table 25) with the exception of diabetes prevalence in HeFH patients (classified using the Dutch Lipid Criteria), which was higher in the cohort with a valid LDL-C measurement (20% versus 7%). The company suggested this finding might be explained by the fact that primary prevention patients with diabetes may be more likely to have an LDL-C measurement (in routine clinical practice) than those without diabetes. Therefore, the 7% diabetes prevalence rate was used in the model for the HeFH primary prevention base case.

Table 24 THIN cohort demographic characteristics, overall study population and by CV and non-CV patients (Source: Appendix 11 of the company's submission)

	N of patients	Age		Sex (Male)	Charlson		BMI		LDL		DBP		SBP		eGFR		Smoking Status
		Mean	SD		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
CV Patients	187,538	72.8	11.7	59.7%	2.3	1.9	28.4	5.6	2.6	3.6	74.4	9.9	133.4	16.7	63.1	17.2	31.9%
Non-CV patients	152,649	61.6	15.9	50.4%	2.2	1.5	30.7	6.7	2.6	2.1	76.6	9.7	134.0	15.7	69.1	18.2	27.4%
All Patients	340,187	67.6	14.9	55.5%	2.3	1.8	29.6	6.3	2.6	3.0	75.4	9.9	133.6	16.2	65.8	17.9	29.8%
Dutch Lipid (Primary)	9,166	54.9	13.2	35.4%	1.5	1.6	30.0	6.4	3.6	1.6	78.7	9.6	131.6	15.7	70.8	16.5	46.1%
Dutch Lipid (Secondary)	1,562	66.4	11.3	48.0%	2.3	2.0	29.7	5.8	3.8	2.1	76.0	9.9	133.9	17.3	66.9	18.1	24.3%

Table 25 THIN cohort demographic characteristics by patient population, total cohort and LDL-C measured cohort (Source: Appendix 11 of the company's submission)

	N	Mean Age	% diabetes	Mean LDL-C
Total cohort				
Dutch Lipid Secondary prevention	1,562	66.4	26%	3.0
Established CVD	187,538	72.8		2.3
ACS ≤ 12 months prior to index	6,159	69.8	22%	2.1
Ischemic Stroke	20,723	74.6	24%	2.2
ACS 12-24 months prior to index	5,300	69.8	22%	2.2
Other CHD	128,553	72.7	23%	2.3
PAD	26,803	72.9	23%	2.5
Dutch Lipid Primary prevention	9,166	54.9	7%	3.6
LDL-C measured cohort				
Dutch Lipid Secondary prevention	1,424	66.2	26%	3.8
Established CVD	148,051	72.6		2.6
ACS ≤ 12 months prior to index	4,717	69.8	23%	2.5
Ischemic Stroke	15,835	74.5	25%	2.5
ACS 12-24 months prior to index	4,107	69.7	23%	2.6
Other CHD	104,408	72.5	24%	2.6
PAD	18,984	73.0	26%	2.5
Dutch Lipid Primary prevention	2,975	58.0	20%	3.6

The primary endpoint of the analysis of the THIN data was a subsequent CV event (composite of MI, UA, coronary revascularization, ischaemic stroke or cardiovascular death. Secondary endpoints included the individual CV outcomes and all-cause mortality. The cohort was followed-up for a maximum of 12 months post-index date, or until the first subsequent CV event or death occurred, or the patient transferred out of the database. However, the company noted a challenge with respect to sporadic recording of cause of death in the THIN database. As a result an assumption was made to calculate the number of CV deaths as a proportion of all deaths using data from the recent CTT meta-analysis.[99] This reported that 62% of all deaths observed in included statin trials were CV deaths, which was also reported as being consistent with estimates from the GRACE registry.[103] The company

also explored an alternative approach whereby they subtracted age/sex matched non-CV mortality rates (from UK life-tables) from all-cause mortality rates in THIN, to estimate CV mortality rates in the THIN cohort. They provided a breakdown of these estimates in response to clarification, and it was noted they were similar (but slightly higher) than those obtained when applying a constant proportion. Regarding the transition probabilities used in the model for non-CV death, these increased with age and were based on UK age-sex specific life tables[104] and applied for the lifetime time horizon of the model.

Kaplan Meier survival analysis was used to model the time to event data for each of the population-CV history groupings of interest, for each of the endpoints. This approach provided estimates of one year transition probabilities between the model states for each population group included in the model. These analyses were also split by the presence/absence of prevalent diabetes. The results are replicated in Tables 26 – 28 below. It should be noted, however, that the company has performed an upward adjustment of 25% to the raw data from THIN for all non-fatal events. This was supported by a published study by Herret[105] which found that primary care recording missed 25% of all non-fatal MIs that were recorded in any source. The ERG feel the adjustment is justified for MI, but are less certain about its applicability to ischaemic stroke. However, it does seem plausible that similar recording issues will apply to stroke as well.

Table 26 presents the results from the THIN analysis for the hierarchical classification of patients (depending on their CV history – e.g. used in the situation where two endpoint events occurred on the same date) and Tables 27-28 the results for the prevalent classification of patients (depending on their prevalent medical history – for use in informing transition probabilities in the model) with diabetes and without diabetes respectively.

Table 26 THIN analysis results, hierarchical for cohort with measured LDL-C (Source: Appendix 11 of the company's submission)

		CV Death		ischemic stroke		MI		Unstable Angina		Elective Revascularization	
	One-year Event Rate (composite endpoint)	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate
With diabetes											
Dutch Lipid Secondary prevention	6.8%	12	3.4%	3	0.8%	3	0.9%	1	0.3%	5	1.4%
ACS ≤ 12 months prior to index	17.4%	59	6.0%	12	1.3%	37	3.9%	25	2.5%	37	3.7%
Ischemic Stroke	7.5%	153	4.1%	67	1.8%	31	0.9%	13	0.4%	10	0.3%
ACS 12-24 months prior to index	9.3%	37	4.1%	8	0.9%	19	2.1%	14	1.6%	5	0.6%
Other CHD	5.3%	585	2.4%	150	0.6%	246	1.0%	150	0.6%	171	0.7%
PAD	5.9%	175	3.7%	35	0.8%	37	0.8%	10	0.2%	17	0.4%
Dutch Lipid Primary prevention	2.1%	6	1.0%	2	0.4%	3	0.5%	1	0.2%	0	0.0%
Diabetes without ASCVD	2.0%	1,771	1.2%	438	0.3%	409	0.3%	88	0.1%	184	0.1%
Without diabetes											
Dutch Lipid Secondary prevention	3.5%	13	1.3%	5	0.5%	9	0.9%	3	0.3%	5	0.5%
ACS ≤ 12 months prior to index	11.1%	99	2.9%	20	0.6%	105	3.1%	60	1.8%	94	2.7%
Ischemic Stroke	6.5%	417	3.6%	197	1.7%	84	0.7%	29	0.3%	23	0.2%
ACS 12-24 months	6.0%	68	2.2%	12	0.4%	53	1.8%	29	1.0%	18	0.6%

		CV Death		ischemic stroke		MI		Unstable Angina		Elective Revascularization	
	One-year Event Rate (composite endpoint)	**N of patients with events**	**One-year Event Rate**	**N of patients with events**	**One-year Event Rate**	**N of patients with events**	**One-year Event Rate**	**N of patients with events**	**One-year Event Rate**	**N of patients with events**	**One-year Event Rate**
prior to index											
Other CHD	4.1%	1475	1.9%	366	0.5%	614	0.8%	325	0.4%	420	0.5%
PAD	4.7%	397	2.9%	95	0.7%	96	0.7%	15	0.1%	44	0.3%
Dutch Lipid Primary prevention	1.3%	4	0.2%	3	0.1%	15	0.6%	4	0.2%	5	0.2%

Table 27 THIN analysis results, prevalent for cohort with measured LDL-C – WITH DIABETES (Source: Appendix 11 of the company's submission)

PREVALENT		CV Death		ischemic stroke		MI		Unstable Angina		Elective Revascularization*	
	One-year Event Rate (composite endpoint)	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate
Dutch Lipid Secondary prevention	6.8%	12	3.4%	3	0.8%	3	0.9%	1	0.3%	5	1.4%
ACS (0-1 years)[1]	17.4%	59	6.0%	12	1.3%	37	3.9%	25	2.5%	37	3.7%
ACS (1-2 years)[1]	9.3%	37	4.1%	8	0.9%	19	2.1%	14	1.6%	5	0.6%
ACS (>2 years, i.e., old MI/UA)[1]	6.2%	302	2.8%	78	0.7%	125	1.2%	90	0.8%	69	0.7%
Other CHD (excluding ACS 0-2 years)	5.8%	689	2.7%	192	0.7%	272	1.1%	159	0.6%	178	0.7%
CHD due to elective revasc	6.1%	135	2.2%	38	0.6%	86	1.4%	60	1.0%	53	0.9%
CHD due to elective revasc and had prior ACS *	6.7%	71	2.5%	18	0.6%	40	1.5%	36	1.3%	22	0.8%
CHD due to elective revasc and had no prior ACS	5.8%	63	2.0%	20	0.6%	46	1.4%	24	0.8%	31	1.0%
Ischemic Stroke	8.3%	182	4.2%	87	2.1%	47	1.1%	22	0.5%	17	0.4%
Ischemic stroke and any ACS (0-1 years,	12.7%	74	6.2%	30	2.6%	26	2.3%	10	0.8%	9	0.8%

PREVALENT		CV Death		ischemic stroke		MI		Unstable Angina		Elective Revascularization*	
	One-year Event Rate (composite endpoint)	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate
1-2 years, or >2 years)											
Ischemic stroke and any ACS (0-1 years)	25.4%	6	6.1%	4	3.9%	7	7.0%	5	4.6%	4	3.8%
Ischemic stroke and any ACS (1-2 years)	18.6%	3	3.7%	6	7.3%	4	4.8%	1	1.4%	1	1.4%
Ischemic stroke and old MI/UA	10.9%	65	6.4%	20	2.1%	15	1.6%	4	0.4%	4	0.4%
- Ischemic stroke or PAD, and any ACS (0-1 years, 1-2 years, or >2 years)	9.8%	255	4.6%	80	1.5%	101	1.9%	50	0.9%	46	0.9%
- Ischemic stroke or PAD, and any ACS (0-1 years)	26.9%	20	8.3%	6	2.6%	16	6.9%	12	4.7%	11	4.4%
- Ischemic stroke or PAD, and any ACS (1-2 years)	12.2%	10	4.8%	6	2.9%	6	3.0%	2	1.0%	1	0.5%
- Ischemic stroke or PAD, and old MI/UA	8.9%	225	4.5%	68	1.4%	79	1.6%	36	0.7%	34	0.7%
PAD	7.5%	420	4.1%	88	0.9%	126	1.3%	55	0.6%	63	0.6%
Dutch Lipid Primary prevention	2.1%	6	1.0%	2	0.4%	3	0.5%	1	0.2%	0	0.0%

Table 28 THIN analysis results, prevalent for cohort with measured LDL-C – WITHOUT DIABETES (Source: Appendix 11 of the company's submission)

PREVALENT		CV Death		ischemic stroke		MI		Unstable Angina		Elective Revascularization*	
	One-year Event Rate (composite endpoint)	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate
Dutch Lipid Secondary prevention	3.5%	13	1.3%	5	0.5%	9	0.9%	3	0.3%	5	0.5%
ACS (0-1 years)[1]	11.1%	99	2.9%	20	0.6%	105	3.1%	60	1.8%	94	2.7%
ACS (1-2 years)[1]	6.0%	68	2.2%	12	0.4%	53	1.8%	29	1.0%	18	0.6%
ACS (>2 years, i.e., old MI/UA)[1]	4.8%	732	2.2%	167	0.5%	350	1.1%	169	0.5%	147	0.5%
Other CHD (excluding ACS 0-2 years)	4.3%	1,709	2.0%	466	0.6%	671	0.8%	349	0.4%	438	0.5%
CHD due to elective revasc	4.1%	250	1.5%	69	0.4%	162	1.0%	95	0.6%	106	0.6%
CHD due to elective revasc and had prior ACS *	4.8%	121	1.7%	35	0.5%	93	1.3%	50	0.7%	43	0.6%
CHD due to elective revasc and had no prior ACS	3.7%	129	1.4%	34	0.4%	69	0.7%	45	0.5%	63	0.7%
Ischemic Stroke	6.9%	490	3.8%	226	1.8%	103	0.8%	38	0.3%	31	0.2%
Ischemic stroke and any ACS (0-1 years, 1-2 years, or >2 years)	10.1%	138	5.5%	50	2.0%	35	1.4%	17	0.7%	12	0.5%

PREVALENT		CV Death		ischemic stroke		MI		Unstable Angina		Elective Revascularization*	
	One-year Event Rate (composite endpoint)	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate	N of patients with events	One-year Event Rate
Ischemic stroke and any ACS (0-1 years)	14.7%	11	5.3%	8	4.0%	2	1.1%	5	2.4%	4	1.9%
Ischemic stroke and any ACS (1-2 years)	13.2%	13	7.4%	2	1.1%	5	2.9%	2	1.3%	1	0.5%
Ischemic stroke and old MI/UA	9.3%	115	5.3%	40	1.9%	28	1.3%	10	0.5%	7	0.3%
- Ischemic stroke or PAD, and any ACS (0-1 years, 1-2 years, or >2 years)	8.2%	514	4.2%	155	1.3%	179	1.5%	72	0.6%	69	0.6%
- Ischemic stroke or PAD, and any ACS (0-1 years)	15.7%	27	5.3%	9	1.9%	17	3.5%	10	1.9%	16	3.1%
- Ischemic stroke or PAD, and any ACS (1-2 years)	12.4%	27	6.1%	5	1.1%	13	2.9%	7	1.6%	3	0.7%
- Ischemic stroke or PAD, and old MI/UA	7.8%	460	4.1%	141	1.3%	149	1.4%	55	0.5%	50	0.5%
PAD	6.0%	891	3.3%	240	0.9%	265	1.0%	79	0.3%	122	0.5%
Dutch Lipid Primary prevention	1.3%	4	0.2%	3	0.1%	15	0.6%	4	0.2%	5	0.2%

Further adjustments to baseline CV risks

Whilst the data in Tables 26 to 28 provide the base case transition probabilities, they are further adjusted for age and baseline LDL-C when incorporated for use in the economic model. This is required as the base case characteristics of the modelled cohorts are somewhat different with respect to age and mean LDL-C concentrations (Table 21) compared to the corresponding subgroups in the THIN data (Table 25).

In estimating CV risk according to the modelled severity of hypercholesterolaemia, the difference between the mean baseline LDL-C being modelled and the mean LDL-C in the corresponding THIN cohort is used to adjust the risk of CV events using the relationship between absolute changes in LDL-C and CV risk as estimated from the CTT meta-analysis.[99 100] The CTT meta-analysis found evidence of a linear/log-linear relationship between absolute LDL-C reductions observed in statin trials and the relative rate of CV events. The rate ratio per 1 mmol/L reduction in LDL-C differs for specific types of event. The relationship is represented by a set of equations which are then appropriately used in the model to adjust the CV risk based on the baseline LDL-C:

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

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

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

Where:

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

The CTT collaboration also published an alternative specification for the relationship between baseline LDL-C and CV risk using a Cox model. The company has used the log-linear relationship in the base case and the Cox model in a scenario analysis.

The baseline CV risk in the model is also adjusted at the start of the model to reflect differences in the mean age of the modelled cohorts compared with the mean age of those in the corresponding THIN cohorts. For this purpose, hazard ratios reflecting the relative increase in non-fatal and fatal CV events, per year increase in age, are applied in the model. These estimates of 1.03 and 1.05, for non-fatal and fatal events respectively, were obtained from a published US study.[106] The CV risks in the model are also increased annually using these same hazard ratios, reflecting the increasing age of the modelled cohort.

In addition, the CV risks are increased for individuals modelled to experience recurrent CV events in the model. This is informed by data on ~387,000 MIs in England reported by Smolina et al.,[107] which showed that the risk of death in survivors of recurrent MI was 1.5 times higher than that of survivors of a first MI. This was captured in the model by multiplying the baseline probability of CV death by 1.5 in all the post-ACS health states for the sub-populations starting with a prior history of ACS (ACS 0-1 year, ACS 1-2 year, CHD, polyvascular and HeFH secondary prevention sub-populations). This increase was also applied to the probability of further ACS events in all post-ACS health states for the sub-populations with prior history of ACS. Finally, the same logic was applied to the probability of CV death and ischaemic stroke in the post-IS health states for the subpopulations with prior history of ischaemic stroke.

Alternative baseline risks for the HeFH secondary prevention cohort

For the secondary prevention HeFH cohort, the company's submission noted that the patient characteristics of the cohort identified using the Dutch Lipid Criteria on the THIN database still raised some questions relating to face validity. The rate of diabetes was found to be higher than expected at 26%, and the mean age was also relatively high at 66 years. Given the known low prevalence of diabetes in HeFH patients, the company undertook additional analyses using data from Morschladt and colleagues[97] which provided rates of CV events and CV death in secondary prevention FH patients. The advantage of this study was that it included patients with a confirmed diagnosis of HeFH, but it was also quite old with a relatively small sample size (131 secondary prevention patients, with 1105 years of follow-up). The study reported the rate of all CV events (143 per 1000 patient years) and the rate of

fatal CV events (12 per 1000 patient years), and also the distribution by type of CV event. Since PAD manifestations were included as events, these were subtracted from the rate of all CV events given that the company's model does not include PAD. The mean age of the secondary prevention cohort in Morschladt et al.[97] was 54 years. The mean LDL-C post-statin treatment was estimated as 4.51. Given the uncertainty surrounding the validity of the THIN data for HeFH secondary prevention cohort, the base case analysis used data from the Morschladt et al.'s study.[97] However, the company also presented results using THIN data which they stated showed good agreement. It should be noted however that the baseline composite risk of a CV event is more than 50% lower using data from THIN ([redacted] versus [redacted]).

Effects of alirocumab and comparators on LDL-C

The effects of alirocumab on baseline LDL-C were estimated for the different populations and dosing strategies from pooled on-treatment meta-analyses of percentage reductions in LDL-C compared with placebo or baseline (where ezetimibe was the active comparator). The majority of trials used a starting alirocumab dose of 75 mg, with up-titration at 12 weeks depending on LDL-C at 8 weeks and level of risk. Therefore, the efficacy of the alirocumab 75 mg dose was estimated as the percent reduction in LDL-C from baseline to week 12 weeks (before up-titration to 150 mg). Efficacy of the 150 mg dose was estimated as the percentage reduction from baseline to week 24 based on pooled analyses of trials that used this dose. The meta-analysis pooled trials specific to the populations and comparisons in the economic model.

Table 29 presents the estimated mean percentage changes from baseline LDL-C that are applied in the economic model (Table 60 of the company's submission) with further information provided in the company's response to the ERG's query regarding sources of the values used.

Where ezetimibe in combination with a statin is the active comparator for alirocumab in combination with a statin, the pooled percentage reduction with ezetimibe from baseline LDL-C on statin (23.9%) is used to model its efficacy on top of the mean baseline LDL-value. Where ezetimibe is modelled as the active comparator for those intolerant of statins (monotherapy), the estimate of an 18% reduction from baseline

comes from the ALTERNATIVE trial. These mean percent changes in LDL-C (with ezetimibe) are multiplied by the mean baseline LDL-C levels in the model to estimate the absolute reductions in LDL-C achieved with ezetimibe versus those achieved with alirocumab in the different modelled populations. The absolute reductions in LDL-C are then combined with external sources linking LDL-C reductions with relative reductions in CV event rates.

In general, the ERG is satisfied with the approach used to estimate the percentage reductions in LDL-C with alirocumab versus placebo (on maximally tolerated background LLT). It should be noted that varying proportions of patients were on statin alone and statin+ezetimibe as background therapy in the placebo controlled trials that inform these estimates. However, subgroup meta-analysis from the clinical effectiveness section of the company's submission suggests that the percentage reduction achieved with alirocumab does not differ significantly by background LLT (Figure 25 in the company's submission). The model results are applicable to patients who remain above the defined LDL-C thresholds on maximally tolerated LLT, whether that be statin alone or statin + ezetimibe; i.e. when statin + ezetimibe is assumed as background LLT in the model, there is no downward adjustment of the mean baseline LDL-C level compared to that applied for background treatment on statin alone. The prescribed background therapy only affects costs, and does so in both arms of the model.

Table 29 Mean % change from baseline LDL-C with alirocumab treatment used in the model (revised table provided by company at clarification)

			Percent Reduction in LDL-C		Standard Error		
			As Monotherapy	As Add-On To Statin	As Monotherapy	As Add- On To Statin	Source
Comparison vs Placebo [1]	**FH**	Alirocumab (75 mg)	49.3%	49.3%	1.9%	1.9%	Pooled FH I and FH II prior to up-titration (week 12) – values versus placebo
		Alirocumab (150 mg)	59.6%	59.6%	2.3%	2.3%	Pooled High FH and HeFH patients from LONG-TERM – values versus placebo at week 24
	High CV Risk	Alirocumab (75 mg)	49.3%	49.3%	1.6%	1.6% (NB previously stated 3.2% - in error)	FH I and FH II and COMBO I pooled prior to up titration (week 12) – values versus placebo
		Alirocumab (150 mg)	62.5%	62.5%	1.2%	1.2%	LONG-TERM – values versus placebo at week 24
Comparison vs Ezetimibe [2]	**FH**	Alirocumab (75 mg)	51.2%	51.0%	1.7%	1.1%	Assumed same as high CV risk.
		Alirocumab (150 mg)	59.6%	59.6%	2.3%	2.3%	Assumed same as vs placebo Pooled High FH and HeFH patients from LONG-TERM – values versus placebo at week 24

			Percent Reduction in LDL-C		Standard Error		
			As Monotherapy	As Add-On To Statin	As Monotherapy	As Add- On To Statin	Source
	High CV Risk	Alirocumab (75 mg)	51.2%	51.0%	1.7%	1.1%	Values are percent reduction from baseline prior to up-titration (at week 12). For monotherapy, value from ALTERNATIVE was used. For combination therapy, pooled from COMBO II, OPTIONS I and OPTIONS II
		Alirocumab (150 mg)	62.5%	62.5%	1.2%	1.2%	Assumed same as vs placebo
Ezetimibe (10 mg)			18.0%	23.9%	1.8%	1.4%	Represents percent reduction from baseline for ezetimibe. For monotherapy, value from ALTERNATIVE; for combination therapy, pooled from COMBO II, OPTIONS I and II

Effects of alirocumab and comparators on CV outcomes

The effects of alirocumab on CV outcomes were incorporated in the model as hazard ratios (HRs) reported by Navarese et al.[82] from a meta-analysis of 24 phase II and III trials of PCSK9 inhibitors. These were expressed as HRs per 1 mmol/L reduction in LDL-C, and scaled in the model to the size of absolute modelled reductions in LDL-C – assuming a linear/log-linear relationship between LDL-C reduction and the rate ratios for CV events.

The meta-analysis by Navarese et al.[82] pooled the effects from all PCSK9 inhibitor trials, not just those for alirocumab. Based on all included trials, the reported hazard ratios for MI and CV death were 0.49 (95% CI: 0.26 to 0.93) and 0.49 (95% CI: 0.23 to 1.07) respectively. No HR was reported for stroke. From the trials included in the meta-analysis, the company calculated the corresponding average reduction in LDL-C (1.6 mmol/L, weighted by sample size). The rate ratios per 1 mmol/L reduction in LDL-C were then calculated as follows (Table 30):

RR per 1 mmol/l reduction in LDL-C = EXP(LN(HR)/absolute reduction)

Table 30 Rate ratios per 1 mmol/L reduction in LDL-C for different CV events (Source: Table 60 of the company's submission)

Event	Mean RR value (95% CI)
Non-fatal MI	RR per 1 mmol/L reduction in LDL-C = EXP(LN(0.49)/1.6) = **0.64**
Coronary revascularisation	No results presented – assumed to be the same as other non-fatal CV events
IS	No results presented – assumed to be the same as other non-fatal CV events
Vascular death	RR per 1 mmol/L reduction in LDL-C = EXP(LN(0.49)/1.6) = **0.64**

In the absence of direct evidence for the effect of PCSK9 inhibitors on ischaemic stroke and coronary revascularisation, the estimated HR for MI was applied to these events. This is a somewhat controversial assumption, since data from other studies suggest that the effect of LDL-C lowering on IS may not be as great as it is for ACS events (CTT meta-analysis).

Alternative data sources for informing the HRs associated with LDL-C reductions on alirocumab treatment were also explored in scenario analysis – including use of the CTT meta-analysis, LONG-TERM trial data, and the pooled analysis of ODYSSEY phase III placebo controlled trials.

The ERG has a number of further concerns relating to the scaling of alirocumab's effects to the modelled reductions in LDL-C. One relates to the use of all trials included in the Navarese et al.'s meta-analysis,[82] being used to estimate the weighted mean reduction in LDL-C associated with the reported HRs, rather than only using those trials used in the meta-analyses for the different types of CV events. The ERG sought clarification on this. In response the company provided estimates of LDL-C reduction derived specifically from the trials informing the HRs for MI and CV-death. This led to an estimated LDL-C reduction of 1.3 mmol/L in trials informing the HR for CV death, and a 1.8 mmol/L reduction from those informing the HR for MI. Using these values the rate ratios per 1 mmol/L reduction in LDL-C are 0.58 for CV death and 0.68 for MI. The ERG considers these new values to be the more relevant; if assuming a linear/log-linear relationship to extrapolate the specific effects observed in Navarese et al.[82] to alternative reductions in LDL-C.

The ERG's further uncertainty relates to the extrapolation of alirocumab's effects on CV events, to larger LDL-C reductions than those observed in the trials informing the estimated hazard ratios reported by Navarese et al. (i.e. weighted average 1.6 mmol/L).[82] A linear/log-linear relationship is assumed between LDL-C reductions achieved with PCSK9 inhibitors and proportional reductions in CV events; i.e. extrapolation is based on a straight line, on the log scale, through the estimated HR of 0.49 (LDL-C reduction 1.6 mmol/L) and an HR of 1 (for an LDL-C reduction of zero mmol/L). This relationship is then used to scale the observed hazard ratios to absolute reductions in LDL-C. This results in modelled reductions in CV event rates, per unit reduction in LDL-C, that are (on average) greater than those predicted for equivalent statin induced LDL-C reductions based on the CTT meta-analysis. For example, for a modelled 2.7 mmol/L reduction in LDL-C, the HR for MI would be 0.30 (0.64^2.7).

In response to clarification on this issue, the company noted that this is what the best available estimates for the direct effects of PCSK9 inhibitors suggest to date. They

also noted that "*the CTT meta-analysis pulled together CVOT results from a very broad set of patient populations that are not part of the intended alirocumab population*". In particular, they noted the inclusion of trials that examined the effect of statins in novel patient populations that were later shown not to be impacted by lipid lowering therapy (e.g. patients with end-stage renal disease and renal transplant patients). By contrast, they note, that "*data from the PCSK9 trials are taken from studies including patient populations that have been shown to benefit from LDL-C reduction and represent specifically the intended population for alirocumab therapy.*" In addition, they noted genetic studies which show that mutations that affect LDL-C reductions through the PCSK9 pathway, result in greater reductions in the incidence of CHD events than do equivalent statin/ezetimibe induced LDL-C reductions – Figure 2 of the company's submission.[108] However, they also noted that this steeper reduction in CHD events observed with genetic studies is hypothesized to be due to the impact of life-long cholesterol reduction. Finally, the company suggest that there are potentially additional effects of PCSK9 inhibitors that may contribute to a steeper relationship between LDL-C reductions and CV event rates. They noted in response to clarification:

"Several recent studies have explored the potential positive benefits of PCSK9 inhibition on parameters directly related to atherosclerosis progression, beyond the effect of reducing LDL-C concentrations. In particular, PCSK9 inhibitors decrease the serum concentration of lipoprotein(a) by around 25%."[109] *The robust and specific association between elevated Lp(a) levels and increased cardiovascular disease (CVD)/coronary heart disease (CHD) risk, together with recent genetic findings, indicates that elevated Lp(a), like elevated LDL-cholesterol, is causally related to premature CVD/CHD. The association is continuous without a threshold or dependence on LDL- or non-HDL-cholesterol levels. Mechanistically, elevated Lp(a) levels may either induce a prothrombotic/anti-fibrinolytic effect as apolipoprotein(a) resembles both plasminogen and plasmin but has no fibrinolytic activity, or may accelerate atherosclerosis because, like LDL, the Lp(a) particle is cholesterol-rich, or both.*[110] *Yet no available therapies in Europe (including statins) have shown a reduction in Lp(a) concentrations. Therefore, it has been hypothesised that the ability of PCSK9 inhibitors to reduce levels of Lp(a) may have an incremental effect on reducing relative risk of CV events."*

The ERG accept that the point of the estimates for the relative reductions in CV event rates (from Navarese) are greater than predicted for equivalent reductions in LDL-C based on the CTT meta-analysis.[99,100] However, the hazard ratios reported by Naverese et al. are based on small numbers of events (i.e. 25 CV deaths; 38 MIs) reported in trials of mostly short duration (< 6 months), which were not designed to assess CVOT end-points. The 95% confidence intervals are correspondingly wide (0.26-0.93 for MI; 0.23-1.07 for CV death) and include the estimates that would be predicted by the CTT meta-analysis). For example, for a 1.6 mmol/L reduction in LDL-C, the CTT would predict a rate ratio of 0.62 (=0.74^1.6) for MI and 0.82 (=0.88^1.6) for CVdeath.

The established relationship between LDL-C reductions and CV events derived from CTT meta-analysis, was estimated based on data from 26 trials with at least 1000 patients randomized (to either more statin versus less statin, or stain versus placebo) and at least two years of treatment duration. This provided data on 24,323 events in ~170,000 randomised patients.[100] The company used this approach in a more conservative scenario analysis. The company also presented alternative scenarios where the effects of alirocumab were extrapolated using an estimated hazard ratio for CV events derived from a post-hoc analysis of all major adverse cardiovascular events in the LONG TERM trial (HR = 0.7 per 1 mmol/L reduction in LDL-C), and based on a pooled analysis of CV events in all the phase III placebo controlled ODDSEY trials (HR = 0.79 per mmol/L reduction in LDL-C).

For head-to-head comparisons with ezetimibe, the effects of ezetimibe on CV event risks were modelled using the same approach as outlined above, using the estimated HR reported for ezetimibe in the IMPROVE-IT trial (0.928 for a 0.33 mmol/L reduction in LDL-C) (IMPROVE-IT).[111] Scaled to a 1 mmol/L reduction in LDL-C, this equates to an HR of 0.8 (EXP(LN(0.928)/0.33) = 0.8. However, it has also been noted that the rate ratio for ezetimibe is consistent with that predicted by the estimated relationship between LDL-C and CV events in the CTT meta-analysis (IMPROVE-IT).[111] Thus, it could be argued that it is appropriate to model the effects of ezetimibe through the HRs derived from the CTT meta-analysis.[99]

Discontinuations and compliance

Treatment continuation and compliance are both assumed to be 100% over the cohorts' lifetime. The high compliance is in line with the high ~ 98% compliance rate observed in those continuing with treatment in the ODYSSEY trials. These assumptions are also consistent with the base case modelling conducted in CG181 and TA132.[29 35] The company presented scenarios assuming a certain percentage of patients discontinue alirocumab and comparator treatment each year (3-8%), and the ERG believe these scenarios are more realistic.

5.2.7 Health related quality of life

The company assessed quality of life using the EQ-5D in most of the phase-III trials of the ODYSSEY programme (i.e. FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM clinical trials). The estimated mean baseline health state utility values (HSUVs) for each defined subpopulations are presented in Table 31 (i.e. ACS 0-1 year; ACS 1-2 years; CHD; ischaemic stroke; PAD, HeFH). These are stratified by whether patients in each subpopulation had a history of other CV events or not.

Table 31 Baseline utilities estimated from some of the clinical trials within the ODYSSEY programme (Source: Table 63 of the company's submission)

Patient subpopulation	Overall			No other CV event/condition		At least one other CV event/condition	
	n	Mean age (SD)	Mean EQ-5D (SD)	n	Mean EQ-5D (SD)	n	Mean EQ-5D (SD)
ACS 0–1 year	198	56.2 (10.2)	0.844 (0.197)	142	0.848 (0.201)	56	0.832 (0.189)
ACS 1–2 years	192	58.7 (9.1)	0.858 (0.187)	120	0.874 (0.185)	72	0.832 (0.190)
CHD	2731	61.4 (9.7)	0.851 (0.194)	813	0.860 (0.191)	1918	0.847 (0.195)
IS	344	63.8 (9.5)	0.797 (0.228)	164	0.804 (0.212)	180	0.791 (0.242)
PAD	188	62.8 (9.1)	0.771 (0.233)	98	0.775 (0.253)	90	0.767 (0.211)
HeFH (all)**	1254	52.7 (12.3)	0.905 (0.149)	682	0.930 (0.130)	572	0.875 (0.164)

ACS, acute coronary syndrome; CHD, coronary heart disease; CV, cardiovascular; EQ-5D, EuroQol-five dimensions; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; IS, ischaemic stroke; PAD, peripheral arterial disease; SD, standard deviation
*Includes all randomised patients regardless of treatment assignment; data include prevalent patient groups, i.e. non-mutually exclusive.
**Refers to both primary and secondary prevention.

The estimated HSUVs from the ODYSSEY programme were not used to inform the base case analysis in the model due to a lack of data collected around the time of CV events and also due to the small number of CV events captured in the programme. Instead a systematic literature review was undertaken by the company to identify studies reporting health related quality of life (HRQoL).

Appendix 13 details the searches that were undertaken to identify relevant HRQL data. These were specified as cardiovascular events associated with hypercholesterolaemia. MEDLINE, EMBASE, Econlit, NHS EED and the HTA Database were searched in addition to included relevant reports found from the economic evaluations searches.

The search strategies combined two search facets using the Boolean operator AND: cardiovascular conditions and health utilities. In general, an appropriate range of both controlled vocabulary and text terms were included in each strategy for the clinical

conditions but no controlled vocabulary terms were used for the utilities facet. *Cost Benefit Analysis* for MEDLINE and *Cost Utility Analysis* for EMBASE in particular would have been beneficial to include. It is therefore uncertain if all relevant studies were identified.

The systematic literature review was designed to retrieve all studies reporting HSUVs associated with CV events in patients with hypercholesterolaemia, including: non-fatal MI, unstable angina, revascularisations, ischaemic stroke, non-specific stroke (i.e. transient ischaemic attack (TIA)), peripheral vascular disease, and heart failure. All studies reporting HSUVs that were either directly elicited from the general population or indirectly elicited from individuals with a CV event (using the EQ-5D, SF-6D or HUI3) were eligible for inclusion. The company assessed the quality of included studies using the minimum standard checklist described by Jacobs et al., and tabulated the key details of studies meeting the inclusion criteria. After assessing all the studies identified from the systematic literature review, the company opted to use the HSUVs estimated by Ara and Brazier[112] in the base case analysis. This study was selected based on the results of the quality assessment exercise, and because it was the most complete and coherent source of utility values for all the health states included in the model.

Ara and Brazier analysed data from the 2003 and 2006 Health Survey for England (HSE) where a random sample completed the EQ-5D questionnaire and which also included questions about history of CVD.[112] Based on these data, Ara and Brazier were able to estimate mean EQ-5D utility weights for members of the general population (N = 26,679) by history of different types of CV event within a year of a primary event, and in subsequent years following an event. They were also able to estimate values for those experiencing multiple events. Given that these health state utilities (Table 5.12) are from a single source and are representative of the population with and without CVD in England, these do appear to be the best available source for the model. The study also included a regression analysis to estimate baseline utility by age and sex for individuals with and without a history of a CV events and for the general population. This allowed estimation of age and sex adjusted health state utility multipliers, which can be applied multiplicatively to the relevant baseline utility to

capture the impact of CV events. The estimated age-adjusted utility multipliers reported by Ara and Brazier are provided in Table 32.

The company applied different age adjusted multipliers for first year and subsequent years after modelled CV events. These were applied in line with the Technical Support Document (TSD) produced by NICE's Decision Support Unit (DSU).[113] The company used the regression equation for individuals with no history of CVD reported by Ara and Brazier[112] to estimate age and sex adjusted baseline health state utility in the primary prevention model.

$$\text{No CVD } EQ-5D = 0.9454933 + 0.0256466 * male - 0.0002213 * age - 0.0000294 * age^2$$

This yields EQ-5D norms for the population without a history of CVD given the age and sex distribution of the modelled cohort, and updates annually in the model with increasing age. Within the model, the estimated age adjusted health state utility multipliers for identified CV events (and post-event states) were multiplied by corresponding age related background utility to estimate the utility values for the different states in the model. Table 33 shows the multipliers that were applied for the different states.

Table 32 Age-adjusted multipliers calculated from Ara et al (Source: Table 64 of the company's submission)

	Baseline utility in HSE data	Mean Age	Calculated multiplier*
Angina <12 months, history of just angina**	0.615	68.8	0.765
No event <12 months, history of just angina	0.775	68.0	0.960
Heart attack <12 months, history of just heart attack***	0.615	68.8	0.765
No event <12 months, history of just heart attack	0.742	65.1	0.906
Stroke <12 months, history of just stroke	0.626	67.9	0.775
No event <12 months, history of just stroke	0.668	66.8	0.822
No event <12 months, history of heart attack + other CV condition	0.685	69.2	0.854

* Note: The values above correspond to an assumption of 50% male

**Angina is assumed to apply to unstable angina in the model

*** Note: The sample size for the acute post-MI utility in Ara et al [17] was very small (N=31). Thus, the acute post-MI utility is assumed to be the same as the acute post-unstable angina utility.

Table 33 Summary of age-adjusted health states utility multipliers used in the model (Source: Table 65 of the company's submission)

CV event based utilities	Mean			SE		
	First year	Second year	Stable beyond 2 years	First year	Second year	Stable beyond 2 years
NF MI	0.765	0.906	0.906	0.019	0.020	0.020
UA	0.765	0.960	0.960	0.019	0.015	0.015
ACS	0.765	0.924	0.924	0.019	0.018	0.018
Revascularisation	N/A	N/A	1.000	N/A	N/A	N/A
IS	0.775	0.822	0.822	0.038	0.018	0.018

ACS, acute coronary syndrome; CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; N/A, not available; NF, non-fatal; SE, standard error; UA, unstable angina

The company used the same general approach as for primary prevention to estimate health state utilities for secondary prevention cohorts. However, for these groups the company multiplied the age-adjusted utility for patients with no history of CVD (the same equation as above) by the age-adjusted multiplier for the relevant type of CV event history in the initial states in the model. For example, for patients starting the model with a previous history of MI, the baseline utility is estimated by multiplying the age-adjusted utility for people with no history of CVD by the "chronic" multiplier for patients with a previous heart attack; i.e. 0.906 (see Table 33) Then, when a subsequent event is modelled to occur, the appropriate acute and chronic multipliers are applied in the model (Table 34).

Table 34 Multipliers for secondary prevention baseline (Source: Table 66 of the company's submission)

Baseline utility multipliers	Multiplier	SE
HeFH (secondary prevention)	0.924	0.018
ACS (0–12 months)	0.765	0.019
History of IS	0.822	0.018
ACS (13–24 months)	0.924	0.018
CHD	0.924	0.018
PAD	0.924	0.018
HeFH (primary prevention)	N/ A (1.000)	N/A
Polyvascular	0.854	0.024

ACS, acute coronary syndrome; CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolaemia; IS, ischaemic stroke; N/A, not available; PAD, peripheral arterial disease; SE, standard error

Utility data from ODYSSEY

As mentioned above, EQ-5D data were also collected in some of the trials in the ODYSSEY programme. The company applied the mean baseline HSUVs from the ODYSSEY programme in a sensitivity analysis. In contrast with the base case analysis, the company assumed that the baseline HSUVs are constant throughout the model with no decline due to age. All baseline utility data from the ODYSSEY programme, which are applied in the model, are presented in Table 35.

Table 35 Baseline utility data from the ODYSSEY programme applied in the model (Source: Table 67 of the company's submission)

Baseline Utilities	Mean	Standard Error Values
HeFH (Secondary Prevention)	0.875	0.007
ACS (0-12 months)	0.844	0.014
History of Ischaemic Stroke	0.797	0.014
ACS (13-24 months)	0.858	0.013
CHD	0.860	0.007
PAD	0.775	0.026
HeFH (Primary Prevention)	0.930	0.005
Diabetes	0.814	0.006
Polyvascular	0.771	0.018

In general, the ERG believes that the way in which HSUVs are estimated and implemented in the model are appropriate.

5.2.8 Resources and costs

CV event costs

The company included direct CV event costs and background therapy and comparator costs in the model. The CV event costs were all obtained from the modelling conducted for CG181, and the company did not conduct a systematic literature review. In the CG181, a detailed assessment of costings was conducted to support the analysis of the impact of lipid modification with statins via its impact on CV events. Costs for each health state were estimated in the CG181 based on the resource use that a typical adult with that CV condition would be expected to receive in line with NICE guidance and standard NHS practice. Unit costs were sourced from the NHS Drug Tariff, NHS Reference costs, PSSRU Unit Costs of Health & Social Care and the BNF.

The CV event costs are incorporated in the model as those associated with the acute event (to 6 months) and then the annual incremental follow-up costs. The company stated that they only included CV events costs in the model up to three years following the event in the base case analysis. If the patient has a second CV event within three years of the previous one, the follow-up costs for the first event stop and costs for the second event start accumulating. The cost of an ACS event is calculated

based on the weighted average of non-fatal MI and unstable angina requiring hospitalization. The proportional weights are estimated based on the average one-year event probabilities for MI and UA in the target populations in the THIN data. The company also included the cost of urgent revascularisation (i.e. occurring within 30 days of an ACS) within the event cost for MI/unstable angina requiring hospitalisation.

The cost of elective revascularization in stable patients with a history of ACS is calculated separately in the model, for those transiting to this state in the model (i.e. based on the estimated transition probabilities from the THIN data). As discussed under model structure, patients could transit to the elective revascularisation state from the initial model states due to the unrealistic positive impact on utility and CV risk that would be associated with transitions from the post-ACS and post-IS states. However, since in reality a proportion of patients in the stable post-ACS and stable post-IS health states would receive elective revascularization, the costs of this were applied to proportions of patients in these states. The company did not include non-CV costs. A summary of the costs associated with each health state are presented in the Table 36.

Table 36 Health states cost used in the company's model (Source: Table 69 of the company's submission)

	Event cost (£)	Incremental second year costs (£)	Incremental third year costs (£)
NF MI	3337.00	788.00	788.00
UA	3313.00	385.00	385.00
ACS	3329.00	653.67	653.67
Revascularisation	3802.32	N/A	N/A
IS	4092.00	155.00	155.00
CV death	1174.00	N/A	N/A
Non-CV death	0.00	N/A	N/A

ACS, acute coronary syndrome; CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; N/A, not available; NF, non-fatal; UA, unstable angina

Since the acute CV event costs reported in the CG181[29] only capture the costs for the first 6 months following the event, it would seem appropriate to apply 6 months' worth of follow-up costs to the first year costs following the event. However, it is the ERGs understanding that the company has not included these follow-up costs to cover the second half of the annual cycle immediately following CV events. It is also unclear for the ERG how the cost of revascularisation is estimated.

In contrast to previous modelling undertaken to inform NICE guidance, including TA132[35] and CG181,[29] the company only included CV event follow-up costs in their base case analysis up to three years following the acute event. The ERG believes that this assumption is probably unrealistic and conservative. Following cardiovascular events, especially stroke, patients may require ongoing social care and medical attention.[114 115] It is a challenging parameter to estimate for the current model structure, since what is required is the mean post-stoke annual health and social care cost associated with the index stoke event, but excluding any costs associated with subsequent vascular events following the index stroke. Given the way published studies have estimated and reported costs in the years following stroke, it is difficult to separate out the component required for the model. However, given the magnitude of mean post stroke costs reported in relevant UK studies[115 116] and the expected distribution of stroke severity[115] the ERG believe that costs associated with the post stroke states may be underestimated. As an alternative approach we have explored the impact of applying an estimate of the mean social care costs (Youman et al 2003) for UK stroke patients; £1,257 (2001.2002 prices) inflated to £1,769 (2013/2014 prices) per year using the NHS Hospital and Community Health Service Pay and Prices Index. The acute costs were also considered low by the ERG in comparison with available UK data. As an alternative value for this parameter, we inflated a previous estimate for acute stroke costs form a UK population based study[117] £6,906 (2004/2005 prices) to £8,618 (2013/14 prices).

Intervention and comparators' costs and resource use

The company estimated the annual cost of background treatment including statins and non-statin LMT. When background therapy includes statins, it is costed based on high dose, high intensity statins (i.e. atorvastatin and rosuvastatin). The model has the capacity to include other types of statin drug in the background treatment cost

estimation. Unit costs for the drugs are taken from the BNF 2015 (January edition) (see Table 37).[118] Annual costs were calculated on the basis of daily usage assuming no wastage. Since alirocumab is expected to be considered appropriate in those patients who are already on a high intensity statin, only atorvastatin and rosuvastatin are included in the estimation of the background therapy cost. The company estimated the proportion of the cohort on the different doses of these drugs based on market research data. Where ezetimibe is included as a background therapy or competitor, this is costed at 10mg per day. Alirocumab costs were estimated based on subcutaneous injection once every two weeks and assuming no wastage. The list price of both the 75 and 150 mg doses are the same, and the list price of a two pen injection pack (£336) is exactly twice the price of a single injection pen (£168). Thus annual intervention drug costs at list price equate to £4,383 (168*(365.25/14)). A patient access scheme, in the form of a simple discount, was submitted mid-way through the appraisal process, and results in this report are based on that agreed PAS.

Table 37 Drug costs (Source: Table 68 of the company's submission)

Treatment	Dose	Annual cost in model (£)	Pack price from BNF October 2015	Annual cost based on October BNF version (£)
Ezetimibe	10 mg	342.97	Ezetimibe 10 mg daily – Ezetrol - £26.31 per 28 tablet pack, annual cost = £26.31/ 28 x 365 days	342.97
Atorvastatin (Lipitor)	10 mg	15.51	Cost of 28 tab pack = £1.15	14.99
	20 mg	18.90	Cost of 28 tab pack = £1.38	17.99
	40 mg	21.77	Cost of 28 tab pack = £1.57	20.47
	80 mg	34.94	Cost of 28 tab pack = £2.73	35.59
Rosuvastatin (Crestor)	5 mg	235.03	Cost of 28 tab pack = £18.03	235.03
	10 mg	235.03	Cost of 28 tab pack = £18.03	235.03
	20 mg	339.19	Cost of 28 tab pack = £26.02	339.19
	40 mg	386.51	Cost of 28 tab pack = £29.69	387.03

Monitoring cost

The company did not include monitoring and other related costs in the model because it was argued that alirocumab is going to be positioned on top of maximally tolerated

current therapy, and it is therefore expected that resource usage will be identical between arms. The company mentioned that it is "*anticipated that alirocumab will be initiated and continued in secondary care via a sponsored homecare service*" and "*with a follow up consultation in line with current practice for follow‑up of people started on statin treatment*" (CG181).[29] However, very little detail was provided about the intended sponsored home care service. If injections were to be managed from GP practices or community pharmacies, then there would potentially be some extra administration costs to the NHS which have not been included in the model. The ERG feel that the company's assumptions are not unreasonable here; monitoring could continue unchanged, and with regards to administration, most patients would be self-administering; those requiring help would almost certainly be needing help for other reasons, so administration is unlikely to place a significant extra burden on the NHS.

Adverse event costs

Since based on the results from the trials included in the ODYSSEY programme total adverse event rates were similar between the alirocumab and control groups, including placebo, the company did not include costs of adverse events in the model. Whilst the reported adverse event rates in included trials were similar, the occurrence of local injection site reactions was significantly higher in the alirocumab group, at a reported incidence of 6 per 100 person years. However, these were reportedly mild and transient. The ERG feel it is reasonable to assume that the impact of local injection site reactions would largely fall on the patient in terms of discomfort - there would be little by way of extra therapy required, and if fully informed in advance, possibly not even an extra consultation.

5.2.9 Cost effectiveness results

The ERG originally received the company's submission reporting ICERs based on list prices. Mid-way through the review period the ERG received the company PAS submission, which was later confirmed as agreed with the department of health. Therefore, all the subsequent results are reported for the agreed PAS drug price, based on simple discount.

All estimated costs and outcomes were summarized in the results section of the company's submission. The disaggregated results for total costs, health state costs and

clinical outcomes were presented for each strategy. Total QALYs accrued in the different health states were also summarised for the alirocumab and comparator arms.

The company's estimated base case results are replicated for each patient population in Table 38.

The base case analyses for HeFH are provided for cohorts aged 50, LDL-C ≥ 2.59 mmol/L (mean LDL-C = 4.82 mmol/L for primary prevention, 4.56 for secondary prevention), 50% male. For alirocumab used as an add-on to current maximal LMT (maximal dose of statins combined with ezetimibe) the ICER is £36,793 in the primary prevention HeFH population. For the secondary prevention HeFH cohort, the estimated ICER is £16,896 based on CV risks data from Morschladt et al.[97].

The base case analysis for high risk CVD is conducted for a cohort aged 65 years, 60% male, LDL-C ≥ 3.36 mmol/L. The recurrent events/ polyvascular disease cohort has the same characteristics, except an LDL-C threshold of 2.59 mmol/L is applied (mean = 3.31 mmol/L).

For the high risk CVD cohort, the estimated ICER for alirocumab as an add-on to maximal statin treatment is £19,751. For the cohort with recurrent events/ polyvascular disease, the corresponding ICER is £19,447.

Table 38 Base case results in HeFH with PAS (Source; Table 2 of the company's PAS submission)

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	**Alirocumab + current maximal therapy (statins + ezetimibe)**	[redacted]	[redacted]	[redacted]	52,256	1.62	1.42	36,793
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L)	**Alirocumab + current maximal therapy (statins + ezetimibe)**	[redacted]	[redacted]	[redacted]	39,306	3.04	2.33	16,896
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L)	**Alirocumab + current maximal therapy (statins)**	[redacted]	[redacted]	[redacted]	34,684	2.38	1.76	19,751
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	**Alirocumab + current maximal therapy (statins)**	[redacted]	[redacted]	[redacted]	31,953	2.42	1.64	19,447
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				

HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; LYG, life-years gained; QALY, quality-adjusted life-year

Base case results for high risk CVD and recurrent events/ polyvascular disease, for those intolerant to statin

In the original submission, prior to the agreed PAS results being provided, the company reported cost-effectiveness results for alirocumab plus ezetimibe versus ezetimibe alone for the high risk CVD and recurrent events/ polyvascular disease cohorts. These results are relevant to those who are completely intolerant to statins, who are inadequately controlled on ezetimibe alone. For these analyses, higher mean baseline LDL-C levels were applied (4.55 mmol/L for the high risk CVD, 4.0 mmol/L for recurrent events/ polyvascular disease).

Whilst these results with agreed PAS have not been submitted by the company, the ERG has replicated them here based on back calculation of the PAS discount. For this analysis the ICER comes to £17,256 in high risk CVD cohort and £15,853 in the recurrent events/ polyvascular disease cohort (Table 39).

In the original submission, the company also conducted additional analyses comparing alirocumab directly with ezetimibe in all the above subpopulations (Tables 75 and 76 of the company's submission). These analyses may be relevant for cohorts remaining above LDL-C thresholds on statin alone, but they have not been provided by the company with the agreed PAS, and so are not commented on here. The ERG has included these comparisons in further exploratory analysis reported in section 5.4 below.

Table 39 Base case results for high risk CVD and recurrent events/ polyvascular disease – *statin intolerant patients* (Source: Table 74 of the company's original submission, but with results updated by the ERG to incorporate the agreed PAS)

Patient population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs baseline (QALYs)
High-risk CVD (baseline LDL-C ≥3.36mmol/L)	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	35,146	2.76	2.04	17,256
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	32,719	3.03	2.06	15,853
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; LYG, life-years gained; QALY, quality-adjusted life-year; SI, statin intolerance

Subgroup analysis

Further subgroup analysis was presented by the company in the original submission, showing the cost-effectiveness of alirocumab as an add-on to statin (+/- ezetimibe) using three alternative LDL-C cut-off thresholds for the four modelled populations. These results were not provided by the company with the agreed PAS, but have been generated in Table 40 by the ERG. Other, than LDL-C levels, the cohort's characteristics remain unchanged from the base case analyses.

Table 40 Subgroup analyses by LDL-C levels (Source: adapted from Table 99 and Table 57 of the company's submission, with results updated by the ERG to incorporate the agreed PAS)

Patient population	LDL-C cut-off (mmol/L) ≥	Average Baseline LDL-C (mmol/L)	Incremental costs £	Incremental QALY	ICER
HeFH primary prevention	2.59	4.82	52,256	1.42	36,793
	3.36	5.28	52,005	1.64	31,750
	4.14	5.59	51,804	1.79	28,923
HeFH secondary prevention	2.59	4.56	39,306	2.33	16,896
	3.36	4.80	39,224	2.48	15,838
	4.14	5.23	39,023	2.74	14,242
High Risk CVD	2.59	3.31	34,701	1.37	25,287
	3.36	4.03	34,684	1.76	19,751
	4.14	4.76	34,493	2.15	16,043
Recurrent events / Polyvascular disease	2.59	3.31	31,953	1.64	19,447
	3.36	4.05	32,085	2.09	15,332
	4.14	4.78	32,013	2.54	12,606

HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life-year

5.2.10 Sensitivity analyses

Probabilistic sensitivity analyses

The company performed probabilistic sensitivity analysis to address parameter uncertainty in the model. Key parameters in the model, including cohort baseline characteristics, treatment effects on LDL-C, rate ratios linking LDL-C reductions to CV event reductions, costs and utilities were defined as distributions in the model. Results were presented as scatter plots on the incremental cost-effectiveness plane, and cost-effectiveness acceptability curves (CEACs). All the parameters and respective distributions used in the model are summarised in Table 41 below.

Table 41 Distributions used for the key parameters in the PSA (Source: Table 78 of the company's submission)

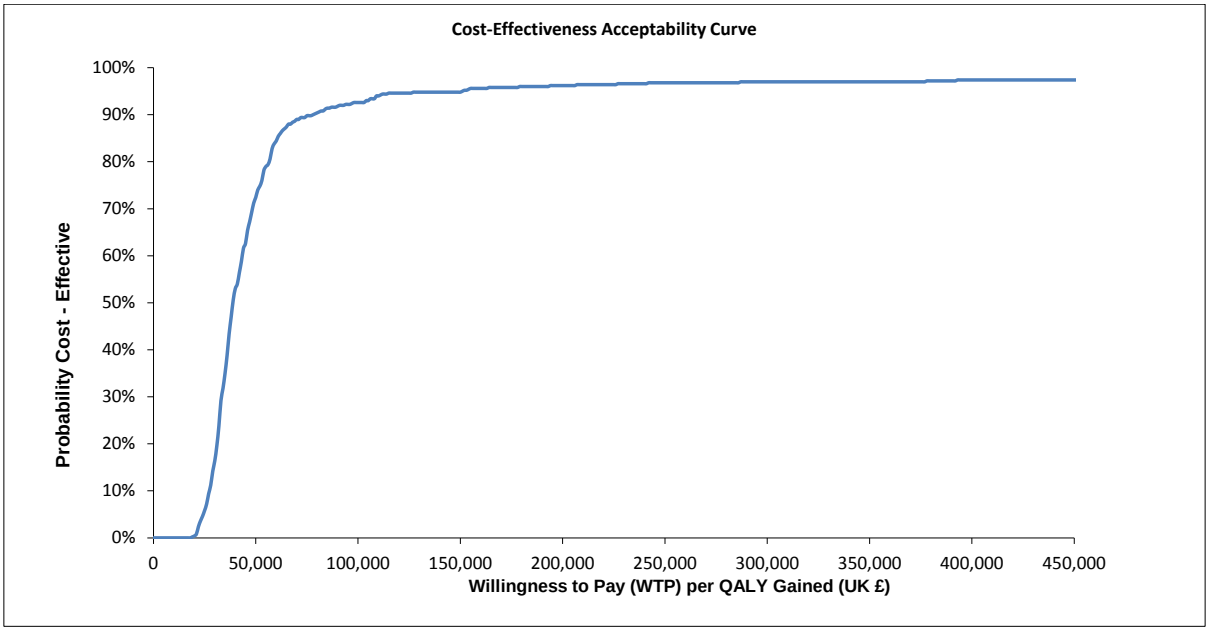
Variable	Distribution	Variation
Cohort characteristics		
Proportion with diabetes	Normal	SE from proportion of population with diabetes in THIN (1%)
Proportion of males	Normal	Standard error calculated as +/- 25% / 6
Baseline LDL-C	Log-Normal	Standard error calculated as +/- 25% / 6
Initial age	Normal	Standard error calculated as +/- 25% / 6
LDL-C lowering efficacy for alirocumab and comparators	Normal	ODYSSEY trial programme
CV costs	Gamma	Standard error calculated as +/- 25% / 6
Utilities	Beta	According to uncertainty in original estimates in Ara paper (multipliers recalculated each time)
Relative risk reduction	Log-Normal	According to CIs reported in Navarese et al. 2015 [82]
Annual increase in CV risk due to age	Normal	According to CIs reported in Wilson 2012 [34]

CI, confidence interval; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; N/A, not available

The ERG believe that in general appropriate distributions were assigned for the included model parameters but the formula used to estimate standard errors for some of the variables was not very well justified; +/- 25% of the mean / 6 for several cost inputs, diabetes prevalence, initial LDL-C levels and age.

For the high risk CVD cohort, the proportion of patients with different types of CVD history (i.e. history of ACS (MI or unstable angina requiring hospitalisation), other CHD, ischaemic stroke and PAD) were defined deterministically, which will may have caused the uncertainty surrounding the ICERs to be somewhat underestimated.

The scatter plots and CEACs for each modeled subpopulation are presented in Figures 4-7 below. In the PAS submission, the company did not provide the mean ICERs or the probabilities of cost-effectiveness at given ceiling ratios of willingness-to-pay per QALY for these analyses.



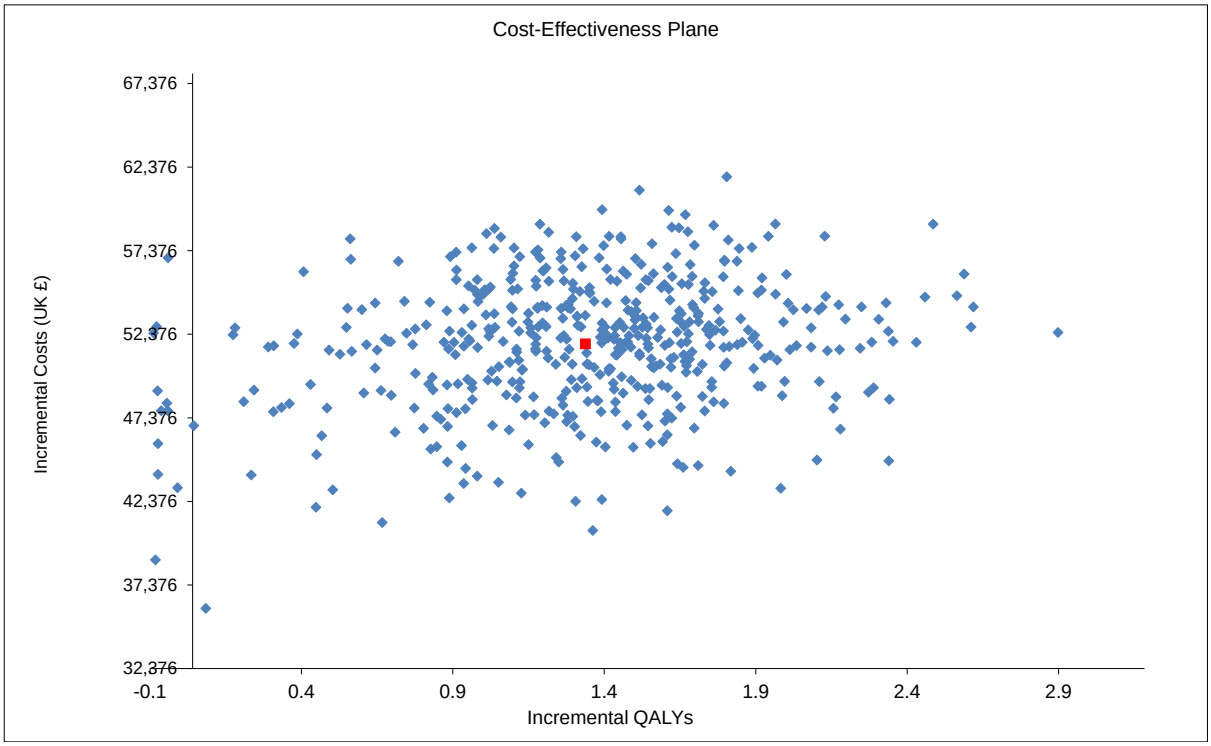
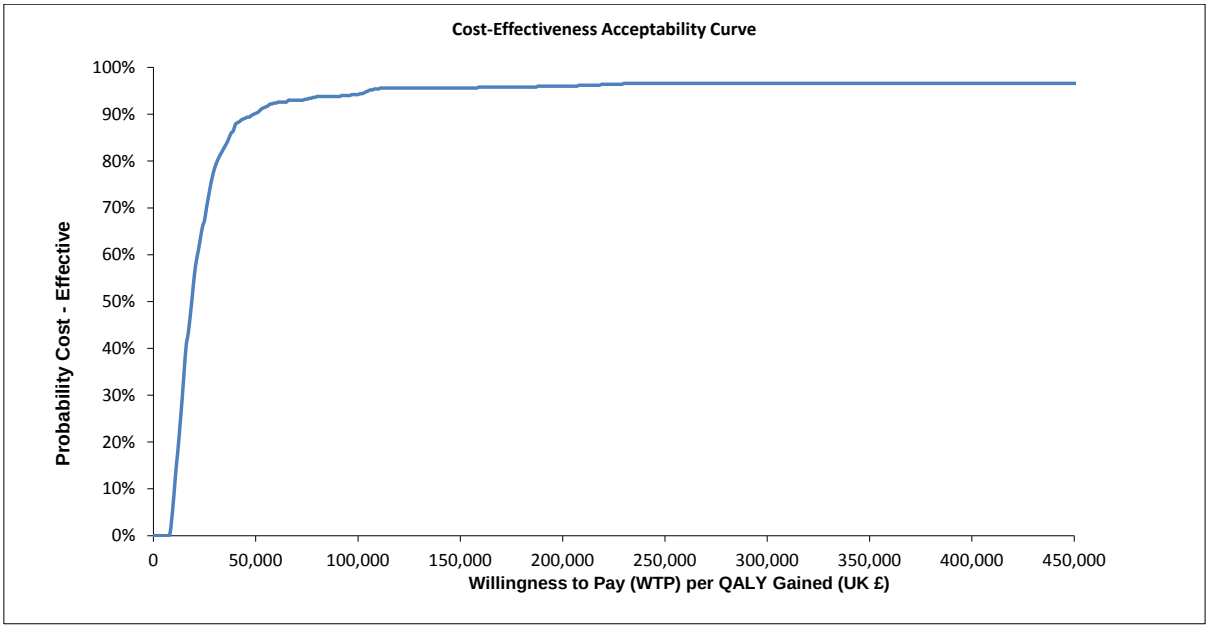


Figure 4 HeFH primary prevention, Scatter plot and CEAC with PAS (Source: Figure 1 of the company's PAS submission)



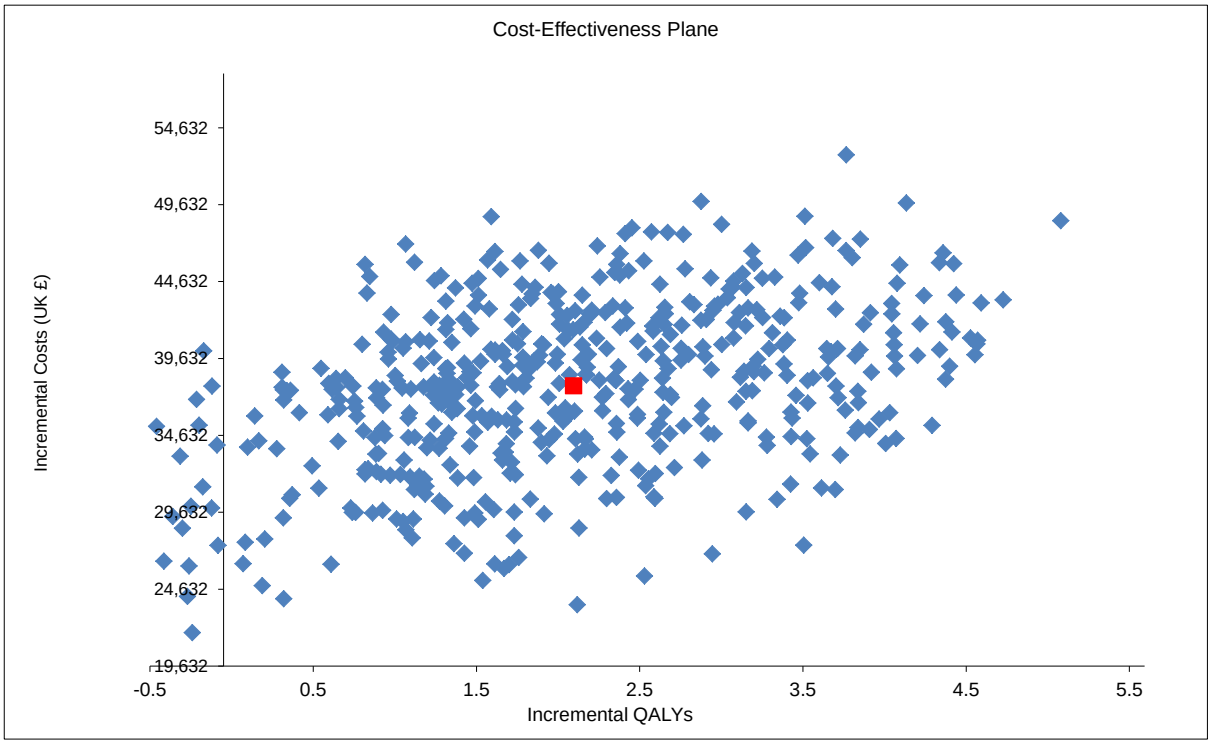
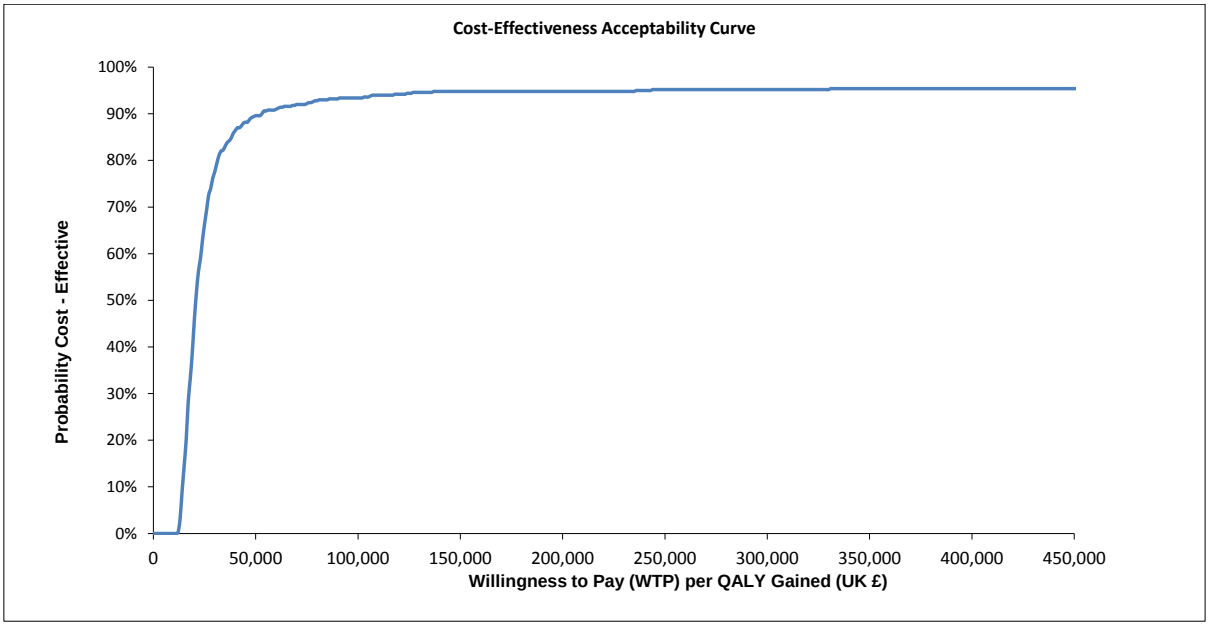


Figure 5 HeFH secondary prevention, Scatter plot and CEAC with PAS

(Source: Figure 2 of the company's PAS submission)



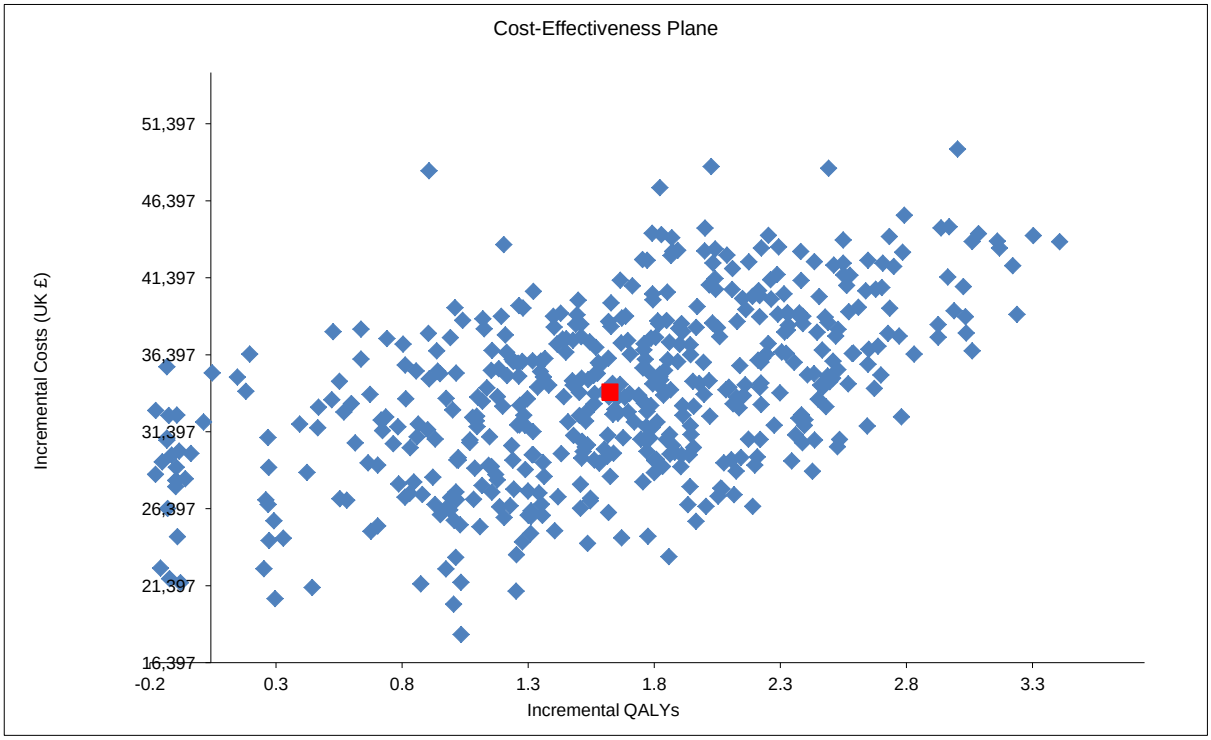
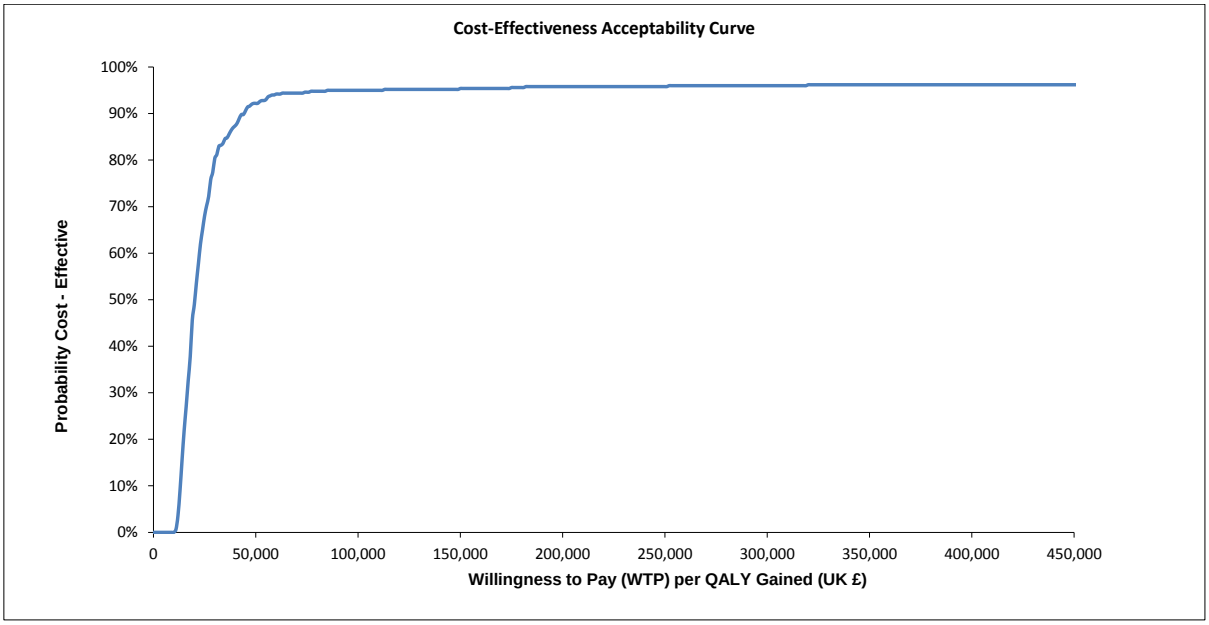


Figure 6 High Risk CVD, scatter plot and CEAC with PAS (Source: Figure 3 of the company's PAS submission)



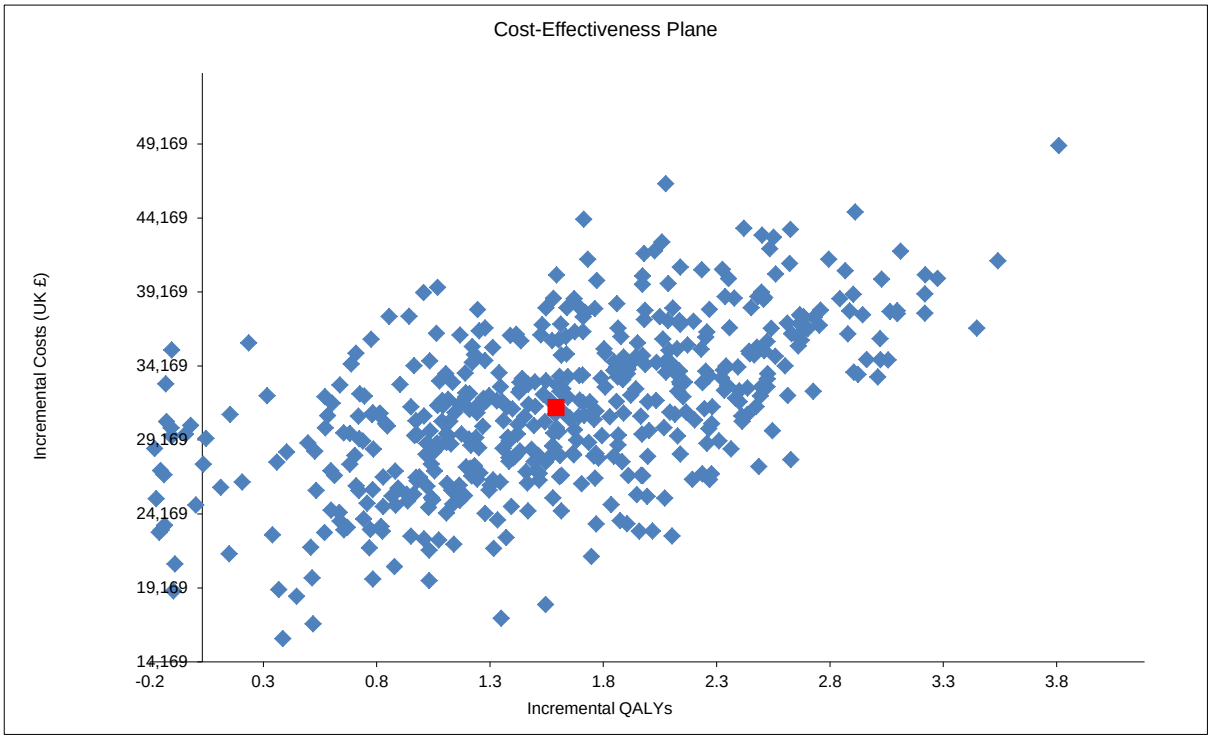


Figure 7 Polyvascular, scatter plot and CEAC with PAS (Source: Figure 4 of the company's PAS submission)

Deterministic sensitivity analyses

The company conducted a series of deterministic one-way sensitivity analysis for all modelled subpopulations, changing one variable at a time while keeping all other variables constant. The variables included in the one-way sensitivity analysis were: annual CV risk, adjustment of CV risk by age, CV event costs, alirocumab efficacy (LDL-C lowering), the rate ratios per 1 mmol/L reduction in LDL-C for adjustment of baseline CV risk, the rate ratios per 1 mmol/L reduction in LDL-C for modelleing treatment effect, baseline utilities, acute CV disutilities, and chronic CV disutilities. The range of possible values for these variables together with the estimated results are presented in Tables 42-45 below.

The results from the one-way sensitivity analysis show the ICERs to be most sensitive (in terms of change form from the base case) to changes in the treatment effect rate ratios per unit reduction in LDL-C, and the annual CV event risk parameters. Alirocub is dominated at the upper limits for the treatment effect rate ratios, as the upper confidence limit for the hazard ratio for CV death is greater than 1.

Table 42 HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe deterministic sensitivity analysis with PAS (Source: Table 3 of the company's PAS submission)

Parameter	Variation	ICER (£/QALY)
Base case with PAS		**36,793**
Annual CV risk	–20%	47,504
Annual CV risk	+20%	30,047
Adjustment of CV risk by age	–20%	37,023
Adjustment of CV risk by age	+20%	36,428
CV costs	–20%	37,094
CV costs	+20%	36,492
CV event costs	Doubled	35,287
Alirocumab efficacy (LDL-C lowering)	Lower CI	38,146
Alirocumab efficacy (LDL-C lowering)	Upper CI	35,659
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	33,828
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	39,413
Rate ratio per 1 mmol/L for treatment effect	Lower CI	29,787
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	36,448
Acute CV disutilities	Upper CI	37,144
Baseline utilities	Lower CI	36,793
Baseline utilities	Upper CI	36,793
Chronic CV disutilities	Lower CI	35,751
Chronic CV disutilities	Upper CI	37,897

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio

Table 43 HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe deterministic sensitivity analysis with PAS (Source: Table 4 of the company's PAS submission)

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**16,896**
Annual CV risk	–20%	20,018
Annual CV risk	+20%	14,806
Adjustment of CV risk by age	–20%	16,932
Adjustment of CV risk by age	+20%	16,919
CV costs	–20%	17,192
CV costs	+20%	16,600
CV event costs	Doubled	15,416
Alirocumab efficacy (LDL-C lowering)	Lower CI	17,690
Alirocumab efficacy (LDL-C lowering)	Upper CI	16,222
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	16,020
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	17,622
Rate ratio per 1 mmol/L for treatment effect	Lower CI	12,477
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	16,756
Acute CV disutilities	Upper CI	17,038
Baseline utilities	Lower CI	17,574
Baseline utilities	Upper CI	16,268
Chronic CV disutilities	Lower CI	16,722
Chronic CV disutilities	Upper CI	17,074

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio;

Table 44 High risk CVD, alirocumab + statins versus statins deterministic sensitivity analysis with PAS (Source: Table 5 of the company's PAS submission)

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**19,751**
Annual CV risk	–20%	23,910
Annual CV risk	+20%	17,009
Adjustment of CV risk by age	–20%	19,710
Adjustment of CV risk by age	+20%	19,784
CV costs	–20%	19,979
CV costs	+20%	19,522
CV event costs (doubled)		18,608
Alirocumab efficacy (LDL-C lowering)	Lower CI	20,600
Alirocumab efficacy (LDL-C lowering)	Upper CI	19,021
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	18,650
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	20,689
Rate ratio per 1 mmol/L for treatment effect	Lower CI	14,518
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	19,621
Acute CV disutilities	Upper CI	19,882
Baseline utilities	Lower CI	20,549
Baseline utilities	Upper CI	19,012
Chronic CV disutilities	Lower CI	19,578
Chronic CV disutilities	Upper CI	19,926

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio

Table 45 Recurrent events/ polyvascular disease - alirocumab + statins versus statins, deterministic sensitivity analysis with PAS (Source: Table 6 of the company's submission)

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**19,447**
Annual CV risk	–20%	22,901
Annual CV risk	+20%	17,153
Adjustment of CV risk by age	–20%	18,799
Adjustment of CV risk by age	+20%	20,096
CV costs	–20%	19,649
CV costs	+20%	19,245
CV event costs	Doubled	18,435
Alirocumab efficacy (LDL-C lowering)	Lower CI	20,623
Alirocumab efficacy (LDL-C lowering)	Upper CI	18,460
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	18,919
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	19,872
Rate ratio per 1 mmol/L for treatment effect	Lower CI	13,268
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	19,331
Acute CV disutilities	Upper CI	19,564
Baseline utilities	Lower CI	20,585
Baseline utilities	Upper CI	18,429
Chronic CV disutilities	Lower CI	19,358
Chronic CV disutilities	Upper CI	19,537

CI, confidence interval; CV, cardiovascular; ICER, incremental cost-effectiveness ratio

Scenario analysis results

In addition to the one-way sensitivity analysis, the company conducted some further scenario analyses. The scenarios assessed and their impacts on the cost-effectiveness findings are summarised in Tables 46 to Table 49 below.

The results in this section show that, the impact of changing the discontinuation rate on the estimated ICERs in all the subpopulations (from 0% to 3% and 8%) is relatively modest (in an upward direction), as it impacts both the benefit and costs of treatment. The company assumed that when patients discontinue alirocumab, the effects and costs cease immediately.

The company showed that applying a discount rate of 0% resulted in a substantial reduction in the ICER, reflecting the fact that many of the benefits of LDL-C lowering are accrued in the future. The company also showed that estimating the results over a shorter time horizon can increase the ICER dramatically, due to truncation of the future QALY gains and cost-savings. Assumed shorter treatment durations with base case time horizon have smaller impacts on the ICER

The scenario analyses indicate that the results are sensitive to the use of different relationships linking LDL-C reductions to proportional reductions in CV events (i.e. using the CTT meta-analysis, the LONG-TERM trial or a pooled analysis of Placebo-controlled phase III trials). Substantially higher ICERs were found using the estimates from the CTT meta-analysis; above £30,000 for all the modelled populations. The use of relative risks derived from a post hoc analysis of the LONG TERM trial had less of an influence. This is as expected since LONG TERM was one of the most influential trials included in the meta-analysis by Navarese et al.,[82] which was used in the base case analysis.

Table 46 HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe-scenario analyses with PAS (Source: Table 7 of the company's PAS submission)

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with PAS**			**36,793**
Discontinuation rate	0%	3%	38,168
		8%	41,852
Cost and benefit discount rates	3.50%	0%	24,821
		5%	43,533
Treatment duration	Lifetime	1 year	50,197
		5 years	47,326
Model time horizon	Lifetime	5 years	398,895
		10 years	197,133
The relative risk for LDL-C reduction for alirocumab cohort	Navarese et al. 2015 meta-analysis	CTT meta-analysis	60,736
		LONG TERM study	40,929
		Pooled phase III vs placebo	52,476
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	37,592
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	28,679
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	39,235
		100% use of 150 mg	35,954

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non fatal; QALY, quality-adjusted life-year

Table 47 HeFH secondary prevention alirocumab + statins + ezetimibe versus statins + ezetimibe – scenario analyses with PAS (Source: Table 8 of the company's PAS submission)

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			**16,896**
Baseline risk data	As per Morschladt 2004	As per THIN	19,060
Discontinuation rate	0%	3%	17,264
		8%	17,949
Cost and benefit discount rates	3.5%	0%	13,984
		5%	18,306
Treatment duration	Lifetime	1 year	18,863
		5 years	18,102
Model time horizon	Lifetime	5 years	64,199
		10 years	36,856
The relative risk for LDL-C reduction for alirocumab cohort	Navarese et al. 2015 meta-analysis	CTT meta-analysis	32,937
		LONG TERM study	19,294
		Pooled phase III vs placebo	25,741
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	16,734
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	13,347
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	18,259
		100% use of 150 mg	16,348

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; HSE; Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non-fatal

Table 48 High risk CVD, alirocumab + statins versus statins – scenario analyses with PAS (Source: Table 9 of the company's PAS submission)

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			19,751
Discontinuation rate	0%	3%	19,979
		8%	20,601
Cost and benefit discount rates	3.5%	0%	16,181
		5%	21,472
Treatment duration	Lifetime	1 year	20,148
		5 years	20,660
Model time horizon	Lifetime	5 years	85,694
		10 years	44,495
The relative risk for LDL-C reduction for alirocumab cohort	Navarese et al. 2015 meta-analysis[82]	CTT meta-analysis	41,431
		LONG TERM study	22,578
		Pooled phase III vs placebo	30,218
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	19,654
Utility	Age-adjusted, according to Ara 2010 publication[112]	ODYSSEY	15,761
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	21,571
		100% use of 150 mg	18,781

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; CVD, cardiovascular disease; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P-NF, post-non-fatal

Table 49 Recurrent events/ polyvascular disease, alirocumab + statins versus statins – scenario analyses with PAS (Source: Table 10 of the company's PAS submission)

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			**19,447**
Discontinuation rate	0%	3%	19,738
		8%	20,353
Cost and benefit discount rates	3.5%	0%	16,317
		5%	20,931
Treatment duration	Lifetime	1 year	20,869
		5 years	20,222
Model time horizon	Lifetime	5 years	72,896
		10 years	38,468
The relative risk for LDL-C reduction for alirocumab cohort	Navarese et al. 2015 meta-analysis[82]	CTT meta-analysis	44,154
		LONG TERM study	22,651
		Pooled phase III vs placebo	31,181
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	19,336
Utility	Age-adjusted, according to Ara 2010 publication[112]	ODYSSEY	15,968
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	20,969
		100% use of 150 mg	17,915

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P-NF, post-non-fatal

5.2.11 Model validation and face validity check

The company's submission describes how three advisory boards were held as part of the model development process. Additional consultation was sought from clinical experts and health economists to inform key parameters. The company assessed the internal validity of the model using extreme value checks, Markov traces and tracing of the estimated QALYs and costs over time. Structural sensitivity analyses were performed, as were deterministic and probabilistic sensitivity analysis, to assess the impact of changes on results.

In terms of the model face validity, the ERG believes that the structure of the model and the possible transitions are plausible. The ERG has performed internal consistency checks on the model and have identified no internal programming errors. The ERG can replicate all the company's results. An appropriate UK primary care database was used by the company to inform the model parameters in terms of baseline CV event rates. However the estimated CV events rates were not estimated from subpopulations with characteristics (i.e. baseline LDL-C and age) exactly matching those of the modelled cohorts, but were rather calibrated to the selected model age and LDL-C levels using published statistical relationships. In light of data limitations, this does seem reasonable. The baseline LDL-C adjustments in have been applied using a well-accepted relationship[31 32 99 100] between statin induced reduction in LDL-C and CV event rates. The ERG had some concerns relating to the inflation of subsequent events following recurrent ASC and ischaemic stroke, but have performed sensitivity analysis the results are not heavily influenced by this parameter. It also seems reasonably well justified to inflate these risks in the model.

The company did not assess the external or cross validity of their model. Since the company had access to THIN data, it might have been possible to generate longer-term survival curves of time to CV events, and then cross checked these against those predicted by their model over equivalent time horizons. The ERG has cross checked the composite baseline probabilities of CV events for the modelled high risk CVD population, and these do appear to be generally consistent with those used to represent baseline (of treatment) risks in previous models.[29] Given that the modelled patient populations represent those who have high baseline LDL-C despite current LMT, it doesn't seem unreasonable that they should have similar risks to the mean off-

treatment risks for the CVD population as a whole. Based on comparing projected survival from the model with published survival data for a UK cohort with MI,[107] there also seems to be good agreement with respect to medium-term (seven year) survival expectations for the modelled ACS cohorts.

The Secondary prevention HeFH cohort has a very high estimated composite annual CV event probability when based on data from Morschladt et al.[97] ([redacted]), compared with a much smaller risk when based on data from THIN ([redacted]). The ERG has been unable to verify the most appropriate rate against any other external data sources.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has undertaken some additional analyses, applying the following changes to the company's base case model. Details of these changes and their justification are provided below:

1) As mentioned in the section 5.2.8, the company's submission only included CV event follow-up costs in the base case analysis up to three years following the acute event. The ERG considers that this assumption may be overly conservative. Following cardiovascular events, especially stroke, patients may require ongoing social care and medical attention (in the absence of subsequent vascular events). The ERG has applied the annual post-CV event costs in perpetuity over the modelled time horizon.
2) Since the acute CV event costs reported in CG181 only capture costs to 6 months following the event, it would seem appropriate to apply 6 months' worth of follow-up costs to the first year costs following the CV event. However, it is the ERGs understanding that the company has not included these follow-up costs. The ERG has applied this in the model.
3) The ERG believes that the state costs for the stroke and post stroke health states may be underestimated. There is some information available regarding health care costs following stroke which indicate that the acute and annual post stroke costs are significantly higher than the values applied in the model. Yet, it is important not to double count costs of subsequent vascular events in the state costs, as subsequent events are modelled explicitly. Whilst the ERG have been unable to identify an ideal data source for these parameter, we have updated the acute cost by using an inflated estimate from a UK population study,[112] £8,618 (2013/2014

prices). For post stroke costs, we apply an inflated estimate of mean annual social care costs from Youman et al.[113] £1,769 per year.

4) To estimate hazard ratios for CV events per 1 mmol/L reduction LDL-C with alirocumab, the company used a weighted average of the LDL-C reductions across all the trials included in the review my Navarese et al.,[82] rather than only using those informing the estimated hazard ratios applied in the model. The resulting rate ratios were 0.64 per 1 mmol/L reduction in LDL-C for both MI and CV death. In response to the ERGs request for clarification, the company provided estimates of the mean LDL-C reductions based only on the trials informing the pooled hazard ratios for each specific event. This rescaling resulted in a rate ratio of 0.58 per 1 mmol/L reduction in LDL-C for CV death, and 0.67 per 1mmol/L reduction in LDL-C for MI. These specific values are applied in the model for analyses using rate ratios from Navarese et al.
5) The meta-analysis by Navarese et al. provided no estimate for the effect of LDL-C lowering on ischaemic stroke. Therefore, in the base case analysis, the company applied the same rate ratio for MI to stroke. In response to clarification, the company did provide a scenario where no effect for stroke was included. As a middle ground, we model the effect on LDL-C lowering with alirocumab through the CTT meta-analysis; i.e. rate ratio = 0.79 per 1 mmol/L reduction in LDL-C, as opposed to 0.64.
6) We apply an annual discontinuation rate in keeping with those observed in the ODDYSEY trials, of 8% per year. This is consistent with the discontinuation rate observed in the LONG TERM trial beyond one year.
7) When ezetimibe is the active comparator to alirocumab in the model, its effects on CV events are based on the hazard ratio reported in the IMPROVE-IT trial (IMPROVE-IT) – scaled to the modelled absolute reduction in LDL-C. However, it has been noted that the observed CV rate reduction in IMPROVE-IT was consistent with expectations based on the CTT meta-analysis.[100] We have therefore explored the impact of modelling the effects of ezetimibe (in direct comparisons with alirocumab) through the rate ratios per 1 mmol/L reduction in LDL-C reported by the CTT collaborative.

All these changes are implemented in the the ERGs updated base case analyses, presented for each patient population included in the model; i.e. HeFH primary

prevention (Table 50). Finally, given the uncertainty surrounding the relationship between LDL-C reductions achieved with alirocumab and proportional CV event rates, we present a further more conservative scenario analysis with the updated model for each comparison; here we model all the effects for alirocumab through the estimated relationships from the CTT meta-analysis (as per one of the company's scenario analysis).

5.3.1 The ERG updated base case and scenario analysis (deterministic)

The following Tables present the company's base case ICERs (Table 50) and then the ERGs updated base case; incorporating points 1-7 above with the company's preferred approach of scaling the hazard ratios from Navarese et al.[82] (Table 51). The results in Table 52 then present the more conservative scenario using the CTT meta-analysis to model all effects of alirocumab on CV events. Tables 53 to 55 then present the corresponding ICERs for statin intolerant patients.

With the ERGs updated base case, the ICERs are remain very similar to the company's base case ICERs (Tables 51). As an add-on to optimal statin therapy (+/- ezetimibe), they are below £20,000 in the HeFH secondary prevention, high risk CVD, and recurrent CVD/polyvascular disease populations. The ICER remains above £30,000 in the HeFH primary prevention population (Table51). The ICERs also remain below £20,000 for the statin intolerant CVD cohorts (Table 54).

Consistent with the company's scenario analysis, using the CTT to model the effects of alirocumab on CV event rates raises the ICERs above £30,000 for alirocumab as an adjunctive to maximally tolerated statin therapy (Table 52) - although the ICER in the HeFH secondary prevention cohort is close to £30,000 (£33,339) using the risk data from Morschladt et al. Using the CTT approach for statin intolerant patients, the ICERs are slightly above £30,000 in the HeFH secondary prevention, high CV risk, and the recurrent CVD/polyvascular disease populations (Table 55). Note the ICERs for the statin intolerant HeFH populations are based on the ERGs assumption of a baseline LDL-C of 5.8 (assumed 20% reduction from the baseline value of 7.27 reported by Morschladt et al.)

Table 50 The company's base case results

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	**Alirocumab + current maximal therapy (statins + ezetimibe)**	[redacted]	[redacted]	[redacted]	52,256	1.62	1.42	36,793
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L)	**Alirocumab + current maximal therapy (statins + ezetimibe)**	[redacted]	[redacted]	[redacted]	39,306	3.04	2.33	16,896
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L)	**Alirocumab + current maximal therapy (statins)**	[redacted]	[redacted]	[redacted]	34,684	2.38	1.76	19,751
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	**Alirocumab + current maximal therapy (statins)**	[redacted]	[redacted]	[redacted]	31,953	2.42	1.64	19,447
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 51 The ERG base case results (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitors from Navarese et al. meta-analysis)

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	23,079	0.63	0.56	41,243
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from Morschladt et al.	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	20,151	1.54	1.19	16,933
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from THIN	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	20,848	1.43	1.07	19,394
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	19,224	1.35	0.99	19,432
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	18,557	1.45	0.98	19,021
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 52 The ERG additional scenario analysis results (with rate ratios per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis)

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	**Alirocumab + current maximal therapy (statins + ezetimibe)**	[redacted]	[redacted]	[redacted]	22,819	0.35	0.34	67,215
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from Morschladt et al.	**Alirocumab + current maximal therapy (statins + ezetimibe)**	[redacted]	[redacted]	[redacted]	18,554	0.64	0.56	33,339
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from THIN	**Alirocumab + current maximal therapy (statins + ezetimibe)**	[redacted]	[redacted]	[redacted]	19,371	0.59	0.49	39,912
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L)	**Alirocumab + current maximal therapy (statins)**	[redacted]	[redacted]	[redacted]	17,974	0.53	0.43	42,131
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	**Alirocumab + current maximal therapy (statins)**	[redacted]	[redacted]	[redacted]	16,823	0.50	0.38	44,759
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 53 The company's base case results - *statin intolerant patients*

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
High risk CVD (LDL-C ≥3.36 mmol/L) *	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	35,146	2.76	2.04	17,256
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L) **	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	32,719	3.03	2.06	15,853
	Ezetimibe	[redacted]	[redacted]	[redacted]				

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

*****Mean baseline LDL-C=4.55; ****** Mean baseline LDL-C=4

Table 54 The ERG's base case results (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitor from Navarese et al. meta-analysis) – *statin intolerant patients*

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
High risk CVD (LDL-C ≥3.36 mmol/L) *	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	19,319	1.53	1.13	17,130
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L) **	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	18,744	1.76	1.19	15,791
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year
*****Mean baseline LDL-C=4.55; ****** Mean baseline LDL-C=4

Table 55 The ERG additional scenario analysis results (with rate ratio per 1.0 mmol/L reduction from CTT meta-analysis) - *statin intolerant patients*

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L) *	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	22,772	0.35	0.34	67,077
	Ezetimibe	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from Morschladt et al. *	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	18,469	0.64	0.56	33,185
	Ezetimibe	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from THIN*	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	19,292	0.59	0.49	39,749
	Ezetimibe	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L) **	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	17,721	0.64	0.51	34,600
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L) ***	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	16,400	0.66	0.49	33,519
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year
*Mean baseline LDL-C=5.8 mmol/L; **Mean baseline LDL-C=4.55 mmol/L; *** Mean baseline LDL-C=4 mmol/L

5.3.2 The ERG updated base case and scenario analysis - probabilistic

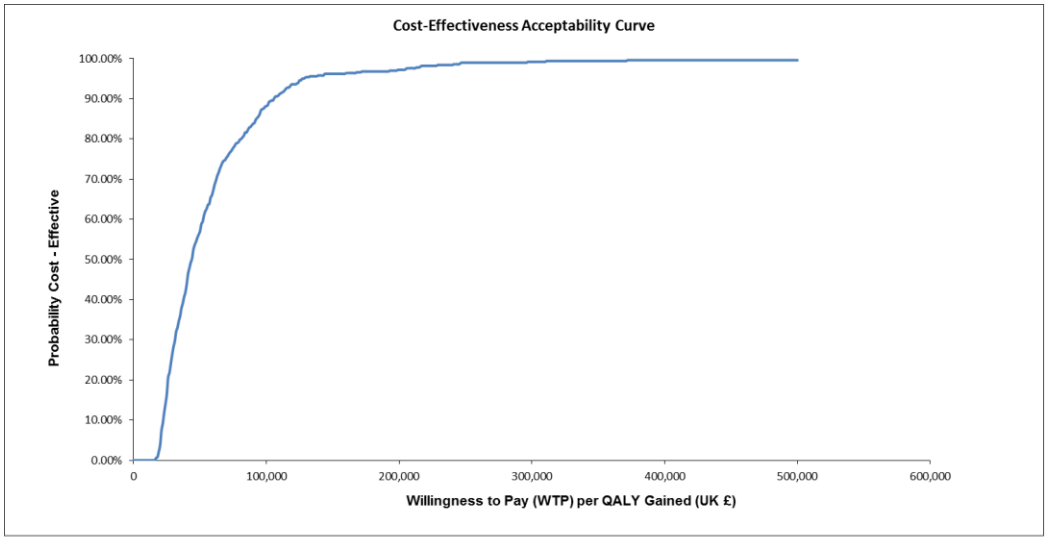
Table 56 and Figures 8 to 11 summarise the results from the ERGs updated base case when running the model probabilistically. All these comparisons are for alirocumab as an adjunct to maximally tolerated statin (+/- ezetimibe) in the respective populations. The findings are generally consistent with the company's base case probabilistic results.

Table 57 and figure 12-14 provide summarise the probabilistic results for the scenario using the CTT rate ratios (on top of the ERGs other changes) to model the effects of alirocumab. With this approach the probabilities of cost-effectiveness are low at accepted ceiling ratios of willingness-to-pay per QALY.

Table 56 The ERG base case results (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitor from Navarese et al. meta-analysis) - Probabilistic analysis

Patient population	Incremental costs	Incremental QALYs	ICER	Probability of being cost effective		
				£20,000	£30,000	£40,000
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	22,883	0.57	40,440	3.8%	28.2%	43.8%
HeFH secondary prevention (LDL-C ≥2.59 mmol/L)	19,610	1.10	17,796	57.0%	84%	90%
High risk CVD (LDL-C ≥3.36 mmol/L)	18,868	0.88	21,347	45%	83%	91%
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	18,150	0.87	20,924	46%	80%	90%

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year



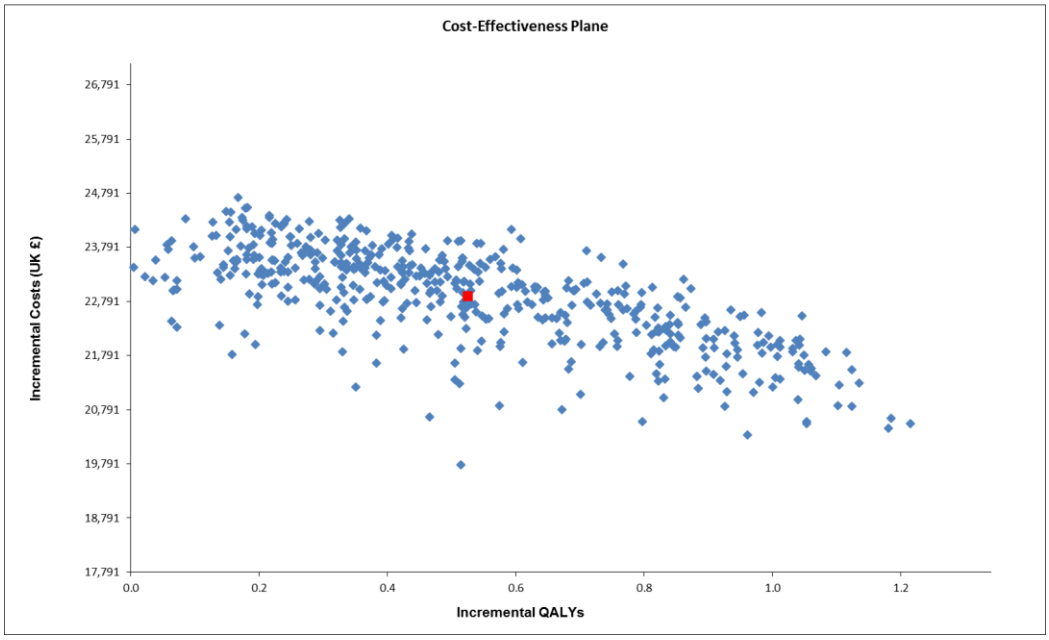
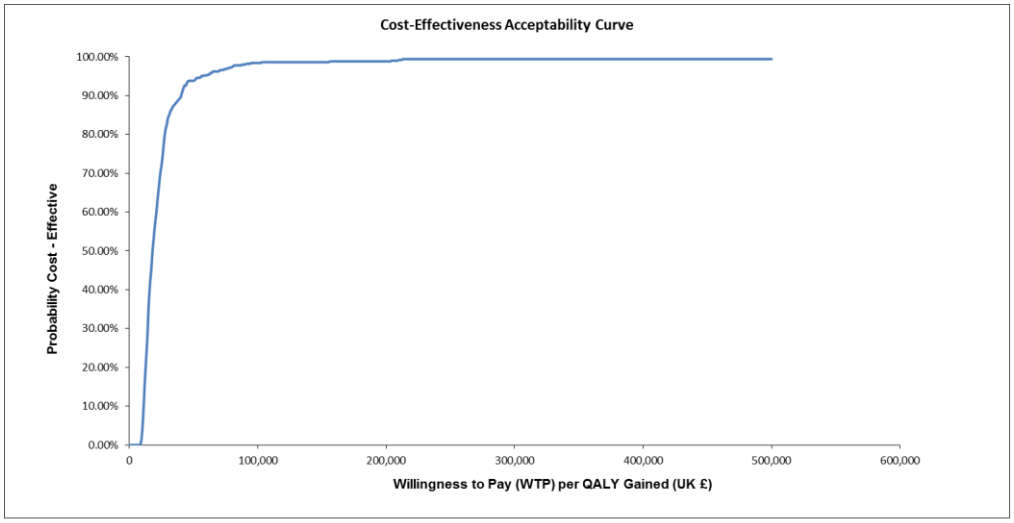


Figure 8 Cost-effectiveness acceptability curve and scatter plot: HeFH primary prevention - with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitor from Navarese et al.'s meta-analysis (alirocumab + statins + ezetimibe vs. statins + ezetimibe)



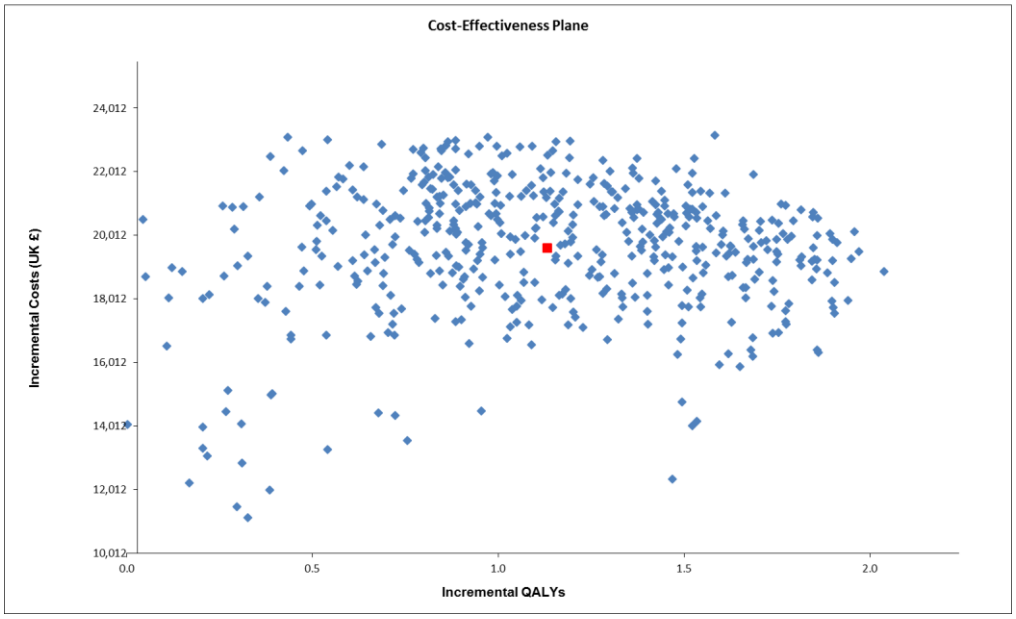
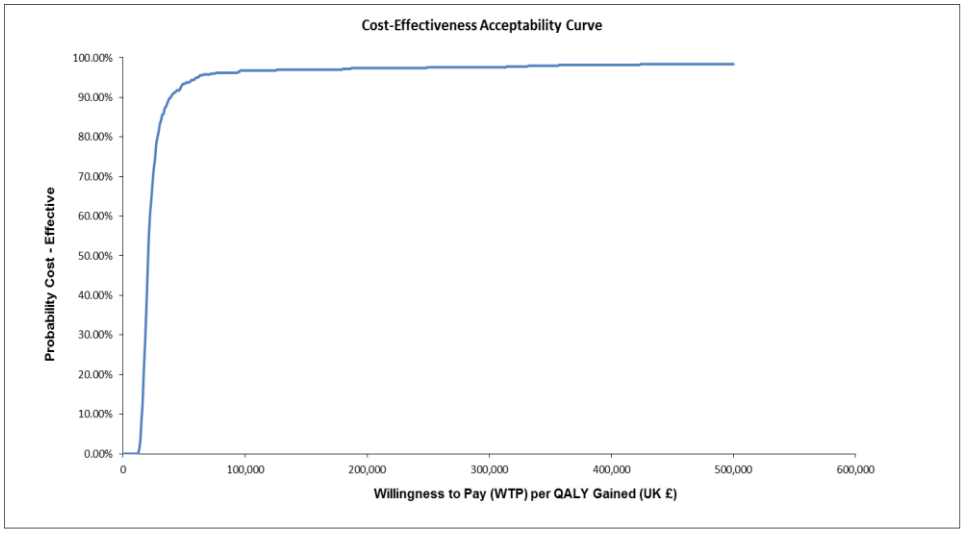


Figure 9 Cost-effectiveness acceptability curve and scatter plot: HeFH secondary prevention (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9 - inhibitor from Navarese et al.'s meta-analysis) (alirocumab + statins + ezetimibe vs. statins + ezetimibe)



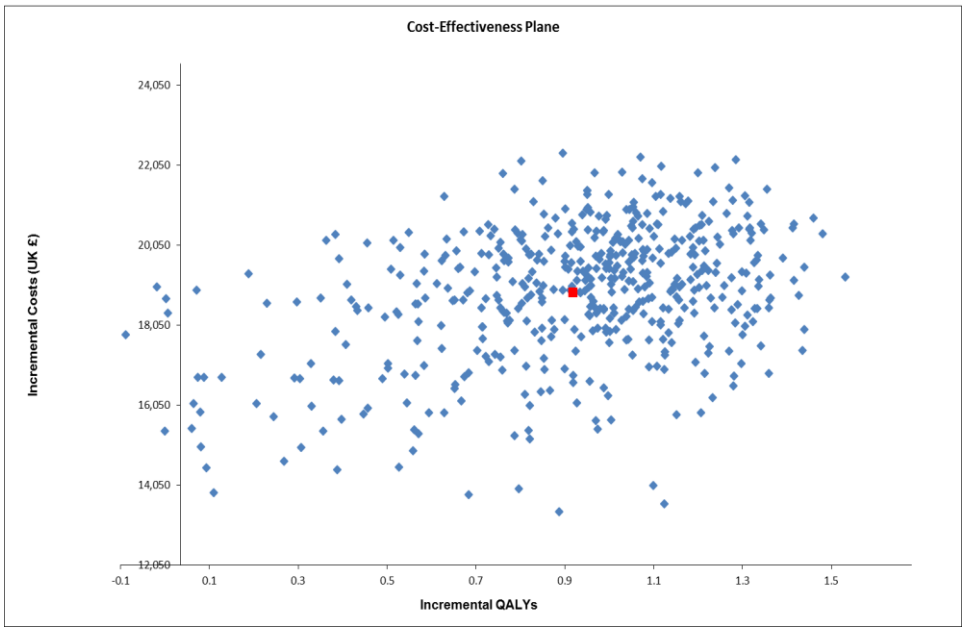
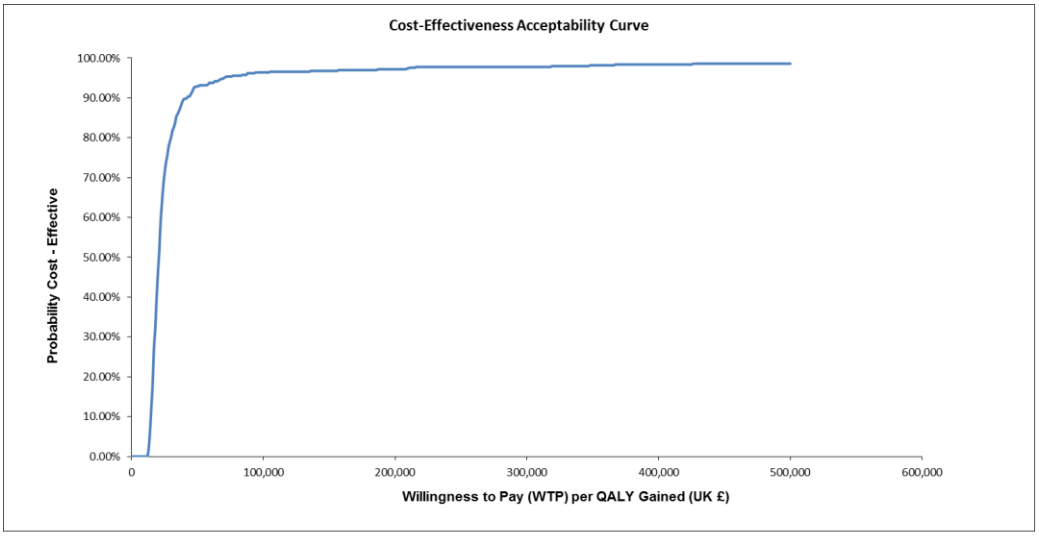


Figure 10 Cost-effectiveness acceptability curve and scatter plot: High risk CVD (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9 - inhibitor from Navarese et al.'s meta-analysis) (alirocumab + statins vs. statins)



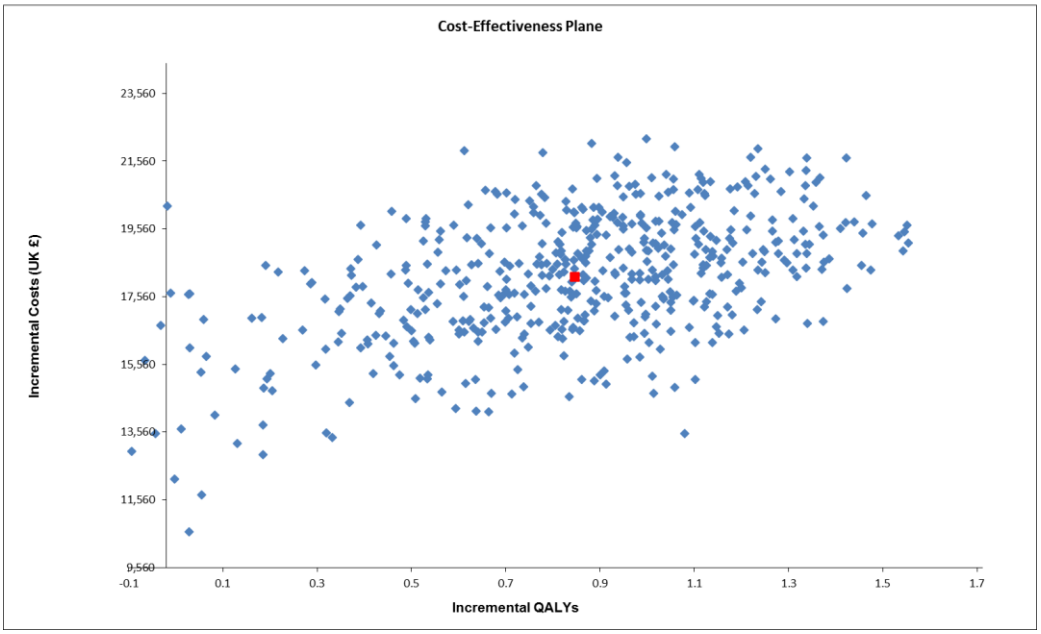
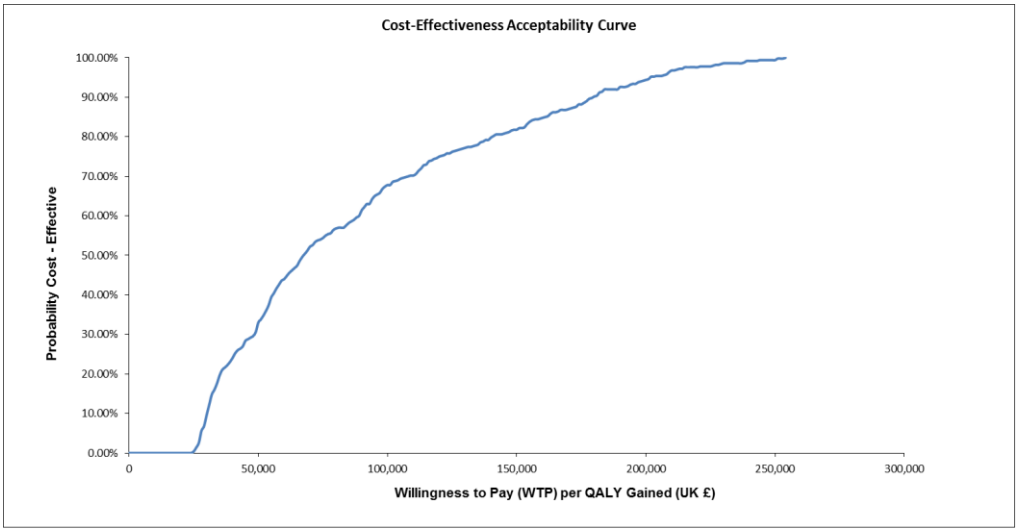


Figure 11 Cost-effectiveness acceptability curve and scatter plot - Recurrent events/ polyvascular disease (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitor from Navarese et al.'s meta-analysis) (alirocumab + statins vs. statins)

Table 57 The ERG additional scenario analysis results (with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis) – probabilistic analysis

Patient population	Incremental costs	Incremental QALYs	ICER	Probability of being cost effective		
				£20,000	£30,000	£40,000
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	22,612	0.38	60,221	0%	10%	24%
HeFH secondary prevention (LDL-C ≥2.59 mmol/L)	18,327	0.57	32,145	18%	39%	58%
High risk CVD (LDL-C ≥3.36 mmol/L)	17,807	0.42	42,264	0%	7%	43%
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	16,677	0.37	44,850	0%	6%	36%

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year



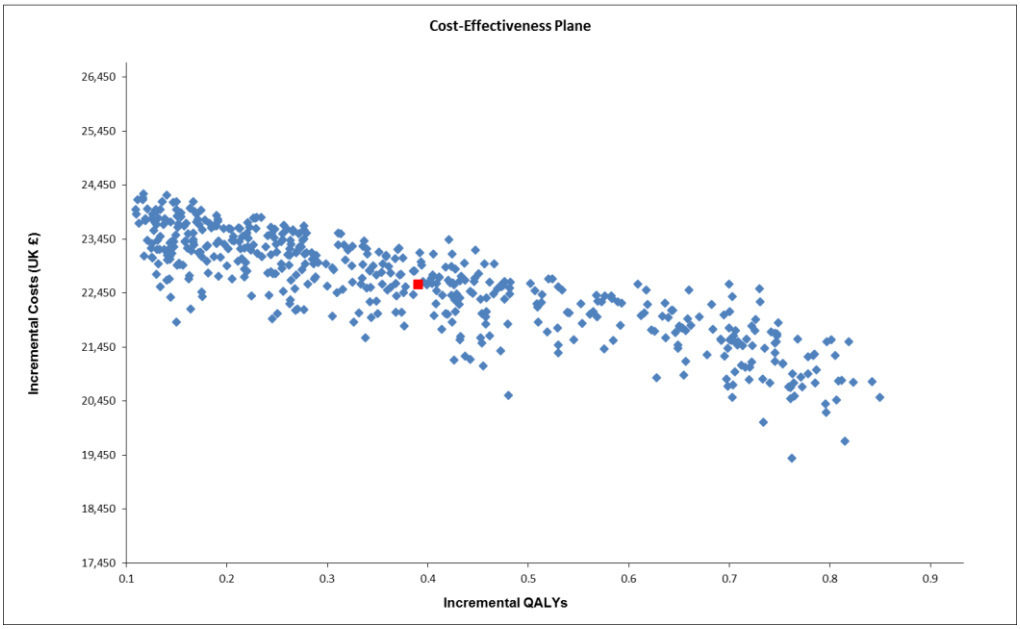
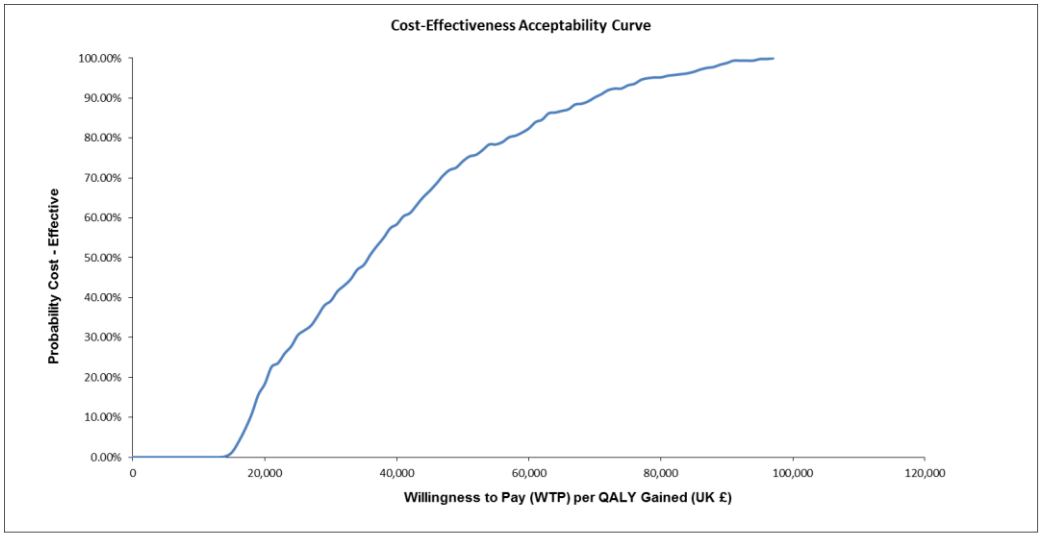


Figure 12 Cost-effectiveness acceptability curve and scatter plot: HeFH primary prevention - with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis (alirocumab + statins + ezetimibe vs. statins + ezetimibe)



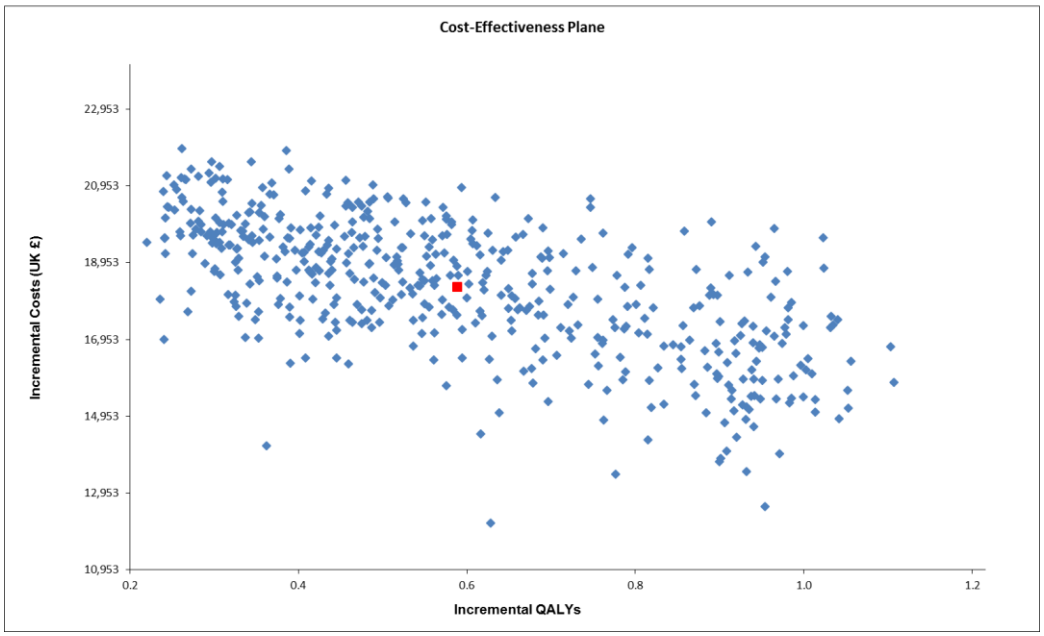
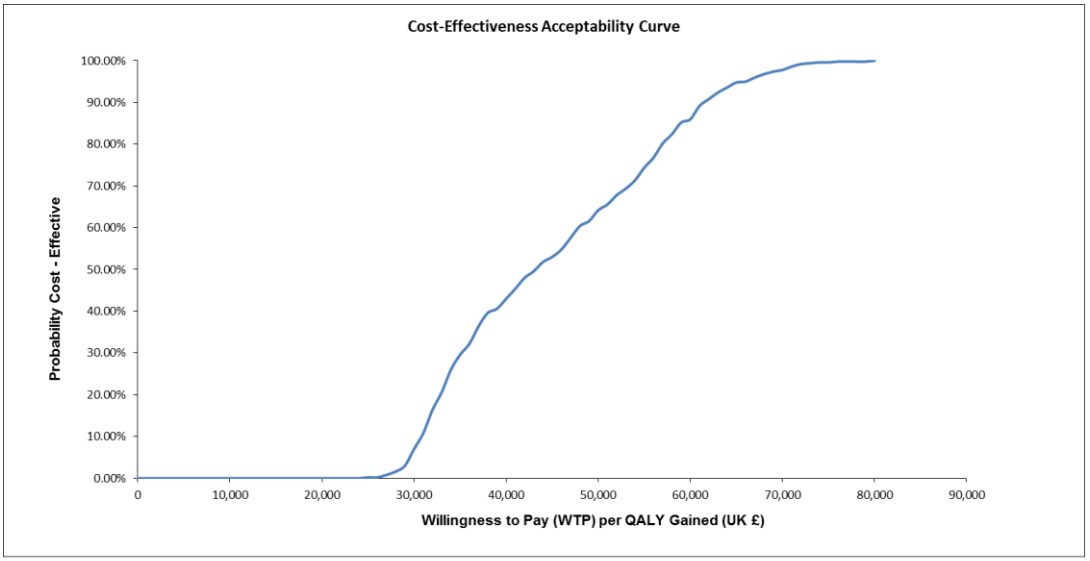


Figure 13 Cost-effectiveness acceptability curve and scatter plot: HeFH secondary prevention - with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis (alirocumab + statins + ezetimibe vs. statins + ezetimibe)



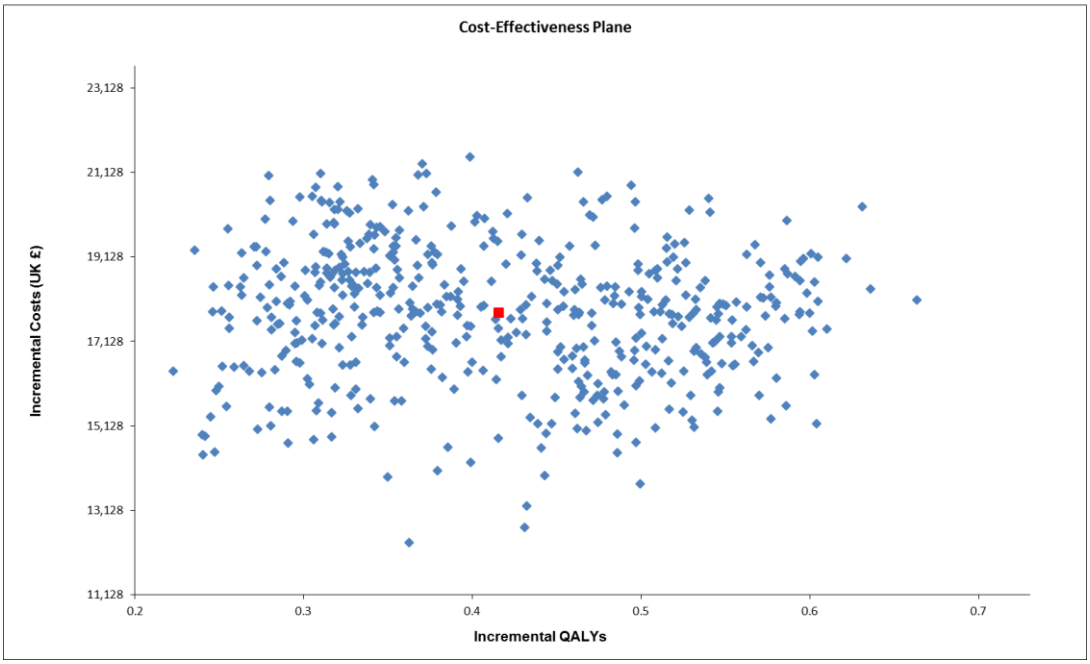


Figure 14 Cost-effectiveness acceptability curve and scatter plot: High risk CVD - with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis (alirocumab + statins vs. statins)

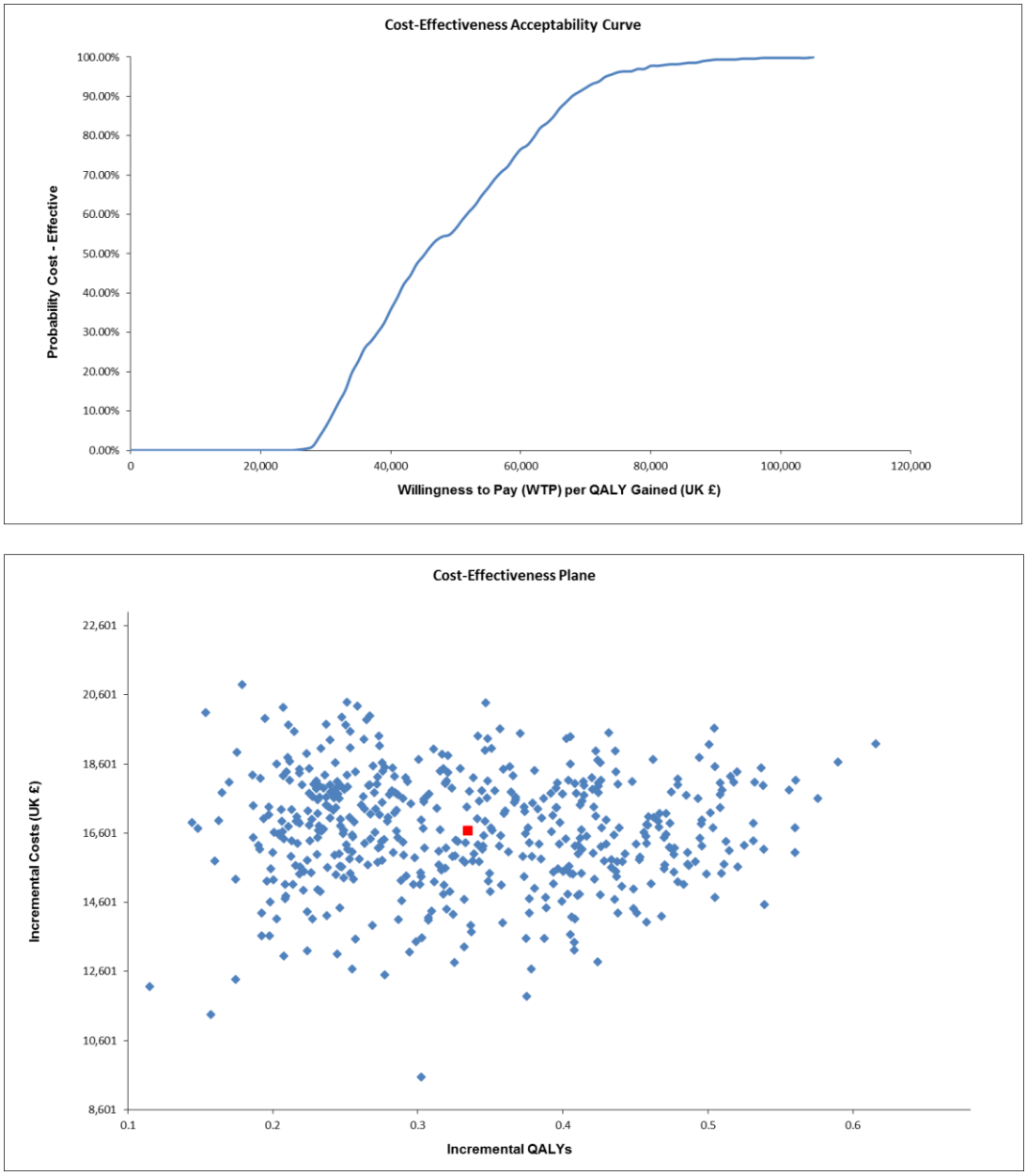


Figure 15 Cost-effectiveness acceptability curve and scatter plot: Recurrent events/ polyvascular disease - with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis (alirocumab + statins versus statins)

5.3.3 The ERG updated base case and additional scenario analysis- additional comparisons

The following tables show the results of direct head-to-head comparisons between alirocumab and ezetimibe, first as an add-on to statin (Tables 58 and 59) and then in statin intolerant patients (Tables 60 and 61). Tables 58 and 60 present results using the updated ERG base case assumptions. Tables 59 and 61 use the CTT meta-analysis to model effects.

These results may be considered applicable to patients who remain above LDL-C targets on statin alone, where adding ezetimibe or alirocumab is a considered an option.

The results show the ICERs to be in the region of £20,000 as an add-on to statin (+/- ezetimibe) using the Navarese hazard ratios (Table 58), and below £20,000 when using the HRs from Naverese in the statin intolerant comparisons (Table 60). Again, switching to the CTT rate ratios increases the ICERs above both £30,000 in both the add-on to statin and statin intolerant comparisons (Tables 59 and 61).

Table 58 The ERG base case results (with rate ratios per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitor from Navarese et al. meta-analysis) - additional comparisons

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	20,441	0.45	0.39	52,363
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	18,052	1.24	0.93	19,437
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	17,496	0.91	0.65	26,895
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	17,434	1.11	0.79	21,932
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	16,882	1.23	0.81	20,891
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 59 The ERG additional scenario analysis results (with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis) - additional comparisons

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	20,275	0.18	0.17	119,161
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	16,763	0.34	0.29	56,968
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	16,473	0.21	0.17	96,269
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	16,182	0.29	0.23	70,081
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	15,138	0.28	0.20	73,941
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 60 The ERG base case results (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitor from Navarese et al. meta-analysis) - *statin intolerant patients - additional comparisons*

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
High risk CVD (LDL-C ≥3.36 mmol/L) *	Alirocumab	[redacted]	[redacted]	[redacted]	16,947	1.42	1.03	16,487
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L) **	Alirocumab	[redacted]	[redacted]	[redacted]	16,438	1.86	1.23	13,342
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year
***** Mean baseline LDL-C=4.95; ****** Mean baseline LDL-C=4.947

Table 61 The ERG additional scenario analysis results (with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis) - *statin intolerant patients- additional comparisons*

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
High risk CVD (LDL-C ≥3.36 mmol/L) *	Alirocumab	[redacted]	[redacted]	[redacted]	15,539	0.47	0.38	41,412
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L) **	Alirocumab	[redacted]	[redacted]	[redacted]	13,998	0.57	0.43	32,742
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year
***** Mean baseline LDL-C=4.95; ****** Mean baseline LDL-C=4.94

5.3.4 Subgroup analysis using for the ERGs updated base case and scenario analysis

The following tables present the main comparisons (i.e. alirocumab as an adjunct to background LLT) for subgroups defined by baseline LDL-C thresholds. Table 62 presents the company's base case subgroup ICERs. Table 63 applies the ERGs updated base case assumptions, and Table 64 uses the updated ERG assumptions with the CTT meta-analysis to model effects of alirocumab. Under the company and updated ERG base case (Table 52 and 63), all the ICERs are below £30,000 except in the HeFH primary prevention cohort. Under the updated scenario using the CTT to model effects, the ICERs are below £30,000 per QALY only in the higher risk populations (HeFH secondary prevention and polvascular disease) at or above the highest baseline LDL-C thresholds (Table 64).

Table 62 The company's base case results - subgroup analysis

Patient population	Baseline LDL-C (mmol/L) threshold	Incremental costs	Incremental QALYs	ICER versus baseline
HeFH primary prevention	**2.59**	52,256	1.42	36,793
	3.36	52,005	1.64	31,750
	4.13	51,804	1.79	28,923
HeFH secondary prevention	**2.59**	39,306	2.33	16,896
	3.36	39,224	2.48	15,838
	4.13	39,023	2.74	14,242
High risk CVD	**2.59**	34,701	1.37	25,287
	3.36	34,684	1.76	19,751
	4.13	34,493	2.15	16,043
Recurrent events/ polyvascular disease	**2.59**	31,953	1.64	19,447
	3.36	32,085	2.09	15,332
	4.13	32,013	2.54	12,606

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 63 The ERG base case results (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitor from Navarese et al. meta-analysis) - subgroup analysis

Patient population	Baseline LDL-C (mmol/L) threshold	Incremental costs	Incremental QALYs	ICER versus baseline
HeFH primary prevention	**2.59**	23,079	0.56	41,243
	3.36	22,877	0.64	35,481
	4.13	22,731	0.70	32,256
HeFH secondary prevention	**2.59**	20,151	1.19	16,933
	3.36	20,038	1.26	15,938
	4.13	19,823	1.37	14,433
High risk CVD	**2.59**	19,474	0.79	24,538
	3.36	19,224	0.99	19,432
	4.13	18,896	1.18	15,975
Recurrent events/ polyvascular disease	**2.59**	18,557	0.98	19,021
	3.36	18,358	1.20	15,286
	4.13	18,072	1.41	12,794

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 64 The ERG additional scenario results (with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis) - subgroup analysis

Patient population	Baseline LDL-C (mmol/L) threshold	Incremental costs	Incremental QALYs	ICER versus baseline
HeFH primary prevention	**2.59**	22,819	0.34	67,215
	3.36	22,587	0.40	55,839
	4.13	22,419	0.45	49,678
HeFH secondary prevention	**2.59**	18,554	0.56	33,339
	3.36	18,355	0.60	30,603
	4.13	17,990	0.68	26,557
High risk CVD	**2.59**	18,456	0.32	58,239
	3.36	17,974	0.43	42,131
	4.13	17,422	0.55	31,795
Recurrent events/ polyvascular disease	**2.59**	16,823	0.38	44,759
	3.36	16,222	0.50	32,622
	4.13	15,550	0.63	24,863

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

5.3.5 One-way sensitivity analysis for the ERGs updated scenario analysis

The final set of tables (Tables 65-68) provide one-way sensitivity analysis for each of the populations using the ERGs updated assumptions, with the effects of alirocumab modelled through the hazard ratios from the CTT meta-analysis. These results indicate that under this more conservative scenario, the results in the HeFH secondary prevention cohort are quite sensitive to changes in several parameters. The ICERs can drop below £30,000 with plausible variation in the mean baseline LDL-C levels, the baseline CV event risk, and the rate ratios for treatment effects (per 1 mmol/L reduction in LDL-C).

HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe

Table 65 HeFH primary prevention, deterministic sensitivity analysis (with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis)

Parameter	Variation	ICER (£/QALY)
Base case mean LDL-C (4.82 mmol/L)		67,215
Baseline mean LDL-C (4.34 mmol/L)	–10%	82,551
Baseline mean LDL-C (5.3 mmol/L)	+10%	55,446
Baseline mean LDL-C (3.85 mmol/L)	–20%	103,055
Baseline mean LDL-C (5.78 mmol/L)	+20%	46,226
Annual CV risk	–20%	87,417
Annual CV risk	+20%	54,592
Adjustment of CV risk by age	–20%	63,057
Adjustment of CV risk by age	+20%	71,559
CV costs	–20%	67,855
CV costs	+20%	66,574
CV event costs	Doubled	65,519
Alirocumab efficacy (LDL-C lowering)	Lower CI	71,252
Alirocumab efficacy (LDL-C lowering)	Upper CI	63,762
Rate ratio per 1 mmol/L for calculation	Lower CI	61,417
Rate ratio per 1 mmol/L for calculation	Upper CI	72,459
Rate ratio per 1 mmol/L for treatment	Lower CI	57,841
Rate ratio per 1 mmol/L for treatment	Upper CI	79,176
Acute CV disutilities	Lower CI	66,461
Acute CV disutilities	Upper CI	67,985
Baseline utilities	Lower CI	67,215
Baseline utilities	Upper CI	67,215
Chronic CV disutilities	Lower CI	64,056
Chronic CV disutilities	Upper CI	70,701
Assuming 0% discontinuation rate		59,449

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio

HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe

Table 66 HeFH secondary prevention, deterministic sensitivity analysis (with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis)

Parameter	Variation	ICER (£/QALY)
Base case mean LDL-C (4.56 mmol/L)		33,339
Baseline mean LDL-C (4.1 mmol/L)	–10%	39,420
Baseline mean LDL-C (5.01 mmol/L)	+10%	28,527
Baseline mean LDL-C (3.65 mmol/L)	–20%	47,341
Baseline mean LDL-C (5.47 mmol/L)	+20%	24,619
Annual CV risk	–20%	39,833
Annual CV risk	+20%	28,926
Adjustment of CV risk by age	–20%	31,444
Adjustment of CV risk by age	+20%	35,523
CV costs	–20%	34,024
CV costs	+20%	32,653
CV event costs	Doubled	31,087
Alirocumab efficacy (LDL-C lowering)	Lower CI	35,625
Alirocumab efficacy (LDL-C lowering)	Upper CI	31,382
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	31,027
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	35,321
Rate ratio per 1 mmol/L for treatment effect	Lower CI	27,530
Rate ratio per 1 mmol/L for treatment effect	Upper CI	41,178
Acute CV disutilities	Lower CI	32,879
Acute CV disutilities	Upper CI	33,811
Baseline utilities	Lower CI	34,677
Baseline utilities	Upper CI	32,100
Chronic CV disutilities	Lower CI	32,265
Chronic CV disutilities	Upper CI	34,486
Assuming 0% discontinuation rate		32,068

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio;

High Risk CVD - alirocumab + statins versus statins

Table 67 High risk CVD, deterministic sensitivity analysis (with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis)

Parameter	Variation	ICER (£/QALY)
Base case mean LDL-C (4.03 mmol/L)		42,131
Baseline mean LDL-C (3.63 mmol/L)	–10%	50,108
Baseline mean LDL-C (4.44 mmol/L)	+10%	35,878
Annual CV risk	–20%	51,576
Annual CV risk	+20%	35,891
Adjustment of CV risk by age	–20%	40,955
Adjustment of CV risk by age	+20%	43,319
CV costs	–20%	42,699
CV costs	+20%	41,562
CV event costs (doubled)		40,235
Alirocumab efficacy (LDL-C lowering)	Lower CI	44,778
Alirocumab efficacy (LDL-C lowering)	Upper CI	39,831
Rate ratio per 1 mmol/L for calculation	Lower CI	39,609
Rate ratio per 1 mmol/L for calculation	Upper CI	44,377
Rate ratio per 1 mmol/L for treatment	Lower CI	33,986
Rate ratio per 1 mmol/L for treatment	Upper CI	53,125
Acute CV disutilities	Lower CI	41,676
Acute CV disutilities	Upper CI	42,595
Baseline utilities	Lower CI	43,833
Baseline utilities	Upper CI	40,555
Chronic CV disutilities	Lower CI	41,218
Chronic CV disutilities	Upper CI	43,085
Assuming 0% discontinuation rate		40,474

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio

Recurrent events/ Polyvascular Disease - alirocumab + statins versus statins

Table 68 Recurrent events/ polyvascular, deterministic sensitivity analysis (with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis)

Parameter	Variation	ICER (£/QALY)
Base case mean LDL-C (3.31 mmol/L)		44,759
Baseline mean LDL-C (2.98 mmol/L)	–10%	52,611
Baseline mean LDL-C (3.64 mmol/L)	+10%	38,587
Baseline mean LDL-C (2.65 mmol/L)	–20%	62,794
Baseline mean LDL-C (3.97 mmol/L)	+20%	33,634
Annual CV risk	–20%	53,258
Annual CV risk	+20%	39,065
Adjustment of CV risk by age	–20%	42,270
Adjustment of CV risk by age	+20%	47,336
CV costs	–20%	45,359
CV costs	+20%	44,159
CV event costs	Doubled	42,778
Alirocumab efficacy (LDL-C lowering)	Lower CI	48,384
Alirocumab efficacy (LDL-C lowering)	Upper CI	41,695
Rate ratio per 1 mmol/L for calculation	Lower CI	43,455
Rate ratio per 1 mmol/L for calculation	Upper CI	45,864
Rate ratio per 1 mmol/L for treatment	Lower CI	35,534
Rate ratio per 1 mmol/L for treatment	Upper CI	57,136
Acute CV disutilities	Lower CI	44,271
Acute CV disutilities	Upper CI	45,258
Baseline utilities	Lower CI	47,378
Baseline utilities	Upper CI	42,415
Chronic CV disutilities	Lower CI	43,939
Chronic CV disutilities	Upper CI	45,610
Assuming 0% discontinuation rate		43,087

CI, confidence interval; CV, cardiovascular; ICER, incremental cost-effectiveness ratio

5.4 Conclusions of the cost effectiveness section

Applying the ERGs updates to the company's base case model and continuing to model the effects of alirocumab using the scaled hazard ratios from Navarese for ACS events, revascularisation and CV death, our ICERs remain very similar to the company's base case ICERs. As an add-on to maximally tolerated lipid lowering therapy, these are below £20,000 per QALY in the HeFH secondary prevention, high risk CVD and polyvascular disease populations, but greater than £40,000 per QALY in the HeFH primary prevention cohort. For those intolerant to statins, the ICERs are also below £20,000.

Under the latter more conservative approach (modelling effects using the rate ratios per unit reduction in LDL-C form the CTT meta-analysis), the ICERs for alirocumab as an add-on to maximally tolerated lipid lowering therapy rise above £30,000 in all the patient populations at the base case LDL-C thresholds - including those for people intolerant to statins with high risk CVD or recurrent CVD/ polyvascular disease.

From repeating further subgroup analysis using the CTT relationship to model effects of alirocumab, the ICERs fall below £30,000 only in the highest risks groups (HeFH secondary prevention and polyvascular disease) at the highest LDL-C threshold applied $\geq$ 4.13 mmol/L on maximally tolerated lipid modifying therapy.

Therefore, the cost-effectiveness results appear most sensitive to the approach used to model the relationship between LDL-C reductions with alirocumab and reductions in CV events. Further areas of uncertainty relate to appropriateness of a $\geq$ 3.36 mmol/L LDL-C threshold in the base case analysis for the high risk CVD population (given that few patients may be expected to meet the this criterion) and appropriate CV event rate to apply for the HeFH secondary prevention cohort.

6 Overall conclusions

The company considered alirocumab as "add on therapy" (in people whose LDL-C was not adequately controlled with maximum tolerated dose of statin or non-statin) or as "monotherapy" (for people in whom statins are not appropriate or not tolerated or whose LDL-C was not adequately controlled with non-statin lipid modifying therapies). The company did not consider evolocumab as a relevant comparator.

The company conducted two systematic reviews, with identical search criteria but slightly different inclusion criteria. The first review, which focused on people at high risk of CVD, identified a total of 32 studies. The second review, which considered people at moderate or high CVD risk, identified 20 studies. Despite the findings of these two systematic reviews of clinical evidence, the company decided to focus exclusively on the 10 phase III clinical trials from the ODYSSEY programme maintaining that that this pivotal trial programme provides sufficient evidence to address the relative effectiveness of alirocumab. Five of these 10 clinical trials compared alirocumab to placebo, two compared alirocumab to ezetimibe and three compared alirocumab to ezetimibe and to a statin. Eight studies evaluated alirocumab at a dose of 75 mg every two weeks with possible up-titration; two studies evaluated alirocumab as 150 mg every two weeks.

The results of the 10 phase III clinical trials provided evidence that alirocumab is effective in reducing LDL-C compared with placebo (mean % reduction from baseline ranged from 39.1 to 61.9), ezetimibe (mean % reduction from baseline ranged from 23.6 to 36.1) or statins (mean % reduction from baseline ranged from 20.4 to 49.2). Similar benefits were found for lipid parameters Total-C, non-HDL-C, Apo(B) and Lp(a). The evidence for the effect of alirocumab was less consistent for Fasting TG, HDL-C and Apo-A1. Results of a several pre-specified pooled analyses conducted by the company showed similar results for the effect of alirocumab on LDL-C compared with placebo (54.1% reduction pooling FH I and FH II, 54.1% reduction pooling FH I, FH II and COMBO I, and -62.5% pooling LONG TERM and HIGH FH).

There was no evidence of differences between groups in the rates of adverse events or mortality.

The ERG considered that the company's systematic reviews of clinical evidence were broadly adequate.

With regard to the economic model, the ERG considers it to be of good quality and in general appropriately structured. The one main structural concern relates to the use of a composite event state for ACS which includes MI and stable angina (UA). This makes it impossible to model different effects for MI and UA. Significant effort has gone into informing the model with real world risk data for relevant UK populations – although this has to be recalibrated to the age and LDL-C levels of the modelled populations. Based on comparing survival from the model with published survival data for UK cohorts, there is good agreement with medium term survival expectations for the high risk CVD and recurrent CV events cohort, and particularly ACS cohorts. The utility weights incorporated in the model were coherent, from a single UK population based source. Whilst the ERG had a number of concerns with some of the parameter estimates and base case assumptions, one of these in particular appeared to have critical impact on the estimated base case ICERs: the method used to extrapolate LDL-C reductions mediated through PCSK9 inhibitors to relative reductions in CV event rates.

6.1 Implications for research

There is extensive research already ongoing related to PCSK9 inhibitors, and outcome data are awaited from this. In particular, the results of the CVOT ongoing trial, which are due to be reported in January 2018, will provide useful information on the effect of alirocumab on CV events. Nevertheless, given the novelty of PCSK9 inhibitors and consequent treatments aimed at them, 'off target' effects will be particularly important to collate. There is also a need to further assess the cost-effectiveness of alirocumab, both as monotherapy and in combination, in a variety of potential relevant patient groups, when the results of CV outcome trials become available (e.g. familial dyslipidaemias, existing cardiovascular disease).

7 References

1. National Institutes of Health. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Third Report of the National Cholesterol Education Program (NCEP). Circulation 2002;**106**(25):3143-421.

2. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. J Clin Lipidol 2015;**9**(2):129-69.

3. Varbo A, Benn M, Nordestgaard BG. Remnant cholesterol as a cause of ischemic heart disease: evidence, definition, measurement, atherogenicity, high risk patients, and present and future treatment. Pharmacol Therap 2014;**141**(3):358-67.

4. Pullinger CR, Kane JP, Malloy MJ. Primary hypercholesterolemia: genetic causes and treatment of five monogenic disorders. Expert Rev Cardiovasc Therap 2003;**1**(1):107-19.

5. Ara R, Tumur I, Pandor A, et al. Ezetimibe for the treatment of hypercholesterolaemia: A systematic review and economic evaluation. Health Technol Assess2008;**12**(21).

6. Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: A prospective registry study. Eur Heart J 2008;**29**(21):2625-33.

7. Thompson GR, Seed M. The management of familial hypercholesterolaemia. Primary Care Cardiovasc J 2014;**7**(2):89-91.

8. 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**(45):3478-90a.

9. Kusters DM, Huijgen R, Defesche JC, et al. Founder mutations in the Netherlands: Geographical distribution of the most prevalent mutations in the low-density lipoprotein receptor and apolipoprotein b genes. Neth Heart J 2011;**19**(4):175-82.

10. European Association for Cardiovascular P, Rehabilitation, Reiner Z, 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**(14):1769-818.

11. Hewing B, Landmesser U. LDL, HDL, VLDL, and CVD Prevention: Lessons from Genetics? Curr Cardiol Report 2015;**17**(7).

12. Bhatnagar D, Soran H, Durrington PN. Hypercholesterolaemia and its management. BMJ 2008;**337**:a993.

13. Ohta T, Kiwaki K, Endo F, et al. Dyslipidemia in young Japanese children: its relation to familial hypercholesterolemia and familial combined hyperlipidemia. Pediat Int 2002;**44**(6):602-7.

14. Genest JJ, Jr., Martin-Munley SS, McNamara JR, et al. Familial lipoprotein disorders in patients with premature coronary artery disease. Circulation 1992;**85**(6):2025-33.

15. LaRosa JC, Hunninghake D, Bush D, et al. The cholesterol facts. A summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. A joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute. Circulation 1990;**81**(5):1721-33.

16. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001;**104**(3):365-72.

17. Stein EA, Raal FJ. Lipid-Lowering Drug Therapy for CVD Prevention: Looking into the Future. Curr Cardiol Report 2015;**17**(11).

18. Identification and management of familial hypercholesterolaemia (FH). NICE CG71. London: National Institute for Health and Care Excellence, 2008.

19. Deanfield J, Sattar N, Simpson I, et al. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014;**100**(SUPPL. 2):ii1-ii67.

20. Labarthe D. *Adverse blood lipid profile.* IN: Epidemiology and prevention of cardiovascular diseases: a global challenge. Sudbury, MA: Jones & Bartlett, 2011:269-304.

21. Reckless L. *Lipid disorders - your questions answered*. London: Elsevier, 2005.

22. *Reducing risk, promoting healthy life*. Geneva: World Health Organization, 2002.

23. Primatesta P, Poulter NR. Levels of dyslipidaemia and improvement in its management in England: Results from the Health Survey for England 2003. Clin Endocrinol 2006;**64**(3):292-98.

24. Ebrahim S, Davey Smith G, McCabe C, et al. Cholesterol and coronary heart disease: Screening and treatment. Qual Health Care 1998;**7**(4):232-39.

25. Heart statistics. Birmingham: British Heart Foundation, 2015. URL: http://www.medicines.org.uk/emc/medicine/12091 [accessed November 2015]

26. Nichols M, Townsdend, N, Scarbourogh,P.. European Cardiovascular Disease Statistics: European Heart Network, 2012.

URL:http://www.ehnheart.org/component/downloads/downloads/1436.html [accessed November 2015]

27. Monroe AK, Gudzune KA, Sharma R, et al. Combination therapy versus intensification of statin monotherapy: an update. Effective Health Care Program Comparative Effectiveness Review No 132. . Rockville, MD: Agency for Healthcare Research and Quality (AHQR), 2014. URL: http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1861 [accessed November 2015]

28. 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. Circulation 2014;**129**(25 SUPPL. 1):S1-S45.

29. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of acrdiovascular disease. NICE CG181. London: National Institute for Health and Care Excellence, 2014. URL: http://www.nice.org.uk/guidance/cg181 [accessed November 2015]

30. Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Molecul Med 2001;**5**(4):378-87.

31. 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**(9493):1267-78.

32. Cholesterol Treatment Trialists C, Fulcher J, O'Connell R, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015;**385**(9976):1397-405.

33. Cardiovascular disease prevention. NICE Pathway. London: National Institute for Health and Care Excellence, 2014. URL: http://pathways.nice.org.uk/pathways/cardiovascular-disease-prevention [accessed November 2015]

34. Markham A. Alirocumab: First Global Approval. Drugs 2015;**75**(14):1699-705.

35. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. London: National Institute for Health and Care Excellence, 2007. URL: http://www.nice.org.uk/guidance/ta132 [accessed November 2015]

36. Familial hypercholesterolaemia. NICE Quality Standard QS41. London: National Institute for Health and Care Excellence, 2013. URL: http://www.nice.org.uk/guidance/ta132 [accessed November 2015]

37. Gagne C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002;**105**(21):2469-75.

38. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): A randomised, double-blind, placebo-controlled trial. Lancet 2015;**385**(9965):341-50.

39. Efficacy and Safety of Combining Alirocumab With Atorvastatin or Rosuvastatin versus Statin Intensification or Adding Ezetimibe in High Cardiovascular Risk Patients: ODYSSEY OPTIONS I and II. . American Heart Association Annual Conference, Chicago, November; 2014.

40. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: The ODYSSEY COMBO II randomized controlled trial. Eur Heart J 2015;**36**(19):1186-94.

41. ODYSSEY HIGH FH: Efficacy and Safety of Alirocumab in Patients with Severe Heterozygous Familial Hypercholesterolemia. . American Heart Association Annual Conference, Chocago, Novemebr; 2014.

42. Kastelein J, Ginsberg HN, Langslet G, et al. Odyssey FH1 and FHII: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J 2015:doi:10.1093/eurheartj/ehv370.

43. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO i study. Am Heart J 2015;**169**(6):906-15.

44. McKenney JM, Koren MJ, Kereiakes DJ, et al. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. Journal of the Am Coll Cardiol 2012;**59**(25):2344-53.

45. 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**(18):1870-82.

46. Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: A phase 2 randomised controlled trial. Lancet 2012;**379**(9836):29-36.

47. Desai NR, Giugliano RP, Zhou J, et al. AMG 145, a monoclonal antibody against PCSK9, facilitates achievement of national cholesterol education program-adult treatment panel III low-density lipoprotein cholesterol goals among high-risk patients: An analysis from the LAPLACE-TIMI 57 trial (LDL-C assessment with PCSK9 monoclonaL antibody inhibition combined with statin thErapy-thrombolysis in myocardial infarction 57). J Am Coll Cardiol 2014;**63**(5):430-33.

48. Hirayama A, Honarpour N, Yoshida M, 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 J 2014;**78**(5):1073-82.

49. Kiyosue A, Honarpour N, Xue A, et al. Effects of evolocumab (AMG 145) in hypercholesterolemic, statin-treated, Japanese patients at high cardiovascular risk: Results from the phase III yukawa 2 study. J Am Coll Cardiol 2015;**1)**:A1369.

50. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: The reduction of LDL-C with PCSK9 inhibition in heterozygous familial hypercholesterolemia disorder (RUTHERFORD) randomized trial. Circulation 2012;**126**(20):2408-17.

51. 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**(9965):331-40.

52. Farnier M, Volpe M, Massaad R, et al. Effect of co-administering ezetimibe with on-going simvastatin treatment on LDL-C goal attainment in hypercholesterolemic patients with coronary heart disease. Int J Cardiol 2005;**102**(2):327-32.

53. Gagne C, Bays HE, Weiss SR, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002;**90**(10):1084-91.

54. Ishimitsu T, Ohno E, Ueno Y, et al. Effects of atorvastatin and ezetimibe on endothelial function in dyslipidemic patients with chronic kidney disease. Clin Experiment Nephrol 2014;**18**(5):704-10.

55. Kastelein JJP, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. New Engl J Med 2008;**358**(14):1431-43.

56. Matsue Y, Matsumura A, Suzuki M, et al. Differences in action of atorvastatin and ezetimibe in lowering low-density lipoprotein cholesterol and effect on endothelial function - Randomized controlled trial. Circulation J 2013;**77**(7):1791-98.

57. Okada K, Iwahashi N, Endo T, et al. Long-term effects of ezetimibe-plus-statin therapy on low-density lipoprotein cholesterol levels as compared with double-dose statin therapy in patients with coronary artery disease. Atherosclerosis 2012;**224**(2):454-56.

58. Roeters Van Lennep HWO, An HL, Dunselman PHJM, et al. The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: Results of the EASEGO study. Curr Med Res Opinion 2008;**24**(3):685-94.

59. Sasaki J, Otonari T, Sawayama Y, et al. Double-dose pravastatin versus add-on ezetimibe with low-dose pravastatin - effects on LDL cholesterol, cholesterol absorption, and cholesterol synthesis in japanese patients with hypercholesterolemia (PEAS study). J Atherosclerosis Thrombosis 2012;**19**(5):485-93.

60. Shiba T, Kawamura M, Kouro T, et al. Combination regimen of statin/ezetimibe and reduction of SD-LDL-C for Japanese patients with type 2 diabetes (Research, a multicenter RCT). Atherosclerosis 2014;**235 (2)**:e259.

61. Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J 2004;**148**(3):447-55.

62. Suzuki H, Watanabe Y, Kumagai H, et al. Comparative efficacy and adverse effects of the addition of ezetimibe to statin versus statin titration in chronic kidney disease patients. Therapeut Adv Cardiovasc Dis 2013;**7**(6):306-15.

63. Torimoto K, Okada Y, Mori H, et al. Efficacy of combination of Ezetimibe 10 mg and rosuvastatin 2.5 mg versus rosuvastatin 5 mg monotherapy for hypercholesterolemia in patients with type 2 diabetes. Lipids Health Dis 2013;**12**(1).

64. Villines TC, Stanek EJ, Devine PJ, et al. The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis). Final Results and the Impact of Medication Adherence, Dose, and Treatment Duration. Journal of the Am Coll Cardiol 2010;**55**(24):2721-26.

65. Watanabe E, Yamaguchi J, Arashi H, et al. Effects of statin versus the combination of ezetimibe plus statin on serum lipid absorption markers in patients with acute coronary syndrome. J Lipids 2015;**2015**(109158

66. Yamazaki D, Ishida M, Watanabe H, et al. Comparison of anti-inflammatory effects and high-density lipoprotein cholesterol levels between therapy with quadruple-dose rosuvastatin and rosuvastatin combined with ezetimibe. Lipids Health Dis 2013;**12**(1).

67. Zieve F, Wenger NK, Ben-Yehuda O, et al. Safety and Efficacy of Ezetimibe Added to Atorvastatin Versus Up Titration of Atorvastatin to 40 mg in

Patients >65 Years of Age (from the ZETia in the ELDerly [ZETELD] Study). Am J Cardiol 2010;**105**(5):656-63.

68. Moriaty P, Thompson P, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE Q1 randomized trial. J Clin Lipidol 2015:doi.org/10.1016/j.jacl.2015.08.006.

69. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. New Engl J Med 2015;**372**(16):1489-99.

70. Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial. Int J Cardiol 2014;**176**(1):55-61.

71. Teramoto T, Kobayashi M, Uno K, et al. Efficacy and safety of alirocumab in japanese patients with hypercholesterolemia on stable statin therapy: First data with the 75 mg every two weeks dose. Circulation 2014;**130**.

72. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. New Engl J Medi 2014;**370**(19):1809-19.

73. Giugliano RP, Desai NR, Kohli P, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): A randomised, placebo-controlled, dose-ranging, phase 2 study. Lancet 2012;**380**(9858):2007-17.

74. Koren MJ, Giugliano RP, Raal FJ, et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the open-label study of long-term evaluation against LDL-C (OSLER) randomized trial. Circulation 2014;**129**(2):234-43.

75. 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**(23):2541-48.

76. Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: The GAUSS randomized trial. JAMA 2012;**308**(23):2497-506.

77. Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: The MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014;**63**(23):2531-40.

78. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. New Engl J Med 2015;**372**(16):1500-09.

79. Roth E, McKenney JM, Hanotin C, et al. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolaemia. New Eng J Med 2012;**367**:1891-900.

80. Systematic reviews: CRD's guidance for undertaking systematic reviews in health care [document on the Internet]. Centre for Reviews and Dissemination. University of York, 2009. [accessed November 2015]

81. Li C, Lin L, Zhang W, et al. 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;**4**(6):e001937.

82. 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 Int Med 2015;**163**(1):40-51.

83. Zhang XL, Zhu QQ, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med 2015;**13**:123.

84. 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**(6):419-27.

85. 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 Therap 2008;**30**(8):1508-23.

86. Kohli M, Attard C, Lam A, et al. Cost effectiveness of adding ezetimibe to atorvastatin therapy in patients not at cholesterol treatment goal in Canada. PharmacoEconomics 2006;**24**(8):815-30.

87. 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 Opinion 2010;**26**(3):529-36.

88. Reckless J, Davies G, Tunceli K, et al. 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**(6):726-34.

89. Soini EJO, Davies G, Martikainen JA, et al. Population-based health-economic evaluation of the secondary prevention of coronary heart disease in Finland. Curr Med Res Opinion 2010;**26**(1):25-36.

90. 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**(2):61-67.

91. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;**313**(7052):275-83.

92. PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks Draft Report. Boston: Institute for Clinical and Economic Review, 2015. . http://cepac.icer-review.org/wp-content/uploads/2015/04/PCSK9_Draft_Report_0908152.pdf [accessed November 2015]

93. Bibbins-Domingo K, Coxson P, Pletcher MJ, et al. Adolescent overweight and future adult coronary heart disease. New Engl J Med 2007;**357**(23):2371-79.

94. Hunink MGM, Goldman L, Tosteson ANA, et al. The recent decline in mortality from coronary heart disease, 1980-1990; The effect of secular trends in risk factors and treatment. JAMA 1997;**277**(7):535-42.

95. Weinstein MC, Coxson PG, Williams LW, et al. Forecasting coronary heart disease incidence, mortality, and cost: The coronary heart disease policy model. Am J Public Health 1987;**77**(11):1417-26.

96. The Health Improvement Network (THIN) Database. University College London: Primary Care & Population Healthand Infection & Public Halth Departments, 2015. http://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/database [accessed November 2015

97. Mohrschladt MF, Westendorp RGJ, Gevers Leuven JA, et al. Cardiovascular disease and mortality in statin-treated patients with familial hypercholesterolemia. Atherosclerosis 2004;**172**(2):329-35.

98. O'Keefe Jr JH, Cordain L, Harris WH, et al. Optimal low-density lipoprotein is 50 to 70 mg/dl: Lower is better and physiologically normal. J Am Coll Cardiol 2004;**43**(11):2142-46.

99. Mihaylova B, Voysey M, Gray A, 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**(9841):581-90.

100. Petretta M, Costanzo P, Perrone-Filardi P, et al. Impact of gender in primary prevention of coronary heart disease with statin therapy: A meta-analysis. Int J Cardiol 2010;**138**(1):25-31.

101. *Familial Hypercholesterolaemia (FH): Report of a second WHO consultation*. Geneva: World Health Organization, 1998.

102. Betteridge DJ, Broome K, Durrington PN, et al. Risk of fatal coronary heart disease in familial hypercholesterolaemia. BMJ 1991;**303**(6807):893-96.

103. Alnasser SM, Huang W, Gore JM, et al. Late Consequences of Acute Coronary Syndromes: Global Registry of Acute Coronary Events (GRACE) Follow-up. Am J Med 2015;**128**(7):766-75.

104. National Life tables, United Kingdom,1980-82 to 2011-13: Office of National Statistics, 2014. URL: http://www.ons.gov.uk/ons/rel/lifetables/national-life-tables/2011-2013/rft-uk.xls [accessed November 2015]

105. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: Cohort study. BMJ 2013;**346**(7909).

106. Wilson PWF, D'Agostino Sr R, Bhatt DL, et al. An international model to predict recurrent cardiovascular disease. Am J Med 2012;**125**(7):695-703.e1.

107. Smolina K, Wright FL, Rayner M, et al. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circulation: 2012;**5**(4):532-40.

108. Ference BA, Majeed F, Penumetcha R, et al. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or Both: A 2 x 2 factorial mendelian randomization study. J Am Coll Cardiol 2015;**65**(15):1552-61.

109. Raal FJ, Giugliano RP, Sabatine MS, et al. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): A pooled analysis of more than 1,300 patients in 4 phase II trials. J Am Coll Cardiol 2014;**63**(13):1278-88.

110. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: Current status. Eur Heart J 2010;**31**(23):2844-53.

111. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. New Engl J Med 2015;**372**(25):2387-97.

112. Ara R, Brazier JE. Populating an economic model with health state utility values: Moving toward better practice. Value Health 2010;**13**(5):509-18.

113. Ara R, Wailoo AJ. The use of health state utility values in decsion models NICE DSU Technical Support Document 12.: NICE Decision Support Unit, 2011.

http://www.nicedsu.org.uk/TSD12%20Utilities%20in%20modelling%20FINAL.pdf [accessed November 2015]

114. Lovibond K, Jowett S, Barton P, et al. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: A modelling study. The Lancet 2011;**378**(9798):1219-30.

115. Luengo-Fernandez R, Leal J, Gray AM. UK research expenditure on dementia, heart disease, stroke and cancer: Are levels of spending related to disease burden? Eur J Neurol 2012;**19**(1):149-54.

116. Youman P, Wilson K, Harraf F, et al. The economic burden of stroke in the United Kingdom. PharmacoEconomics 2003;**21**(Suppl. 1):43-50.

117. Luengo-Fernandez R, Gray AM, Rothwell PM. Population-based study of determinants of initial secondary care costs of acute stroke in the United Kingdom. Stroke 2006;**37**(10):2579-87.

118. British Medical Association RPS. British National Formulary: Medicines Complete, 2015. https://www.medicinescomplete.com/ [accessed November 2015]

Appendices

Appendix 1 Characteristics of alirocumab and evolocumab trials identified in the company's submission but not included in clinical effectiveness assessment

Study ID	Intervention	Number of patients	Study population	Treatment duration
Alirocumab trials				
McKenney 2012, Phase II	Alirocumab 150 mg Q2W	31	High CV risk; patients with LDL-C ≥100 mg/dl (2.59 mmol/l) on stable-dose atorvastatin; treatment goal set to LDL-C<100 mg/dL and <70 mg/dL	12 weeks
	Placebo Q2W	31		
	Alirocumab 50 mg Q2W	30		
	Alirocumab 100 mg Q2W	31		
	Alirocumab 200 mg Q4W/alternating placebo	30		
	Alirocumab 300 mg Q4W/alternating placebo	30		
Stein 2012, Phase II	Alirocumab 150 mg Q2W	16	Heterozygous FH; LDL-C of 2.6 mmol/L or higher	
	Alirocumab 150 mg Q4W	15		
	Alirocumab 200 mg Q4W	16		
	Alirocumab 300 mg Q4W	15		
	Placebo Q2W	15		

Teramoto 2014, Phase II	Alirocumab 50 mg Q2W	25	Hypercholesterolaemia; not adequately controlled with stable dose of atorvastatin or other LMTs; LD-LC≥100 mg/dL	12 weeks
	Alirocumab 75 mg Q2W	25		
	Alirocumab 150 mg Q2W	25		
	Placebo Q2W	25		
Evolocumab vs placebo trials				
Blom 2014 (DESCARTES), Phase II	Evolocumab 420 mg QM	599	Hyperlipidaemia (those with CHD or a CHD risk equivalent) with LDL-C<100 mg/dl; those without CHD (or a CHD risk equivalent with LDL-C <130 mg/dl	52 weeks
	Placebo	302		
Hirayama 2014 (YUKAWA) Phase II	Evolocumab 420 mg QM	53	History of CAD, heterozygous FH, arteriosclerosis obliterans/peripheral artery disease or type 2 diabetes; presence of risk factor relating to age, CAD, reduced high-density lipoprotein etc.	12 weeks
	Placebo	51		
	Evolocumab 280 mg QM	52		
	Evolocumab 70 mg Q2W	50		
	Evolocumab 140 mg Q2W	52		
	Placebo Q2W	52		
Raal 2012 (RUTHERFORD), Phase II	Evolocumab 420 mg Q4W	56	Heterozygous FH; LDL-C ≥2.6 mmol/L (100 mg/dL) with triglycerides≤4.5 mmol/L (400 mg/dL)	12 weeks
	Placebo Q4W	56		

Raal 2015 (RUTHERFORFD 2), Phase III	Evolocumab 140 mg Q2W	110	Heterogygous FH; fasting LDL-C≥3.4 mmol/L; fasting triglycerides≤4.5mmol/L; on a stable dose of statins	12 weeks
	Placebo Q2W	54		
	Evolocumab 420 mg Q4W	110		
	Placebo Q4W	55		
Raal 2015 (TESLA Part B)	Evolocumab 140 mg Q4W	33	Homozygous FH; fasting LDL-C≥3.4 mmol/L; fasting triglycerides ≤4.5mmol/L	12 weeks
	Placebo Q4W	16		
Giugliano 2012, Desai 2014 (LAPLACE-TIMI-57) Phase II	Evolocumab 70 mg Q2W	79	Hypercholesterolaemia, dyslipidemia; stable dose of statin with or without ezetimibe; fasting LDL-C>85mg/dL; fasting triglycerides<400 mg/dL	12 weeks
	Evolocumab 105 mg Q2W	79		
	Evolocumab 140 mg Q2W	78		
	Placebo Q2W	78		
	Evolocumab 280 mg QM	79		
	Evolocumab 350 mg QM	79		
	Evolocumab 420 mg QM	80		
	Placebo QM	79		
Koren 2014 (OSLER), phase II	Evolocumab 420 mg Q4W plus Standard of Care	736	LDL-C≥100 mg/dL and <190 mg/dL; Framingham risk score of 10% or less; fasting triglycerides<400 mg/dL	52 weeks
	Standard of Care	368		

Evolocumab vs active agent trials				
Kiyosue 2015 (YUKAWA-II), Phase III	Evolocumab 140 mg Q2W or 420 mg Q4W plus atorvastatin 5 mg QD	50	At high risk of CV events; on stable statin therapy	12 weeks
	Evolocumab 140 mg Q2W or 420 mg Q4W plus atorvastatin 20 mg QD	51		
	Placebo Q2W plus atorvastatin 5 mg QD	49		
	Placebo QM plus atorvastatin 5 mg QD	50		
	Placebo Q2W plus atorvastatin 20 mg QD	52		
	Placebo Q4W plus atorvastatin 20 mg QD	51		
Sullivan 2012 (GAUSS), Phase II	Evolocumab 280 mg Q4W	32	Hypercholesterolaemia; statin intolerant, LDL-C ≥100 mg/dL with CHD risk or equivalent; LDL-C≥130 mg/dL without CHD or risk equivalent and 2 or more risk factors, or ≥160 mg/dL without CHD or risk equivalent and with 1 or 0 risk factors; fasting triglycerides≤400mg/dL	12 weeks
	Evolocumab 350 mg Q4W	31		
	Evolocumab 420 mg Q4W	32		
	Ezetimibe 10 mg QD plus evolocumab 420 mg Q4W	30		
	Placebo Q4W plus ezetimibe 10 mg QD	32		

Robinson 2014 (LAPLACE), Phase III	Evolocumab 140 mg Q2W or 420 mg Q4W	1117	At screening LDL-C ≥150 mg/dL (no statin), ≤100 mg/dL (non-intensive statin) or =80 mg.dL (intensive statin); fasting triglycerides ≤400 mg/dL	12 weeks
	Ezetimibe 10 mg QD (atorvastatin patients)	221		
	Placebo	558		
Stores 2014 (GAUSS-2), Phase III	Evolocumab 140 mg Q2W	103	No or low dose statins; LDL-C above their National Cholesterol Education Programme Adult treatment Panel III goal; intolerance to more than two statins	12 weeks
	Ezetimibe 10 mg QD plus placebo Q2W	51		
	Evolocumab 420 mg Q4W	102		
	Ezetimibe 10 mg QD plus placebo QM	51		
Koren 2014 (MENDEL-2)	Evolocumab 420 mg QM plus placebo QD	153	LDL-C levels ≥100 mg/dl and <190 mg/dl, triglycerides≤400 mg/dl, and 10-year Framingham coronary heart disease risk scores≤10% (low to moderate CV risk)	12 weeks
	Placebo QM plus placebo QD	78		
	Placebo QM plus ezetimibe QD	77		
	Evolocumab 140 mg Q2W plus placebo QD	153		
	Placebo Q2W plus placebo QD	76		
	Placebo Q2W plus ezetimibe QD	77		

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779]

You are asked to check the ERG report from Aberdeen to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Thursday 10 December 2015** 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 Mistaken reference to stable angina, in place of unstable angina

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"....the use of a composite event state for ACS which includes MI and stable angina (UA)." This makes it impossible to model different effects for MI and UA" Section 1.5 - Summary of the ERG's critique of cost effectiveness evidence submitted, page 8 Section 5.2.2. - Model structure, page 79 Section 6.0 - Overall conclusions, page 177	Unstable angina (UA) rather than stable angina.	These are the typographical errors.	The typographical errors have now been amended (please see the Erratum).

Issue 2 Clarification on comparison to statin uptitration not statin

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"….compared with statin between -20.4% and -49.2%." Section 1.2 - Summary of clinical effectiveness evidence submitted by the company, Page 3 Section 4.2 - Critique of trials of the technology of interest, their	"….compared with statin **uptitration** between -20.4% and -49.2%."	Typographical error	Minor imprecision. No amendments have been made.

analysis and interpretation (and any standard meta-analyses of these), Page 61 Section 6 – Conclusions, Page 176			

Issue 3 Continuous use anticipated in all patients not just those with HeFH

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"In people with HeFH, it is anticipated that alirocumab will be used continuously once initiated." Section 3.2 – Intervention, Page 21	"**<u>In all patients</u>**, it is anticipated that alirocumab will be used continuously once initiated"	Although initial statement is correct, there is no distinction between patient groups and justification is to avoid confusion	The statement has been amended to avoid confusion (please see the Erratum).

Issue 4 Dosing of LONG TERM study only at 150mg

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"Alirocumab 75-150 mg (Q2W)" Section 4.1.4 - Characteristics of identified studies, Table 3, Page 41 - Robinson 2015[69] (LONG TERM)	Alirocumab **<u>150 mg</u>** (Q2W)	Typographical error. LONG TERM Study was 150mg (Q2W) only	The text has been amended (please see the Erratum).

Issue 5 Clarification of ERG Quality Assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The quality assessment scores in Table 4 infer that the SLR undertaken was of low quality, however, the narrative around Table 4 and elsewhere in report recognises it's appropriateness Section 4.1.6 - Quality assessment, Table 4, Page 45	Clarify 'scoring' and potentially adjust score to no bias or low risk of bias	Reader clarification	Table 4 has been amended (please see the Erratum).

Issue 6 Confidence Interval data have been provided upon clarification request

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The results of these various pooled analyses are shown in Table 17 for comparisons at 24 weeks. No confidence intervals were provided by the company." Section 4.2 - Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these), Page 62/63 and Table 17	The results of these various pooled analyses are shown in Table 17 for comparisons at 24 weeks." ~~**No confidence intervals were provided by the company.**~~	Confidence intervals were provided upon request in response to a clarification question	The CIs were not reported in the original submission, but provided in response to clarification A10. We have now amended this oversight.

Issue 7 Modelling of primary and secondary HeFH populations individually and not as a single population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The HeFH population consists of a single homogenous cohort in the model" Section 5.2.3 - Population, Page 87	The two HeFH population**s (primary and secondary prevention)** ~~**consists of a**~~ **are modelled individually as** single homogenous cohort**s** in the model	Typographical errors. HeFH primary and secondary prevention populations are modelled separately, not as a single population	The text has been amended (please see the Erratum).

Issue 8 Base case ages of primary and secondary prevention populations different (50 and 60 years respectively)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The base case analyses for HeFH are provided for cohorts aged 50 , LDL-C ≥ 2.59 mmol/L (mean LDL-C = 4.82 mmol/L for primary prevention, 4.56 for secondary prevention), 50% male" Section 5.2.9 – Cost effectiveness results , Page 122	The base case analyses for HeFH are provided for cohorts aged 50 **(primary prevention) and 60 (secondary prevention)**, LDL-C ≥ 2.59 mmol/L (mean LDL-C = 4.82 mmol/L for primary prevention, 4.56 for secondary prevention), 50% male	Typographical errors. HeFH primary and secondary prevention populations are modelled separately with different ages	The text has been amended (please see the Erratum).

Issue 9 Reference to ASC instead of ACS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The ERG had some concerns relating to the inflation of subsequent events following recurrent ASC and ischaemic stroke" Section 5.2.11 – Model validation and face validity check, Page 143	The ERG had some concerns relating to the inflation of subsequent events following recurrent **ACS ~~ASC~~** and ischaemic stroke	Typographical error	The text has been amended (please see the Erratum).

Issue 10 Different ICERs obtained for HeFH Statin Intolerant populations using ERG model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ICER vs baseline for HeFH populations appear to have been modelled with the default mean baseline LDL-Cs of 4.56 or 4.82mmol/L and not 5.8mmol/L as described Section 5.3.1 - The ERG updated base case and scenario analysis (deterministic), Table 55, Page 151	Model output data to be corrected, to provide ICERs as follows: HeFH primary prevention (LDL-C ≥2.59 mmol/L) - £45,786 HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from Morschladt et al. - £22,042 HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from THIN - £25,869	We believe a simple input selection error has occurred, resulting in ICERs for the HeFH populations which do not reflect the intended analyses	Table 55 did contain some incorrect ICERs for the HeFH populations. These have now been corrected and concur with the company's ICERs (please see the Erratum). The corresponding text in the report referring to Table 55 (on page 146) has also been amended to reflect this correction.

Sent by email:

Single Technology Appraisal

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779]

Dear Charlie

As you know, the alirocumab PAS will initially be applied in specialist secondary care clinics, if recommended by NICE. However, as 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. This has potential implications for the simple discount patient access scheme approved by the DH. The DH alirocumab's PAS approval and referral letter to NICE states:

'*Alirocumab on FP10 prescription:**… alirocumab will initially be used in specialist secondary care clinics. However, as routine lipid management is an area of standard GP practice, it was noted that there may be a potential transition of patients from secondary to primary care after 2 to 3 years. This has potential implications for the proposed simple discount patient access scheme. As simple discounts cannot be realised when drugs are prescribed through FP10 prescriptions, the actual discount received by the NHS may be less than the percentage discount offered in the scheme…..this could affect the Institute's appraisal of the technology's cost-effectiveness…. take any steps you feel appropriate in order to take potential primary care prescribing into account*.'

The alirocumab PAS is applied to <u>all</u> patients prescribed alirocumab in the economic model for all analyses in Sanofi's submissions and your assumption is that all prescribing will be in the secondary care/ home-care setting. Therefore the economic analyses do not take account of the potential for GP prescribing, as noted in the DH PAS approval and referral letter to NICE.

NICE therefore request you to provide the following sensitivity analyses 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 alirocumab through secondary care. The sensitivity analyses should be undertaken for each of the populations in the model. Please also provide the rationale for the value of the inputs used.

In addition to ensure that the appraisal process is as transparent as possible, NICE considers it essential that evidence on which the Committee's decisions are based is publicly available. NICE asks you to <u>lift</u> the commercial in confidential restrictions on total life years and total QALYs on your base case analysis, and all scenario and subgroup analyses within your submission(s) and any related responses to clarification. If this information will enable the back-calculation of specific data that are properly considered confidential, you <u>must</u> provide <u>full details</u> of the calculation you believe can be made. Please see the Guide to the processes of technology appraisals (sections 3.1.24–29) for further information.

Please also note that it is your responsibility to keep us informed of the confidentiality status of your data throughout the appraisal and to submit a revised Checklist of Confidential

Information if any changes occur (for example, following the publication of previously restricted data, or changes in response to this letter).

Your documentation is required by **5pm, Wednesday 9 December.**

Kind regards

Frances

Dr Frances Sutcliffe
Associate Director Technology Appraisals - Committee C
National Institute for Health and Care Excellence

Level 1A | City Tower | Piccadilly Plaza | Manchester M1 4BT | United Kingdom

Dr Frances Sutcliffe
Associate Director Technology Appraisals - Committee C
National Institute for Health and Care Excellence
Level 1A City Tower
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10th December 2015

Dear Frances,

Re: Request to provide additional sensitivity analyses for the NICE appraisal [ID779] - Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Thank you for your invitation to provide additional sensitivity analyses to address a question of the NHS's ability to secure the benefit of the patient access scheme (PAS) discount offered by Sanofi.

You are correct in summarising that our submission and base case does not take into account situations in which the NHS is not able to purchase the medicine at the net price being offered through our simple discount PAS. We believe alirocumab will be prescribed and managed from within the specialist setting in the vast majority of cases – principally via specialist lipid clinics. The majority of these lipid clinics takes place in a hospital outpatient department and are run by a specialist, which could be a lipidologist, cardiologist or clinical biochemist.

The question of prescribing pathways, raised by the Department of Health in November, indicates that the possibility is thought to exist that the NHS cannot buy the medicine in all settings at the PAS discounted price offered by Sanofi; principally where the prescription is written by a General Practitioner using an FP10 form, and that the NHS does not wish to take advantage of primary care rebate schemes.

Sanofi considers that this scenario is very unlikely for alirocumab as we believe the NHS would most effectively deliver alirocumab exclusively within the specialist setting in lipid clinics for the following reasons, and might be further reinforced by Section 1 wording within the recommendation, were NICE to issue positive guidance for alirocumab:

1) The most appropriate use of alirocumab, as detailed within our manufacturer submission, is for the management of people with FH and high risk CVD (i.e. secondary prevention and/or recurrent events), including those with statin intolerance, who cannot achieve optimal LDL-C levels on current maximally tolerated routine lipid management therapies (LMTs). These are patients that require specialist support beyond the routine lipid management services provided by their primary care team.

2) Such high risk patients should be referred by GPs to expert lipid specialists, based in hospitals and specialist lipid clinics, as is recommended in NICE's FH Guideline and Commissioning recommendations[1]; similar views were also expressed by experts from Newcastle upon Tyne and Guy's & St. Thomas' Hospitals in their submissions to the Institute as part of the appraisal of evolocumab[2], and in a recent communication to us from Dr.Viljoen (Consultant Chemical Pathologist) – reproduced in Appendix 3.

3) Alirocumab is listed on the High cost drugs exclusion list proposed for 2016/17[3] and is therefore expected to be funded outside the national tariff. Hospitals will be able to prescribe alirocumab as part of CCG commissioned services and will recover the cost via the high cost drugs

[1] NICE CG71; Familial hypercholesterolaemia: Identifification and management - 1.3.1.13 Healthcare professionals should offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a highintensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).
[2] http://www.nice.org.uk/guidance/indevelopment/gid-tag498/documents
[3] https://www.gov.uk/government/publications/201617-national-tariff-proposal-annexes

reimbursement system. Using hospital directed homecare services, NHS hospitals will also benefit from the VAT savings this route of supply affords.

4) We understand, from our ongoing meetings with CCGs that Commissioners are seeking to limit the use of alirocumab within primary care, aligning their pathways to the most effective care for patients and most efficient funding mechanism, namely commissioned services from speciality care/hospitals only.

5) The majority of a sample of GPs, when surveyed by Adelphi Research in July 2015 (Sanofi-sponsored research), stated that they were 'extremely unlikely' to prescribe a self-injected sub-cutaneous treatment for hypercholesteremia, even if a pre-filled pen device was available. This is also consistent with feedback from multiple advisory boards that Sanofi has conducted with clinicians, where it has been stated they anticipate secondary care initiation and management of PCSK9s.

6) Finally, Sanofi has in place arrangements for the supply of alirocumab to the NHS in England via two routes:

    a. directly to hospital pharmacies, and

    b. via approved homecare companies.

This specialty care supply model for alirocumab is already operating effectively in several EU countries and in the US alongside appropriate Patient Support and Education Programmes. It is our considered view that it is the most appropriate specialty care supply model for England. Accordingly, there are no arrangements in place for the supply of alirocumab into primary care pharmacies in England.

We think the likelihood of any primary care prescribing via FP10 is therefore very low for alirocumab, given the best position for this product in the care pathway, and Sanofi's efforts to support this through tailored secondary care supply to the NHS.

We do recognise that a situation could exist – however unlikely for alirocumab – in circumstances where FP10 prescriptions are written, CCGs may not want to buy a medicine at a net price equivalent to the PAS discounted price, for example via a primary care rebate scheme. Therefore, in anticipation that the Appraisal Committee will be interested in the potential impact of theoretical scenarios, where the NHS does not realise the full benefit of the PAS net price, we have provided some exploratory analyses below.

Approach

We have made some simple adjustments to the economic model that effectively weights the average cost-per-cycle depending on an assumed rate of prescribing in which the NHS does not benefit from the PAS price or any future primary care rebate provided by the company. The model can examine various percentages, cycles (time periods) over which this may apply, and applies simple linear assumptions about growth of non-PAS prescribing up to a defined maximum level.[4]

The scenarios we have examined estimate a range of non-PAS prescribing levels based on IMS sales data for a selection of 'analogue' medicines; namely the monoclonal antibodies used in rheumatoid arthritis (RA), and omalizumab (Xolair™) and denosumab (Prolia™). These are NICE-approved medicines – subject to various PAS arrangements – used in conditions that until severity determines that specialist referral and management is needed, are typically managed in primary care. Uptake in primary care (retail) and secondary care (hospital) settings is estimated from the combined data from IMS XBPI/HPAI datasets (Appendix 1).

All these medicines are monoclonal antibodies. The closest analogue to how Sanofi intends to introduce and supply alirocumab to the NHS is the monoclonal antibodies used in RA. These medicines are initiated and managed from a secondary care setting, by specialists, in specialist clinics,

[4] Please note these scenario analyses take no account of price erosion over time due to competitor entry, or of biosimilar availability following patent expiration or any other price modulations which would take place in reality.

usually with homecare and patient support services providing ongoing support of patients in the community. As can be seen in Table 1, prescribing of the RA drugs is almost exclusively in the hospital setting, many years after the introduction of multiple medicines across multiple indications, and this secondary care provision is consistent over time. A similar pattern is seen for omalizumab.

For the purposes of our modelling, Prolia™ is used to illustrate the expected upper band limit of monoclonal antibody prescribing within primary care. It is not an appropriate analogue itself for alirocumab, being 'in tariff', not exclusively managed in secondary care, and is not supplied via a homecare route. It therefore shows a different pattern of delivery with increasing prescriptions in primary care; [redacted]

Table 1 Hospital and retail sales split for several mono-clonal antibodies (see Appendix 1)

BPIHPA_UK_M_IMS_001		2011	2012	2013	2014	2015
RA Mabs						
	Total Hospital	99.23%	99.26%	99.10%	99.25%	99.73%
	Total Retail	0.77%	0.74%	0.90%	0.75%	0.27%
Xolair™						
	Total Hospital	99.68%	99.18%	99.37%	99.48%	99.73%
	Total Retail	0.32%	0.82%	0.63%	0.52%	0.27%
Prolia™						
	Total Hospital	85.33%	72.47%	63.26%	57.04%	51.75%
	Total Retail	14.67%	27.53%	36.74%	42.96%	48.25%

Source: IMS Health, XBPI/HPA Combined Audit, MAT October 2015.

Using these lower and upper bands, of [redacted] and [redacted] potential uptake in primary care, we model a set of five scenarios, in which uptake increases linearly from year 2 reaching a peak at year 5. The model then maintains the respective maximum uptake in each scenario throughout the remaining model time horizon.

Table 2 Non-PAS prescribing scenarios - ranges based on two analogue medicines

	Base case	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Analogue		[redacted]				[redacted]
Maximum % prescribed in primary care	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Start of transition to primary care	n/a	Year 2	Year 2	Year 2	Year 2	Year 2
Maximum % achieved by year	n/a	Year 5	Year 5	Year 5	Year 5	Year 5

Table 3 presents the Cost-effectiveness results for each scenario, by patient subgroup and Table 4 provides the probabilistic cost-effectiveness results and estimated probability of being cost-effective at three WTP thresholds for the two extreme scenarios; Scenario 1 and Scenario 5.

As would be expected, for each subgroup, the ICER increases as each scenario departs further from the base case assumption that all purchases of alirocumab will be at the PAS price. In scenario 5, the highest non-PAS uptake scenario, the ICERs have increased by around £4000-£10,000. All except the HeFH primary prevention (LDL-C ≥2.59 mmol/L) subgroup have ICERs remaining below £25,000/QALY.

The probabilisitic ICERs are similar to the deterministic ICERs, and the probability of alirocumab being cost-effective at various WTP thresholds remains consistent for Scenario 1 with our submission base case.

For scenario 5, alirocumab has a probability of around 60-70% at a WTP threshold of £30,000/QALY for the subgroups excluding HeFH primary prevention (LDL-C ≥2.59 mmol/L).

Table 3 Cost-effectiveness results for each scenario, by patient subgroup (breakdown provided in Appendix 2)

Patient population	Technology (and comparators)	Base case	Scenario 1 [redacted] by year 5 [start year 2)	Scenario 2 [redacted] by year 5 [start year 2)	Scenario 3 [redacted] by year 5 [start year 2)	Scenario 4 [redacted] by year 5 [start year 2)	Scenario 5 [redacted] by year 5 [start year 2)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	£36,793	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)						
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Morschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	£16,896	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)						
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	£19,751	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)						
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	£19,447	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)						

Table 4 Probabilistic cost-effectiveness results and estimated probability of being cost-effective at three WTP thresholds; Scenario 1 and Scenario 5

Patient population	Scenario 1 [redacted] by year 5 [start year 2) PSA ICER	Scenario 1 [redacted] by year 5 [start year 2) p(C/E @ 20K/Q)	Scenario 1 [redacted] by year 5 [start year 2) p(C/E @ 30K/Q)	Scenario 1 [redacted] by year 5 [start year 2) p(C/E @ 40K/Q)	Scenario 5 [redacted] by year 5 [start year 2) PSA ICER	Scenario 5 [redacted] by year 5 [start year 2) p(C/E @ 20K/Q)	Scenario 5 [redacted] by year 5 [start year 2) p(C/E @ 30K/Q)	Scenario 5 [redacted] by year 5 [start year 2) p(C/E @ 40K/Q)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	[redacted]	10.2%	33.0%	51.2%	[redacted]	0.00%	19.4%	36.6%
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Morschladt et al*	[redacted]	56.6%	79.2%	88.2%	[redacted]	39.6%	69.0%	83.0%
High risk CVD (LDL-C ≥3.36 mmol/L)	[redacted]	45.6%	78.6%	86.4%	[redacted]	21.8%	64.0%	78.6%
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	[redacted]	49.6%	77.0%	86.4%	[redacted]	25.8%	63.4%	82.2%

Sanofi is committed to working with NICE and the NHS, to ensure the appropriate managed entry of this new technology, and that pathways, funding flows, and patient selection will ensure initiation and management will be in the specialist setting, either in hospitals or lipid clinics. In these patients and in these settings, the question is not so much about routine lipid management, as described in the request, but around supplying the medicine to experts to manage the patients whose disorder is most resistant to usual management, or whose risk is especially high and therefore typically beyond the routine.

The company can and will commit to provide the PAS fixed net price irrespective of care setting and therefore the PAS price should be universally available across England and Wales. We anticipate that NICE will review its guidance in around three years time, perhaps by when initiatives currently under discussion as part of the Accelerated Access Review (AAR) process to improve market entry of innovative medicines to the UK, will be able to take an integrated care approach to the application of national PAS schemes so the discounts the industry provides can be made available in both secondary and primary care settings.

Sanofi understands, and supports, the NHS's preference to control the use of this innovative new medicine by seeking to restrict its adoption to patients directly managed in specialist settings, such as those at particularly high risk or with the highest unmet need. As with the adoption of the monoclonal antibody medicines used in the management of auto-immune disease or omalizumab for severe persistent allergic asthma and severe chronic spontaneous urticaria, the NHS in England has long experience of adopting specialist technologies and ensuring their use is appropriately restricted to these secondary care settings.

We would welcome qualification in any future NICE recommendation that supports the provision of this important therapeutic option for patients, who are not responsive to existing LMTs, restricting initiation and management to appropriate specialist prescribing within specialist secondary care settings.

Yours Sincerely

Charlie Nicholls

Head of Health Outcomes
Sanofi

APPENDIX 1

Prescribing pattern analogues

Source of data is the combined IMS XBPI/HPAI dataset with data running to October 2015. This is a national sales audit produced monthly by IMS derived from reported sales via hospital pharmacies and retail pharmacies. Hospital data is defined as the volume sales reported through the HPAI dataset. Retail data is defined as the volume sales reported through the XBPI dataset. All volume data is at unit level e.g. pack level. The annual data as represented are complete calendar years for the years 2011-2014, with 2015 comprising the full set of 2015 data available at the time of analysis (YTD Oct15). No additional filters have been applied to the data.

BPIHPA_UK_M_IMS_001		2011	2012	2013	2014	2015
Hospital	Cimzia	16,126	38,651	40,547	54,318	53,868
	Enbrel	383,688	373,499	406,197	378,613	326,336
	Humira	376,600	437,244	492,608	567,218	524,703
	Mabthera	171,086	192,175	205,647	210,047	180,640
	Orencia	7,119	13,027	22,659	33,641	35,809
	Remicade	313,283	342,687	384,301	427,721	373,285
	RoActemra	30,354	58,013	90,534	116,560	105,155
	Simponi	2,271	15,388	30,022	46,022	48,727
	Total Hospital	1,300,527	1,470,684	1,672,514	1,834,141	1,648,523
Retail	Cimzia	76	256	412	349	201
	Enbrel	6,311	6,314	9,148	8,535	552
	Humira	3,624	4,260	4,348	3,569	2,317
	Mabthera	10	118	1,136	996	867
	Orencia	28	4	4	33	113
	Remicade	24	20	29	95	26
	RoActemra	0	9	2	11	22
	Simponi	1	26	78	202	336
	Total Retail	10,075	11,008	15,156	13,789	4,433
	Total Hospital	99.23%	99.26%	99.10%	99.25%	99.73%
	Total Retail	0.77%	0.74%	0.90%	0.75%	0.27%

Source: IMS Health, XBPI/HPA Combined Audit, MAT October 2015.

BPIHPA_UK_M_IMS_001		2011	2012	2013	2014	2015
Hospital	Prolia	6,202	13,806	20,077	27,144	24,711
Retail	Prolia	1,066	5,244	11,662	20,442	23,038
	Total Hospital	85.33%	72.47%	63.26%	57.04%	51.75%
	Total Retail	14.67%	27.53%	36.74%	42.96%	48.25%

Source: IMS Health, XBPI/HPA Combined Audit, MAT October 2015.

BPIHPA_UK_M_IMS_001		2011	2012	2013	2014	2015
Hospital	Xolair	56,327	71,829	86,977	108,599	111,311
Retail	Xolair	179	597	549	572	297
	Total Hospital	99.68%	99.18%	99.37%	99.48%	99.73%
	Total Retail	0.32%	0.82%	0.63%	0.52%	0.27%

Source: IMS Health, XBPI/HPA Combined Audit, MAT October 2015.

APPENDIX 2

HeFH primary prevention (LDLc ≥2.59 mmol/L)

Base case

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	52,256	1.62	1.42	36,793
C	[redacted]	[redacted]	[redacted]				

HeFH primary prevention (LDLc ≥2.59 mmol/L)

Scenario 1

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	1.62	1.42	[redacted]
C	[redacted]	[redacted]	[redacted]				

HeFH primary prevention (LDLc ≥2.59 mmol/L)

Scenario 2

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	1.62	1.42	[redacted]
C	[redacted]	[redacted]	[redacted]				

HeFH primary prevention (LDLc ≥2.59 mmol/L)

Scenario 3

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	1.62	1.42	[redacted]
C	[redacted]	[redacted]	[redacted]				

HeFH primary prevention (LDLc ≥2.59 mmol/L)

Scenario 4

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	1.62	1.42	[redacted]
C	[redacted]	[redacted]	[redacted]				

HeFH primary prevention (LDLc ≥2.59 mmol/L)

Scenario 5

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	1.62	1.42	[redacted]
C	[redacted]	[redacted]	[redacted]				

HeFH secondary prevention (LDLc ≥2.59 mmol/L) - Morschladt

Base case

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	39,306	3.04	2.33	16,896
C	[redacted]	[redacted]	[redacted]				

HeFH secondary prevention (LDLc ≥2.59 mmol/L) - Morschladt

Scenario 1

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	3.04	2.33	[redacted]
C	[redacted]	[redacted]	[redacted]				

HeFH secondary prevention (LDLc ≥2.59 mmol/L) - Morschladt

Scenario 2

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	3.04	2.33	[redacted]
C	[redacted]	[redacted]	[redacted]				

HeFH secondary prevention (LDLc ≥2.59 mmol/L) - Morschladt

Scenario 3

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	3.04	2.33	[redacted]
C	[redacted]	[redacted]	[redacted]				

HeFH secondary prevention (LDLc ≥2.59 mmol/L) - Morschladt

Scenario 4

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	3.04	2.33	[redacted]
C	[redacted]	[redacted]	[redacted]				

HeFH secondary prevention (LDLc ≥2.59 mmol/L) - Morschladt

Scenario 5

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	3.04	2.33	[redacted]
C	[redacted]	[redacted]	[redacted]				

High risk CVD (secondary prevention) (LDLc ≥3.36 mmol/L)

Base case

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	34,684	2.38	1.76	19,751
C	[redacted]	[redacted]	[redacted]				

High risk CVD (secondary prevention) (LDLc ≥3.36 mmol/L)

Scenario 1

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	2.38	1.76	[redacted]
C	[redacted]	[redacted]	[redacted]				

High risk CVD (secondary prevention) (LDLc ≥3.36 mmol/L)

Scenario 2

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	2.38	1.76	[redacted]
C	[redacted]	[redacted]	[redacted]				

High risk CVD (secondary prevention) (LDLc ≥3.36 mmol/L)

Scenario 3

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	2.38	1.76	[redacted]
C	[redacted]	[redacted]	[redacted]				

High risk CVD (secondary prevention) (LDLc ≥3.36 mmol/L)

Scenario 4

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	2.38	1.76	[redacted]
C	[redacted]	[redacted]	[redacted]				

High risk CVD (secondary prevention) (LDLc ≥3.36 mmol/L)

Scenario 5

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	2.38	1.76	[redacted]
C	[redacted]	[redacted]	[redacted]				

Recurrent events / polyvascular disease (LDL-C ≥2.59 mmol/L)

Base case

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	31,953	2.42	1.64	19,447
C	[redacted]	[redacted]	[redacted]				

Recurrent events / polyvascular disease (LDL-C ≥2.59 mmol/L)

Scenario 1

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	2.42	1.64	[redacted]
C	[redacted]	[redacted]	[redacted]				

Recurrent events / polyvascular disease (LDL-C ≥2.59 mmol/L)

Scenario 2

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	2.42	1.64	[redacted]
C	[redacted]	[redacted]	[redacted]				

Recurrent events / polyvascular disease (LDL-C ≥2.59 mmol/L)

Scenario 3

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	2.42	1.64	[redacted]
C	[redacted]	[redacted]	[redacted]				

Recurrent events / polyvascular disease (LDL-C ≥2.59 mmol/L)

Scenario 4

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	2.42	1.64	[redacted]
C	[redacted]	[redacted]	[redacted]				

Recurrent events / polyvascular disease (LDL-C ≥2.59 mmol/L)

Scenario 5

Arm	Total £	Total LYG	Total QALYs	Inc £	Inc LYG	Inc QALYs	ICER
A	[redacted]	[redacted]	[redacted]	[redacted]	2.42	1.64	[redacted]
C	[redacted]	[redacted]	[redacted]				

APPENDIX 3

Dr Adie Viljoen (Consultant Chemical Pathologist) has provided the following comment about PCSK9i use in primary care.

‘I would disagree with the statement that 'up to 90% of people' will be followed up in primary care. The reasons for this is that patients with FH are treated and followed up in lipid clinics in secondary care as referred to in NICE QS41 and CG71. Patients who have well documented intolerance to statins as referred to in NICE CG181 recommend specialist referral and these patients are subsequently managed in secondary care. Both these groups will be managed in secondary care because of the complexity of their lipid management and requirements for specialist risk assessment and intervention. These cohorts will potentially benefit from PCSK9 inhibition therapy.

I would venture that fewer than 10% would in fact be followed up in primary care even after several years of specialist management. An analogy in my mind would be rheumatology specialists using MoAb therapy.’

Aberdeen HTA Group

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Erratum

Completed 20 December 2015

This report was commissioned by
the NIHR HTA Programme as
project number **14/206/03**.

Contains CIC/AIC

This document is intended to replace pages 8, 21, 41, 45, 62, 79, 87, 122, 143, 146, 151 and 177 of the original ERG assessment report for *Alirocumab for treating primary hypercholesterolaemia and mixed hypercholesterolaemia*, which contained a few inaccuracies. The main issue relates to a model input error in the ERG's calculations behind two of the ICERs reported in Table 55 of the ERGs original report (page 151). These are additional scenario analyses (with rate ratios per 1.0 mmol/L, reduction taken from the CTT meta-analysis) for alirocumab versus ezetimibe in statin intolerant patients with HeFH (primary prevention) and HeFH (secondary prevention). This also had implications for text on page 146 of the report. In addition, we amended a number of further minor (typographical) errors identified in the report. The amended pages follow in order of page number below.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the submitted model to be of good quality and the structure is generally appropriate. Significant effort has gone into informing the model with real world risk data for relevant UK populations. Based on comparing survival from the model with published survival data for UK cohorts, there is good agreement with medium term survival expectations for the high risk CVD and recurrent CV events cohort, and particularly ACS cohorts. The utility weights incorporated in the model were coherent, from a single UK population based source. Appropriate age adjustment was conducted. The ERG has a number of concerns with some of the parameter estimates and base case assumptions applied in the model as detailed below:

- The model structure uses a composite event states for ACS which includes MI and unstable angina (UA). This makes it impossible to model different effects for MI and UA (see below)
- Two options were presented by the company for the secondary prevention HeFH analysis; one using CV risks estimated from analysis of THIN data, and the other using CV risk estimated from a previous published study. The composite annual baseline CV risk using the latter approach is more than twice as high. The ERG has been unable to verify which is more appropriate.
- Costs for the stroke and post-stroke health states appeared low and inconsistent with estimates based on UK population data and values applied in previous technology appraisals.
- Also related to the application of post-CV event costs, it appeared inconsistent with previous technology appraisals, that these should only be applied to 2 years following a CV event (as they were in the company's analysis), particularly for stroke which may result in long-term social care costs.
- The LDL-C threshold applied for the high risk CV cohort in the base case analysis appeared very restrictive, particularly given that statin + ezetimibe is a valid comparator in this population. The base case results for this cohort apply only to those with LDL-C $\geq$ 3.36 mmol/L on maximally tolerated statin. The ERG suspects that a very low proportion of patients in the wider high risk CVD population would meet these criteria. This raises a question over the relevance of the base case analysis for the high risk CVD population. Moreover, if alirocumab is being positioned as an adjunct to statin alone in

According to the Summary of Product Characteristics the usual starting dose for alirocumab (Praluent) is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg administered subcutaneously once every 2 weeks. The dose can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response.

Lipid levels can be assessed four weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dose adjusted accordingly (up-titration or down-titration). Patients should be treated with the lowest dose necessary to achieve the desired LDL-C reduction.

In all patients, it is anticipated that alirocumab will be used continuously once initiated.

Most common adverse reactions with alirocumab include local injection site reactions, upper respiratory tract signs and symptoms, and pruritus.Generic allergic reactions include pruritus, as well as rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis. If signs or symptoms of serious allergic reactions occur, treatment with alirocumab must be discontinued and appropriate symptomatic treatment initiated. Full details of adverse reactions and contraindications are given in the Summary of Product Characteristics.

The list price acquisition cost is £168 per one-pen pack and £336 per two two-pen pack (Table 5 of the company's submission). The company has recently agreed a patient access scheme with the Department of Health.

3.3 Comparators

The NICE final scope specified optimised statin therapy as a comparator, without any further qualifying criteria in terms of previous or current treatment or its effectiveness. The company did not consider this specific configuration of comparator. However, optimised statin therapy was one of two comparators specified by the company for people whose LDL-C was not adequately controlled with optimised (maximum tolerated dose) statin therapy. Both the NICE final scope and the company's

Study ID (trial acronym)	**Intervention**	**Number of patients**	**Study population (**LDL-C in mmol/L)	**Primary outcomes**	**Treatment duration**	**Funders**
	Placebo	107	*Mean LDL-C*: 2.646 (SD 0.820) *HeFH*: not reported *Mean age:* 63 (SD 9.3) *White race*: 258 (81.6%) *CHD:* 247 (78.2%) *CHD risk equivalents:* 136 (43.0%)			
Robinson 2015[69] (LONG TERM)	Alirocumab 150 mg (Q2W)	1553	LDL-C≥1.8 (70 mg/dL) with or without established CHD or CHD risk equivalents *Mean LDL-C*: 3.171(SD 1.092) *HeFH*: 415 (17.7%) *Mean age:* 60.5 (SD 10.4) (range 18-89) *White race*: 2171 (92.7%) *CHD:* 1607 (68.6%) *CHD risk equivalent:* 962 (41.1%)	% change in calculated LDL-C from baseline to week 24	78 weeks	Sanofi and Regeneron
	Placebo	788				
Alirocumab vs active agent						
Bays 2014 [39] (OPTIONS I)	Alirocumab 75-150 mg Q2W plus atorvastatin 20 mg QD	57	Prior CVD with LDL-C=1.8 (70 mg/dL) or CVD risk factors with LDL-C=2.6 (100 mg/dL); stable atorvastatin 20 or 40 mg/day *Mean LDL-C*: 2.723 (SD 0.884)	% change in calculated LDL-C from baseline to week 24	24 weeks	Sanofi and Regeneron
	Alirocumab 75-150 mg Q2W plus atorvastatin 40 mg QD	47				
	Ezetimibe 10 mg QD plus	55				

4.1.5 Critique of data extraction

The ERG considers the methods described in company's submission to be appropriate. Two reviewers independently selected studies and extracted data with any discrepancies resolved by discussion between the two reviewers. Any unresolved issues were adjudicated by a third reviewer.

4.1.6 Quality assessment

The quality of the relevant studies was assessed according to the Cochrane Collaboration's tool for assessing risk of bias of RCTs. The criteria involved assessment of selection bias, performance bias, detection bias, attrition bias, reporting bias and other potential biases. The number of reviewers involved in the quality assessment of the selected studies was not detailed in the submission.

The ERG conducted a broad assessment of the methods used by the company for the systematic review of clinical effectiveness evidence using the CRD criteria. Results are shown in Table 4.

Table 4 Quality assessment of the company's systematic review

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	No*
5. Are the primary studies summarised appropriately?	No*

*Only details of the 10 trials from the ODYSSEY programme are provided but not those of all studies identified by the literature searches

Inclusion/exclusion criteria relating to the primary studies which address the review question are clearly described in Appendix 6 of the company's submission. As highlighted in section 4.1.2, two systematic reviews - with two different sets of inclusion criteria - were conducted by the company: **Review 1** focused on patients at *high risk of CVD* and Review 2 focused on patients *at moderate to high risk of CVD*.

- Baseline Lp(a): various depending on trial (see Table 32, CS)
- Baseline total PCSK9 level: <median, ≥median
- Baseline free PCSK9 level: <median, ≥median

In general, the effect of alirocumab versus its comparators was consistent between subgroups. No further details are provided by the ERG.

Pooled-analysis

The company indicated they undertook some pre-specified pooled analysis for the following trials' populations:

- FH I and FH II for HeFH patients
- ALTERNATIVE and MONO for efficacy versus ezetimibe in patients not receiving statins
- OPTIONS I and OPTIONS II for alirocumab as add on to statin, ezetimibe as add on to statin and statin up titration.

The company indicated that each pooled analysis used individual patient data and results were presented for the primary endpoint and for key secondary efficacy endpoints.

In addition, the company undertook pooled analysis to look at two dosing regimens:

- Alirocumab 75 mg 2QW as initiation dose with potential up titration to 150 mg Q2W (FH I, FH I, COMBO I in combination with statins vs placebo; ALTERNATIVE, MONO without statins vs ezetimibe; COMBO II, OPTIONS I, OPTIONS II in combination with statins vs ezetimibe)
- Alirocumab 150 mg 2QW as initiation dose (LONG TERM, HIGH FH in combination with statins vs placebo).

The results of these various pooled analyses are shown in Table 17 for comparisons at 24 weeks.

appropriately applied to reflect the fact that, in reality, patients move continuously between states over time.

The ERG consider the company's model structure to be generally appropriate to the decision problem, and acknowledge the value of separating the post-event health states into three sub-states reflecting time since the event. One potential problem related to the use of a composite event state for ACS which includes MI and unstable angina (UA). This makes it impossible to model different treatment effects for MI and UA, which is problematic because the primary source of effectiveness data suggests different degrees of uncertainty for these effects. There are also a few limiting structural assumptions which may be conservative. One relates to the omission of TIA and stable angina (although the latter may be partially captured by elective revascularization), and the other relates to the fact that the model has limited capacity to capture multiple CV event histories in terms of their cumulative impact on costs and quality of life (due to the memoryless property of Markov models). For example, patients in the post-stroke state who experience an ACS event, then go on to attract the event costs that reflect average values following the ACS event, and not the expected costs for patients with a history of stroke and ACS. It is possible that these assumptions may somewhat underestimate QALY gains and downstream cost savings associated with more effective treatments. One issue which has the potential to bias in favour of alirocumab is the omission of any treatment emergent adverse event (TEAE) states. The available safety data suggests no significant difference in the percentage of patients experiencing any TEAE, although it does indicate an incidence of injection site reactions of 6 per 100 patient years in the pooled alirocumab data (Table 48 of the company's submission). Whilst the severity of these was reported as generally mild and transient, it is unclear what the cost implications were. It is perhaps reasonable to assume that these would require at most a GP visit and so would be unlikely to have significant impact on cost-effectiveness. General allergic events were also more commonly reported for alirocumab (primarily pruritis), but pooled incidence was low (0.8-1.1%) and severity typically mild.

The two HeFH populations (primary and secondary prevention) are modelled individually, while the high risk CVD population consists of a mixed cohort based on the distribution CV event histories observed in the THIN database. Table 23 presents the relevant proportional distribution. The effect of alirocumab treatment is assumed to be independent of patients' baseline characteristics in the model, i.e. homogenous treatment effects are applied.

Table 23 High risk CVD cohort proportions by patient types (Source: Table 59 of the company's submission)

ACS ≤12 months prior to index	3.28%
ACS 12–24 months prior to index	2.83%
Ischaemic Stroke	11.05%
Other CHD	68.55%
PAD	14.29%

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; IS, ischaemic stroke; PAD, peripheral arterial disease

5.2.4 Interventions and comparators

The intervention - alirocumab alone or in combination with a statin, with or without ezetimibe, or in combination with ezetimibe – is in line with the final scope. Alirocumab in the company's submission is considered in line with its marketing license - "*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 statin (when used as recommended by treatment guidelines); or alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated*" - for patients with primary hypercholesterolaemia who are failing to reach LDL-C goals. The company's submission states that it was assumed that in clinical practice alirocumab will only be prescribed in high risk, high unmet need patients, and will be supported by a homecare delivery service and patient support programme. In the main analyses, alirocumab is modelled as adjunctive treatment for those whose LDL-C is not adequately controlled on statin (+/-) ezetimibe, or ezetimibe alone in those who are intolerant to statins. However, in line with the scope, the company also presents an additional set of comparisons where alirocumab is compared directly against ezetimibe; i.e. as an alternative to ezetimibe

clinical outcomes were presented for each strategy. Total QALYs accrued in the different health states were also summarised for the alirocumab and comparator arms.

The company's estimated base case results are replicated for each patient population in Table 38.

The base case analyses for HeFH are provided for cohorts aged 50 (primary prevention) and 60 (secondary prevention), LDL-C ≥ 2.59 mmol/L (mean LDL-C = 4.82 mmol/L for primary prevention, 4.56 for secondary prevention), 50% male. For alirocumab used as an add-on to current maximal LMT (maximal dose of statins combined with ezetimibe) the ICER is £36,793 in the primary prevention HeFH population. For the secondary prevention HeFH cohort, the estimated ICER is £16,896 based on CV risks data from Morschladt et al.97.

The base case analysis for high risk CVD is conducted for a cohort aged 65 years, 60% male, LDL-C ≥ 3.36 mmol/L. The recurrent events/ polyvascular disease cohort has the same characteristics, except an LDL-C threshold of 2.59 mmol/L is applied (mean = 3.31 mmol/L).

For the high risk CVD cohort, the estimated ICER for alirocumab as an add-on to maximal statin treatment is £19,751. For the cohort with recurrent events/ polyvascular disease, the corresponding ICER is £19,447.

5.2.11 Model validation and face validity check

The company's submission describes how three advisory boards were held as part of the model development process. Additional consultation was sought from clinical experts and health economists to inform key parameters. The company assessed the internal validity of the model using extreme value checks, Markov traces and tracing of the estimated QALYs and costs over time. Structural sensitivity analyses were performed, as were deterministic and probabilistic sensitivity analysis, to assess the impact of changes on results.

In terms of the model face validity, the ERG believes that the structure of the model and the possible transitions are plausible. The ERG has performed internal consistency checks on the model and have identified no internal programming errors. The ERG can replicate all the company's results. An appropriate UK primary care database was used by the company to inform the model parameters in terms of baseline CV event rates. However the estimated CV events rates were not estimated from subpopulations with characteristics (i.e. baseline LDL-C and age) exactly matching those of the modelled cohorts, but were rather calibrated to the selected model age and LDL-C levels using published statistical relationships. In light of data limitations, this does seem reasonable. The baseline LDL-C adjustments in have been applied using a well-accepted relationship[31 32 99 100] between statin induced reduction in LDL-C and CV event rates. The ERG had some concerns relating to the inflation of subsequent events following recurrent ACS and ischaemic stroke, but have performed sensitivity analysis the results are not heavily influenced by this parameter. It also seems reasonably well justified to inflate these risks in the model.

The company did not assess the external or cross validity of their model. Since the company had access to THIN data, it might have been possible to generate longer-term survival curves of time to CV events, and then cross checked these against those predicted by their model over equivalent time horizons. The ERG has cross checked the composite baseline probabilities of CV events for the modelled high risk CVD population, and these do appear to be generally consistent with those used to represent baseline (of treatment) risks in previous models.[29] Given that the modelled patient populations represent those who have high baseline LDL-C despite current LMT, it doesn't seem unreasonable that they should have similar risks to the mean off-

prevention (Table 50). Finally, given the uncertainty surrounding the relationship between LDL-C reductions achieved with alirocumab and proportional CV event rates, we present a further more conservative scenario analysis with the updated model for each comparison; here we model all the effects for alirocumab through the estimated relationships from the CTT meta-analysis (as per one of the company's scenario analysis).

5.3.1 The ERG updated base case and scenario analysis (deterministic)

The following Tables present the company's base case ICERs (Table 50) and then the ERGs updated base case; incorporating points 1-7 above with the company's preferred approach of scaling the hazard ratios from Navarese et al.[82] (Table 51). The results in Table 52 then present the more conservative scenario using the CTT meta-analysis to model all effects of alirocumab on CV events. Tables 53 to 55 then present the corresponding ICERs for statin intolerant patients.

With the ERGs updated base case, the ICERs are remain very similar to the company's base case ICERs (Tables 51). As an add-on to optimal statin therapy (+/- ezetimibe), they are below £20,000 in the HeFH secondary prevention, high risk CVD, and recurrent CVD/polyvascular disease populations. The ICER remains above £30,000 in the HeFH primary prevention population (Table51). The ICERs also remain below £20,000 for the statin intolerant CVD cohorts (Table 54).

Consistent with the company's scenario analysis, using the CTT to model the effects of alirocumab on CV event rates raises the ICERs above £30,000 for alirocumab as an adjunctive to maximally tolerated statin therapy (Table 52) - although the ICER in the HeFH secondary prevention cohort is close to £30,000 (£33,339) using the risk data from Morschladt et al. Using the CTT approach for statin intolerant patients, the ICERs are slightly above £30,000 in the high CV risk, and the recurrent CVD/polyvascular disease populations (Table 55). Note the ICERs for the statin intolerant HeFH populations are based on the ERGs assumption of a baseline LDL-C of 5.8 (assumed 20% reduction from the baseline value of 7.27 reported by Morschladt et al.)

Table 55 The ERG additional scenario analysis results (with rate ratio per 1.0 mmol/L reduction from CTT meta-analysis) – *statin intolerant patients*

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L) *	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	22,228	0.51	0.49	45,786
	Ezetimibe	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from Morschladt et al. *	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	17,332	0.91	0.79	22,042
	Ezetimibe	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from THIN*	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	18,329	0.87	0.71	25,869
	Ezetimibe	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L) **	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	17,721	0.64	0.51	34,600
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L) ***	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	16,400	0.66	0.49	33,519
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year
*Mean baseline LDL-C=5.8 mmol/L; **Mean baseline LDL-C=4.55 mmol/L; *** Mean baseline LDL-C=4 mmol/

There was no evidence of differences between groups in the rates of adverse events or mortality.

The ERG considered that the company's systematic reviews of clinical evidence were broadly adequate.

With regard to the economic model, the ERG considers it to be of good quality and in general appropriately structured. The one main structural concern relates to the use of a composite event state for ACS which includes MI and unstable angina (UA). This makes it impossible to model different effects for MI and UA. Significant effort has gone into informing the model with real world risk data for relevant UK populations – although this has to be recalibrated to the age and LDL-C levels of the modelled populations. Based on comparing survival from the model with published survival data for UK cohorts, there is good agreement with medium term survival expectations for the high risk CVD and recurrent CV events cohort, and particularly ACS cohorts. The utility weights incorporated in the model were coherent, from a single UK population based source. Whilst the ERG had a number of concerns with some of the parameter estimates and base case assumptions, one of these in particular appeared to have critical impact on the estimated base case ICERs: the method used to extrapolate LDL-C reductions mediated through PCSK9 inhibitors to relative reductions in CV event rates.

6.1 Implications for research

There is extensive research already ongoing related to PCSK9 inhibitors, and outcome data are awaited from this. In particular, the results of the CVOT ongoing trial, which are due to be reported in January 2018, will provide useful information on the effect of alirocumab on CV events. Nevertheless, given the novelty of PCSK9 inhibitors and consequent treatments aimed at them, 'off target' effects will be particularly important to collate. There is also a need to further assess the cost-effectiveness of alirocumab, both as monotherapy and in combination, in a variety of potential relevant patient groups, when the results of CV outcome trials become available (e.g. familial dyslipidaemias, existing cardiovascular disease).

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

ADDENDUM to the ERG report

ERG's critique of the company's additional PAS ICERs and additional sensitivity analyses on potential non-PAS prescribing in primary care

Produced by Aberdeen HTA Group

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Date completed 6 January 2016

Contains CIC/AIC

This addendum to the ERG evaluation report provides:

i) the ERG's commentary on an updated PAS submission that was received on 03/12/15 (ID779 Alirocumab Sanofi PAS submisson v0.3 011215 JE [CIC]) after submission of the ERG report. The results of these further analyses are discussed in section A of this addendum;

ii) a critique of the additional sensitivity analyses provided by the company in response to NICE's request, which address the uncertainty relating to the availability of the agreed PAS discount for patients prescribed alirocumab using an FP10 form in a primary care setting. The results of these further sensitivity analyses are presented in section B of this addendum.

SECTION A: Additional PAS analyses submitted by the company

The ERG has checked all the additional PAS analyses submitted by the company and noted that most of these had already been provided by the company or replicated in the original ERG report. However, for completeness, all the company's PAS ICERs are reproduced in this addendum.

Company base case analyses with PAS

First of all, the company presented their updated base case results, for alicorumab as an add-on to maximally tolerated lipid lowering therapy. These are reproduced in Table 1 below. The ERG was able to replicate all of these results. The analysis for the HeFH secondary prevention cohort, using the THIN data to inform baseline risks, was the only ICER that was not presented in the original PAS submission. This shows the ICER to be somewhat higher (£19,060 per QALY) as compared with the ICER using the alternative source of baseline risk data reported by Mohrschladt et al. (ICER = £16,896 per QALY). This is as expected, as the baselines risks are substantially higher when using the Mohrschladt et al. data. This has been commented on the ERG's original report.

Secondly, the company provided updated base case ICERs for alirocumab as an add-on to statin compared directly with ezetimibe as an add-on to statin. These were not provided in the company's original PAS submission, and are reproduced in Table 2. The ERG can also replicate all these analyses. They show that when alirocumab is considered for patients inadequately controlled on statin alone, with ezetimibe as the active comparator, the ICERs are somewhat less favorable - ranging from £20,352 per QALY (HEFH secondary prevention) to £48,193 per QALY (HeFH primary prevention). Note, the company has only presented the HeFH secondary prevention ICER using the baseline risk data from Morschladt et al. The ICER is £23,234 using the THIN data for the baseline CV risks (Table 2b).

Table 3 shows the results of the company analyses for alirocumab as an add-on to ezetimibe, and versus ezetimibe, for those above the respective LDL-C thresholds who are intolerant to statins. Applying the company's inputs for the recurrent CVD/polyvascular disease population intolerant to statins (i.e. mean LDL-C = 4 mmol/L), the ERG get an ICER of £15,853 (Table 3b) rather than the £13,669 reported by the company (Table 3). The ERG believe the company may have inadvertently set the baseline LDL-C to 4.55 mmol/L for this

comparison, which does not match the value for the recurrent CVD/polyvascular disease population with an LDL-C ≥ 2.59 mmol/L in their submission. The ERG was able to replicate the alirocumab monotherapy versus ezetimibe monotherapy comparisons for the high risk CVD and the recurrent CVD/polyvascular disease populations, applying baseline LDL-C levels of 4.95 mmol/L and 4.94 mmol/L respectively. The company's submission indicates that the baseline LDL-C level following the washout period in the ALTERNATIVE trial (i.e. off-treatment) can be used for these head-to-head comparisons. This is stated to be ~4.95 mmol/L.

Table 1 Company's incremental cost-effectiveness results (versus background LLT) – Base cases with Patient Access Scheme

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	52,256	1.62	1.42	36,793
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	39,306	3.04	2.33	16,896
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from THIN*	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	40,733	2.85	2.14	19,060
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	34,684	2.38	1.76	19,751
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	31,953	2.42	1.64	19,447
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				

LLT: lipid lowering therapy; CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 2 Company's incremental cost-effectiveness results (versus ezetimibe) – Base cases with Patient Access Scheme

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	45,962	1.07	0.95	48,193
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + statins	[redacted]	[redacted]	[redacted]	34,632	2.21	1.70	20,352
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
High-risk CVD (baseline LDL-C ≥3.36 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	31,195	1.75	1.29	24,175
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	28,781	1.83	1.25	23,078
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 2b Incremental cost-effectiveness results (versus ezetimibe) for the HeFH secondary prevention cohort (baseline LDL-C ≥2.59 mmol/L) using the THIN data to inform baseline CV risks – Base case with Patient Access Scheme (results produced by the ERG using the company's base case assumptions)

Sub Ref	Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
	HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L) *Baseline risk data from THIN*	Alirocumab + statins	[redacted]	[redacted]	[redacted]	35,806	2.05	1.54	23,234
		Ezetimibe + statins	[redacted]	[redacted]	[redacted]				

Table 3 Company's incremental cost-effectiveness results (versus background LLT) - Base cases with Patient Access Scheme

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
STATIN INTOLERANT								
High-risk CVD (baseline LDL-C ≥3.36mmol/L)	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	35,146	2.76	2.04	17,256
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	32,798	3.52	2.40	13,669
	Ezetimibe	[redacted]	[redacted]	[redacted]				
High-risk CVD (baseline LDL-C ≥3.36 mmol/L)	Alirocumab	[redacted]	[redacted]	[redacted]	30,829	2.40	1.78	17,295
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab	[redacted]	[redacted]	[redacted]	28,820	3.12	2.14	13,469
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 3b Incremental cost-effectiveness results for the recurrent events/polyvascular disease population (baseline LDL-C ≥2.59 mmol/L) - Base cases with Patient Access Scheme (ERG's re-analysis)

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
STATIN INTOLERANT								
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	32,719	3.03	2.06	15,853
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeF H: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Company subgroup analysis with agreed PAS

The company provided subgroup analyses with the agreed PAS by baseline LDL-C level, and these are presented in Table 4 below. The ERG had already replicated and commented on these analyses in their original report (Table 40), and all the ICERs are matched exactly. They are presented below for completeness.

Table 4 Subgroup analyses by LDL-C levels with PAS

Patient population	Baseline LDL-C threshold (mmol/L)	Incremental costs £	Incremental QALY	ICER
HeFH primary prevention	2.59	52,256	1.42	36,793
	3.36	52,005	1.64	31,750
	4.13	51,804	1.79	28,923
HeFH secondary prevention	2.59	39,306	2.33	16,896
	3.36	39,224	2.48	15,838
	4.13	39,023	2.74	14,242
High Risk CVD	2.59	34,701	1.37	25,287
	3.36	34,684	1.76	19,751
	4.13	34,493	2.15	16,043
Recurrent events / Polyvascular disease	2.59	31,953	1.64	19,447
	3.36	32,085	2.09	15,332
	4.13	32,013	2.54	12,606

HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life-year

Company sensitivity analyses with agreed PAS

The company had already provided the following tables (Tables 5-8) in their original PAS submission, which the ERG had access during the course of this technology appraisal. These tables have already been considered and reproduced in the original ERG's report (Tables 42-45). They are reproduced below for completeness.

Table 5 HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe deterministic sensitivity analysis with PAS

Parameter	Variation	ICER (£/QALY)
Base case with PAS		**36,793**
Annual CV risk	–20%	47,504
Annual CV risk	+20%	30,047
Adjustment of CV risk by age	–20%	37,023
Adjustment of CV risk by age	+20%	36,428
CV costs	–20%	37,094
CV costs	+20%	36,492
CV event costs	Doubled	35,287
Alirocumab efficacy (LDL-C lowering)	Lower CI	38,146
Alirocumab efficacy (LDL-C lowering)	Upper CI	35,659
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	33,828
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	39,413
Rate ratio per 1 mmol/L for treatment effect	Lower CI	29,787
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	36,448
Acute CV disutilities	Upper CI	37,144
Baseline utilities	Lower CI	36,793
Baseline utilities	Upper CI	36,793
Chronic CV disutilities	Lower CI	35,751
Chronic CV disutilities	Upper CI	37,897

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio

Table 6 HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe - deterministic sensitivity analysis with PAS

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**16,896**
Annual CV risk	–20%	20,018
Annual CV risk	+20%	14,806
Adjustment of CV risk by age	–20%	16,932
Adjustment of CV risk by age	+20%	16,919
CV costs	–20%	17,192
CV costs	+20%	16,600
CV event costs	Doubled	15,416
Alirocumab efficacy (LDL-C lowering)	Lower CI	17,690
Alirocumab efficacy (LDL-C lowering)	Upper CI	16,222
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	16,020
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	17,622
Rate ratio per 1 mmol/L for treatment effect	Lower CI	12,477
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	16,756
Acute CV disutilities	Upper CI	17,038
Baseline utilities	Lower CI	17,574
Baseline utilities	Upper CI	16,268
Chronic CV disutilities	Lower CI	16,722
Chronic CV disutilities	Upper CI	17,074

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia;

ICER, incremental cost-effectiveness ratio;

Table 7 High risk CVD, alirocumab + statins versus statins - deterministic sensitivity analysis with PAS

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**19,751**
Annual CV risk	–20%	23,910
Annual CV risk	+20%	17,009
Adjustment of CV risk by age	–20%	19,710
Adjustment of CV risk by age	+20%	19,784
CV costs	–20%	19,979
CV costs	+20%	19,522
CV event costs (doubled)		18,608
Alirocumab efficacy (LDL-C lowering)	Lower CI	20,600
Alirocumab efficacy (LDL-C lowering)	Upper CI	19,021
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	18,650
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	20,689
Rate ratio per 1 mmol/L for treatment effect	Lower CI	14,518
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	19,621
Acute CV disutilities	Upper CI	19,882
Baseline utilities	Lower CI	20,549
Baseline utilities	Upper CI	19,012
Chronic CV disutilities	Lower CI	19,578
Chronic CV disutilities	Upper CI	19,926

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio

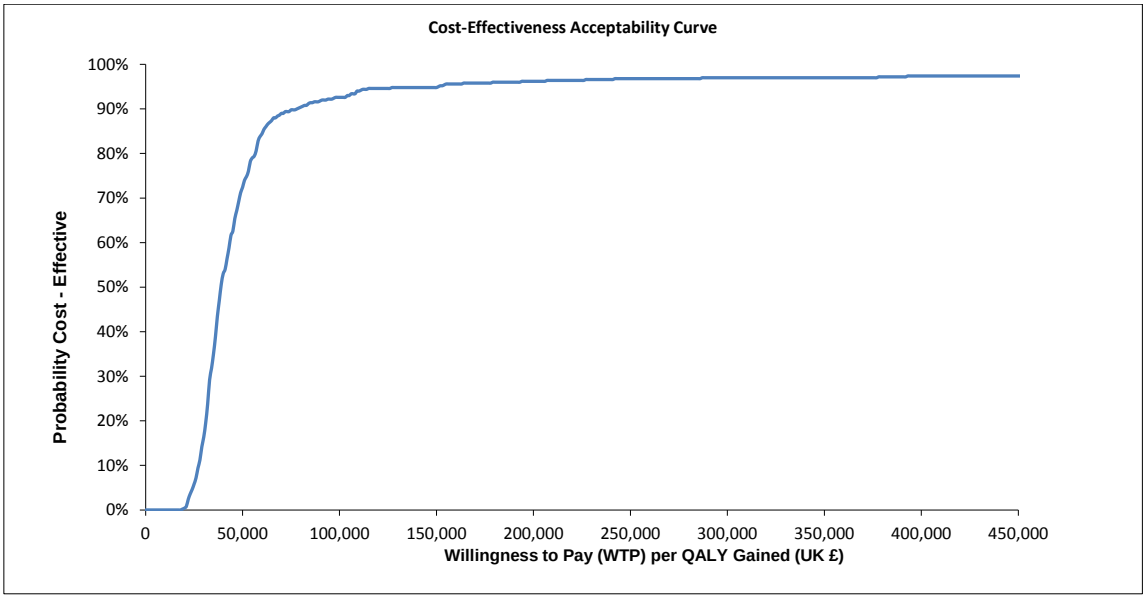
Table 8 Recurrent events/ polyvascular, alirocumab + statins versus statins - deterministic sensitivity analysis with PAS

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**19,447**
Annual CV risk	–20%	22,901
Annual CV risk	+20%	17,153
Adjustment of CV risk by age	–20%	18,799
Adjustment of CV risk by age	+20%	20,096
CV costs	–20%	19,649
CV costs	+20%	19,245
CV event costs	Doubled	18,435
Alirocumab efficacy (LDL-C lowering)	Lower CI	20,623
Alirocumab efficacy (LDL-C lowering)	Upper CI	18,460
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	18,919
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	19,872
Rate ratio per 1 mmol/L for treatment effect	Lower CI	13,268
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Domniated
Acute CV disutilities	Lower CI	19,331
Acute CV disutilities	Upper CI	19,564
Baseline utilities	Lower CI	20,585
Baseline utilities	Upper CI	18,429
Chronic CV disutilities	Lower CI	19,358
Chronic CV disutilities	Upper CI	19,537

CI, confidence interval; CV, cardiovascular; ICER, incremental cost-effectiveness ratio

Company probabilistic sensitivity analysis with agreed PAS

In their original PAS submission, the company had already provided scatter plots and acceptability curves summarising the results of their base case probabilistic analyses with the agreed PAS. These analyses have already been reproduced and commented on as Figures 4-7 in the original ERG's report. They are reproduced below for completeness. Table 9 shows the corresponding probabilities of cost-effectiveness for the respective patient populations at different levels of willingness-to-pay per QALY gained (£20, £30 and £40k). These were not provided in the original PAS submission.



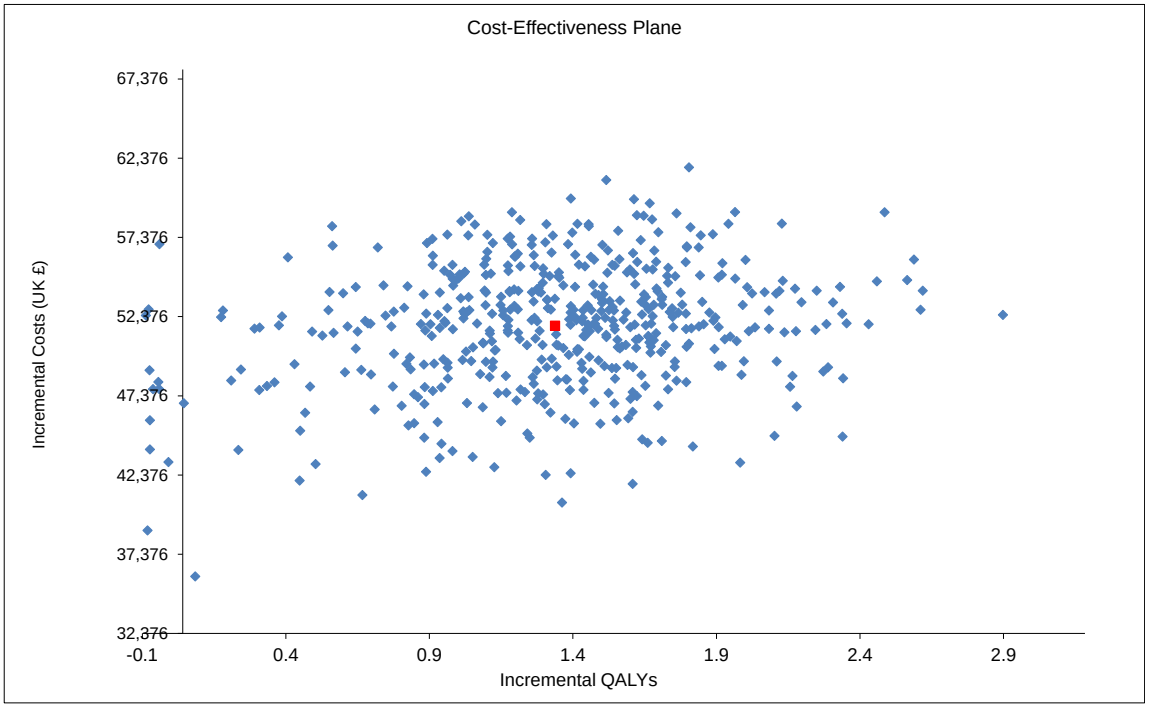


Figure 1 HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe - scatter plot and CEAC

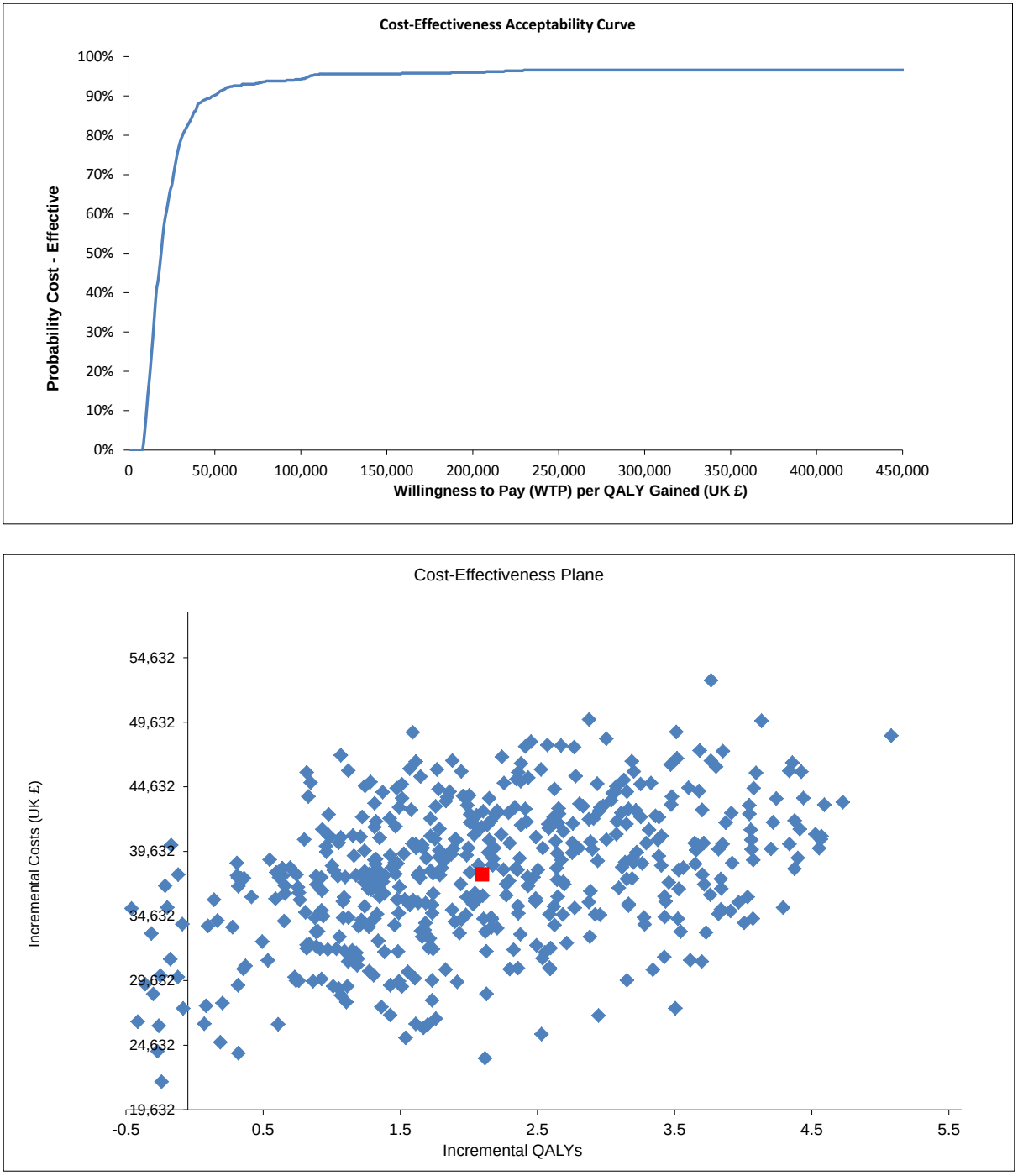
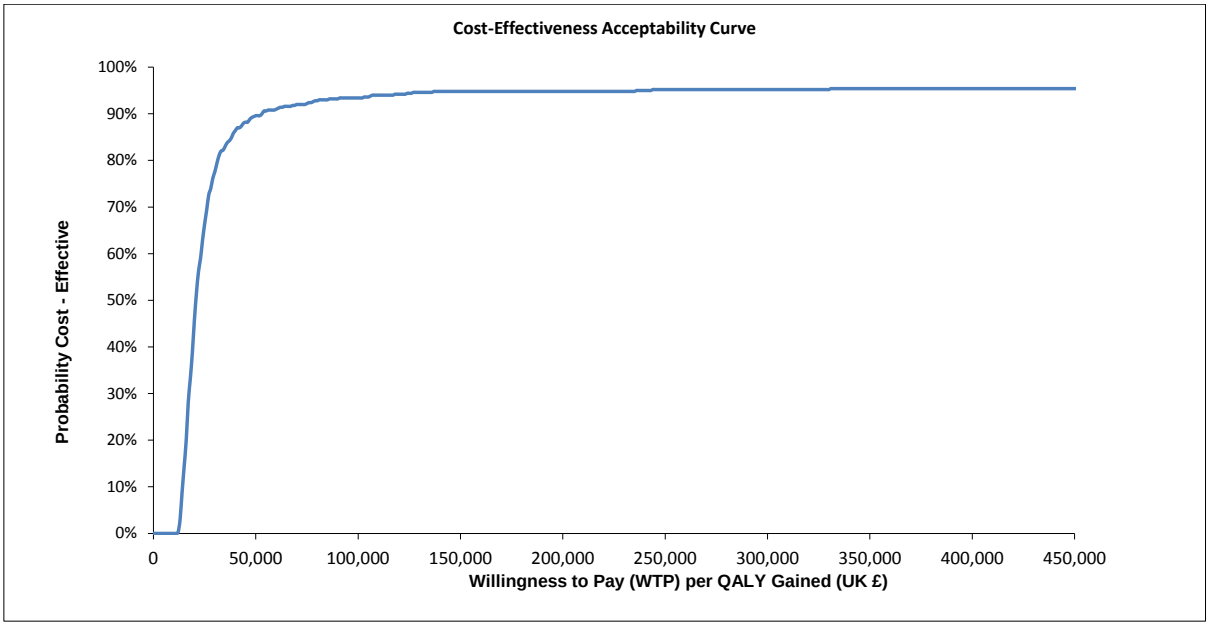


Figure 2 HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe - scatter plot and CEAC



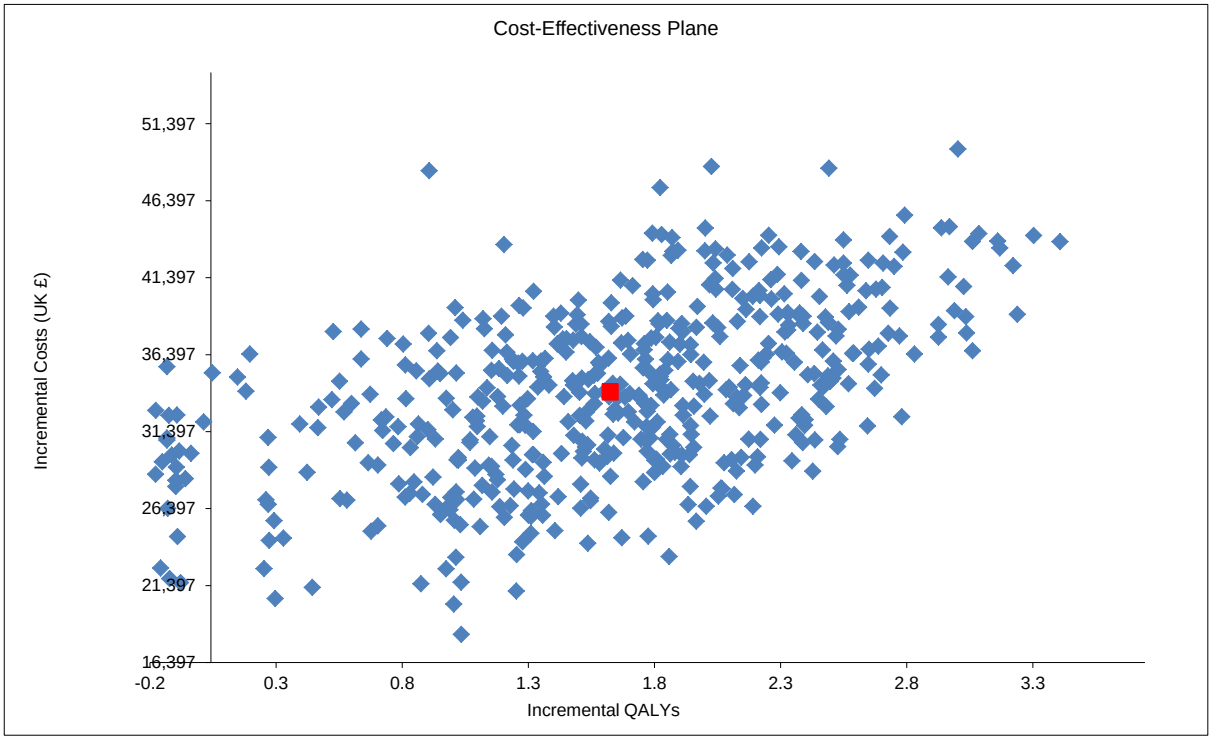
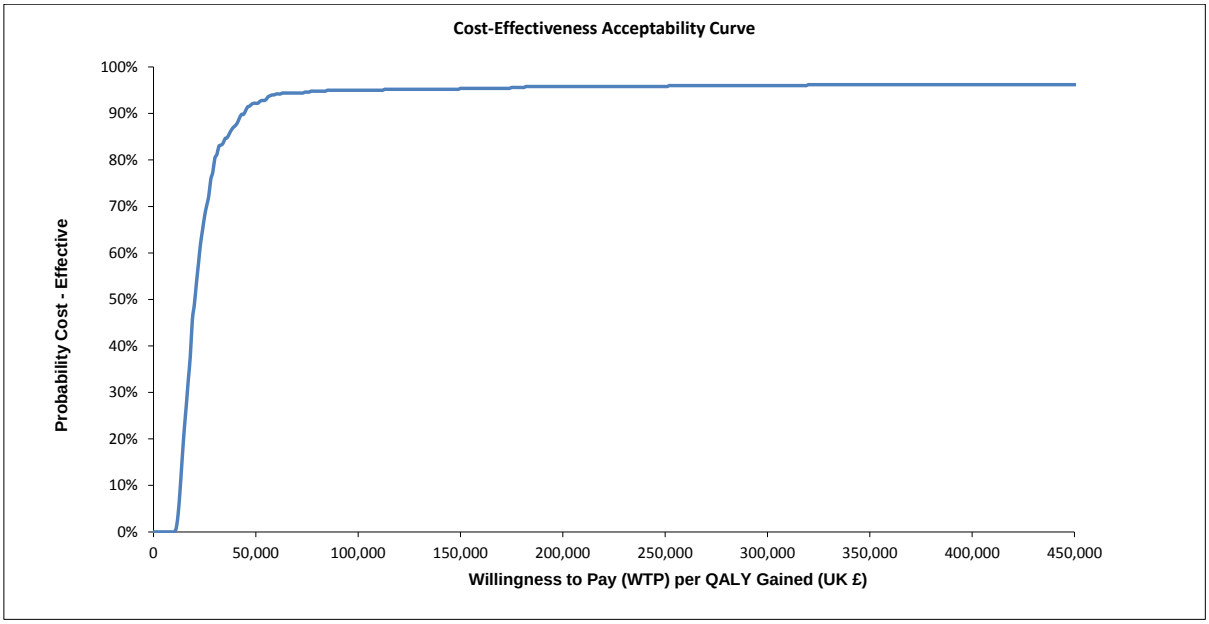


Figure 3 High Risk CVD, alirocumab + statins versus statins - scatter plot and CEAC



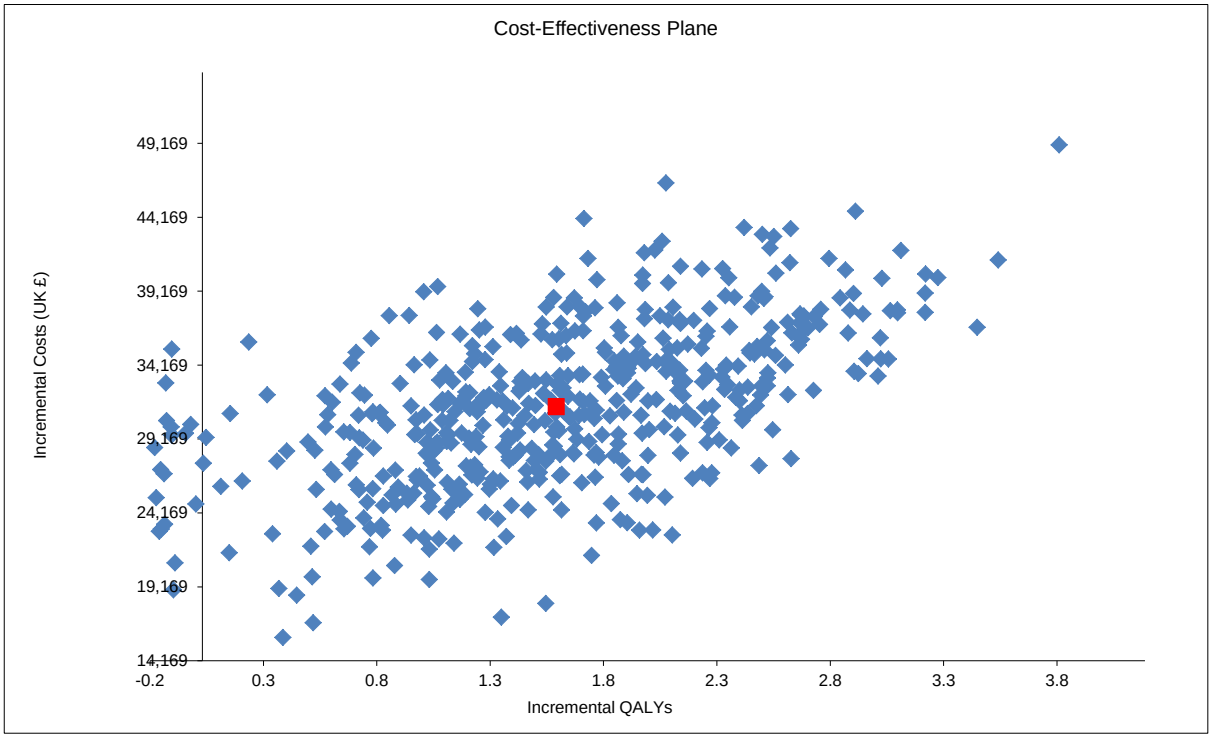


Figure 4 Recurrent events/ Polyvascular disease, alirocumab + statins versus statins - scatter plot and CEAC

Table 9 Probability of cost-effectiveness by Willingness to Pay for key patient groups – with Patient Access Scheme

	HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	High-risk CVD (baseline LDL-C ≥3.36 mmol/L) – alirocumab + statins versus statins	Recurrent events/ polyvascular disease (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins versus statins
Willingness to pay	**Probability of cost-effectiveness**			
20,000/QALY	15%	56%	46%	49%
30,000/QALY	36%	79%	78%	80%
40,000/QALY	51%	88%	86%	87%

CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; QALY, quality-adjusted life-year

Company scenario analysis with agreed PAS

The company had already provided the following tables (Table 1-4), which summarise the results of scenario analyses in their original PAS submission. These analyses have already been reproduced and commented on as Tables 46-49 in the original ERG's report. They are reproduced below for completeness.

Table 10 HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe - scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with PAS**			**36,793**
Discontinuation rate	0%	3%	38,168
		8%	41,852
Cost and benefit discount rates	3.50%	0%	24,821
		5%	43,533
Treatment duration	Lifetime	1 year	50,197
		5 years	47,326
Model time horizon	Lifetime	5 years	398,895
		10 years	197,133
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	60,736
		LONG TERM study	40,929
		Pooled phase III vs placebo	52,476
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	37,592
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	28,679
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	39,235
		100% use of 150 mg	35,954

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non fatal; QALY, quality-adjusted life-year

Table 8 HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe - scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			**16,896**
Baseline risk data	As per Mohrschladt 2004	As per THIN	19,060
Discontinuation rate	0%	3%	17,264
		8%	17,949
Cost and benefit discount rates	3.5%	0%	13,984
		5%	18,306
Treatment duration	Lifetime	1 year	18,863
		5 years	18,102
Model time horizon	Lifetime	5 years	64,199
		10 years	36,856
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	32,937
		LONG TERM study	19,294
		Pooled phase III vs placebo	25,741
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	16,734
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	13,347
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	18,259
		100% use of 150 mg	16,348

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; HSE; Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non-fatal

Table 9 High Risk CVD, alirocumab + statins versus statins – scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			19,751
Discontinuation rate	0%	3%	19,979
		8%	20,601
Cost and benefit discount rates	3.5%	0%	16,181
		5%	21,472
Treatment duration	Lifetime	1 year	20,148
		5 years	20,660
Model time horizon	Lifetime	5 years	85,694
		10 years	44,495
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	41,431
		LONG TERM study	22,578
		Pooled phase III vs placebo	30,218
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	19,654
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	15,761
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	21,571
		100% use of 150 mg	18,781

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; CVD, cardiovascular disease; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P-NF, post-non-fatal

Table 10 Recurrent events/ polyvascular disease, alirocumab + statins versus statins – scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			**19,447**
Discontinuation rate	0%	3%	19,738
		8%	20,353
Cost and benefit discount rates	3.5%	0%	16,317
		5%	20,931
Treatment duration	Lifetime	1 year	20,869
		5 years	20,222
Model time horizon	Lifetime	5 years	72,896
		10 years	38,468
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	44,154
		LONG TERM study	22,651
		Pooled phase III vs placebo	31,181
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	19,336
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	15,968
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	20,969
		100% use of 150 mg	17,915

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P -NF, post-non-fatal

How the agreed PAS affects the ICERs

Finally, the company provided a table in their PAS submission illustrating how the agreed PAS affects the ICERs for the key base case analyses - for alirocumab as add on to maximally tolerated statin (+/- ezetimibe). This is reproduced as Table 11 below. Please note that the PAS was agreed prior to the ERG's report submission. Therefore, all analyses presented and discussed in the ERG's original report are based on the agreed PAS price for alirocumab.

In brief, the ERG was able to replicate all of the company's PAS ICERs using the stated parameter inputs, apart from one minor discrepancy for those with recurrent

CVD/polyvascular (LDL-C ≥ 2.59 mmol/L) disease who are statin intolerant (Alirocumab+ezetimibe versus ezetimibe). This appears to be explained by a simple input error for the baseline LDL-C value (4.55 mmol/L instead of 4 mmol/L) in the company's analysis (see Table 3 and Table3b above).

Table 11 Results showing the impact of patient access scheme on ICERs

	ICERs							
	HeFH Primary Prevention Alirocumab + statins + ezetimibe versus statins + ezetimibe		HeFH Secondary Prevention Alirocumab + statins + ezetimibe versus statins + ezetimibe		High Risk CVD Alirocumab + statins + versus statins + ezetimibe		Recurrent events/ polyvascular disease Alirocumab + statins + versus statins + ezetimibe	
	Without PAS	With PAS	Without PAS	With PAS	Without PAS	With PAS	Without PAS	With PAS
Basecases	[redacted]	£36,793	[redacted]	£16,896	[redacted]	£19,751	[redacted]	£19,447

PAS: patient access scheme

SECTION B: Additional requested sensitivity analyses surrounding the PAS

NICE request for additional sensitivity analysis

Following submission of the ERG's original report, NICE invited the company to submit additional sensitivity analyses to assess the potential impact of the PAS discount for alirocumab not being available when prescribed by a general practitioner using and FP10 form. The Department of Health's PAS approval letter, in fact, stated that: '*…alirocumab will initially be used in specialist secondary care clinics. However, as routine lipid management is an area of standard GP practice, it was noted that there may be a potential transition of patients from secondary to primary care after 2 to 3 years. This has potential implications for the proposed simple discount patient access scheme. As simple discounts cannot be realised when drugs are prescribed through FP10 prescriptions, the actual discount received by the NHS may be less than the percentage discount offered in the scheme.*'

In the company's PAS submission, all patients were assumed to remain under specialist secondary care management, with a sponsored home care service used to deliver medication to patients. Consequently, in the economic model the simple discount PAS was applied to all patients prescribed alirocumab. NICE invited the company to submit additional sensitivity analyses to vary:

i) the proportion of patients who transition from secondary care to primary care and'
ii) the time spent in secondary care before patients move to primary care

NICE specified that the PAS price should only be applied to patients who are prescribed alirocumab through secondary care, that sensitivity analyses should be undertaken for each of the populations in the model, and that justification should be provided for the inputs used.

Company's response to the request for additional sensitivity analysis

In response to NICE's request, the company maintained that FP10 prescribing is very unlikely for alirocumab and offered the following justifications:

1) The populations for which approval is being sought are those with HeFH and high risk CVD (i.e. secondary prevention and/or recurrent events), including

those with statin intolerance, who cannot achieve optimal LDL-C levels on current maximally tolerated routine lipid management therapies (LMTs). These are patients that require specialist support beyond the routine lipid management services provided by their primary care team.

2) Such high risk patients should be referred by GPs to expert lipid specialists, based in hospitals or in specialist lipid clinics, as indicated by the NICE's FH Guideline and Commissioning recommendations.
3) Alirocumab is listed on the high cost drugs exclusion list proposed for 2016/17 and is expected to be funded outside the national tariff. Hospitals will be able to prescribe alirocumab as part of CCG commissioned services and will recover the cost via the high cost drugs
4) The company understands, from their ongoing meetings with CCGs that Commissioners are seeking to limit the use of alirocumab within primary care, aligning their pathways to the most effective care for patients and most efficient funding mechanism, namely commissioned services from speciality care/hospitals only.
5) The majority of a sample of GPs, when surveyed by Adelphi Research in July 2015 (survey sponsored by the company), stated that they were '*extremely unlikely*' to prescribe a self-injected sub-cutaneous treatment for hypercholesteremia, even if a pre-filled pen device was available.

6) The company has in place arrangements for the supply of alirocumab to the NHS in England via two routes:
   a) directly to hospital pharmacies, and
   b) via approved homecare companies.

The company went on to note that this specialty care supply model is already operating effectively for alirocumab in several EU countries and in the US and it is their view that "*it is the most appropriate specialty care supply model for England*". For this reason, the company has no arrangements in place for the supply of alirocumab into primary care pharmacies in England.

The company, however, do also state that they *"…recognise that a situation could exist - however unlikely for alirocumab - in circumstances where FP10 prescriptions*

are written, CCGs may not want to buy a medicine at a net price equivalent to the PAS discounted price, for example via a primary care rebate scheme." They, therefore, provided the requested sensitivity analyses for the committee's consideration.

Company's implementation of the requested sensitivity analyses

The company made a number of simple adjustments to the economic model, which allows the user to specify and vary three additional input parameters: i) the minimum number of years following initiation of alirocumab treatment before any switching to primary care takes place; ii) the maximum percentage of patients who will move from secondary to primary care; and iii) the time in years by which the maximum percentage of patients will have transitioned to primary care. Simple linear interpolation is used to model growth in the percentage of patients transferred to primary care (on non-PAS prescribing) up to the defined maximum level, at the defined time point by which the maximum is reached. Alirocumab treatment costs in the model then become a weighted average of the PAS and non-PAS prices based on the modelled proportions in secondary and primary care.

The company provided results for five different scenarios, where the maximum percentage of patients transiting to primary care was varied between [redacted] and [redacted] and the time by which the maximum percentage is reached was set to 5 years. All patients were assumed to remain in secondary care for the first two years for all scenarios.

To inform the maximum percentage of patients that may transit to primary care, the company reviewed IMS sales data for a selection of 'analogue' medicines. These included monoclonal antibodies used in rheumatoid arthritis (RA), omalizumab (Xolair™), and denosumab (Prolia™). The company noted that these are *"NICE-approved medicines - subject to various PAS arrangements - used in conditions that until severity determines that specialist referral and management is needed, are typically managed in primary care."* The company estimated primary care (retail) and secondary care (hospital) sales volume using data from the combined IMS XBPI/HPAI datasets, held by IMS Health (http://www.imshealth.com/). They note that this is a national sales audit produced monthly by IMS, derived from reported

sales via hospital pharmacies and retail pharmacies. Hospital data is defined as the volume sales reported through the HPAI dataset. Retail data is defined as the volume sales reported through the XBPI dataset. All volume data is at unit level e.g. pack level. The data were reported annually for calendar years from 2011 to 2015 (comprising all 2015 data available at the time of analysis (YTD Oct15)). The company's summary of the data is reproduced in Table 12. A detailed breakdown of sales volume was provided for each individual RA monoclonal antibody as an appendix to the company response. This showed all the RA monoclonal antibodies to have similarly very low primary care prescribing levels. The company stated that they consider these medicines to be the closest analogues for the intended model of introducing the supply of alirocumab to the NHS. They noted that: "*They are initiated and managed from a secondary care setting, by specialists, in specialist clinics, usually with homecare and patient support services providing ongoing support of patients in the community.*"

Table 12 Hospital and retail sales split for several mono-clonal antibodies

BPIHPA_UK_M_IMS_001		2011	2012	2013	2014	2015
RA Mabs						
	Total Hospital	99.23%	99.26%	99.10%	99.25%	99.73%
	Total Retail	0.77%	0.74%	0.90%	0.75%	0.27%
Xolair ™						
	Total Hospital	99.68%	99.18%	99.37%	99.48%	99.73%
	Total Retail	0.32%	0.82%	0.63%	0.52%	0.27%
Prolia ™						
	Total Hospital	85.33%	72.47%	63.26%	57.04%	51.75%
	Total Retail	14.67%	27.53%	36.74%	42.96%	48.25%

For the purposes of the additional sensitivity analyses, the company noted that they used the [redacted] data to represent the upper limit of monoclonal antibody prescribing within primary care. They further noted that they did not consider it an appropriate analogue itself for alirocumab, being 'in tariff', not exclusively managed in secondary care, and not supplied via a homecare route. It consequently shows a

different pattern of delivery with increasing prescriptions in primary care; presently in the order of [redacted]. This was used to inform the upper limit of primary care prescribing reached by 5 years for alirocumab in the scenario analyses. The company's estimated ICERs from these additional scenario analyses are reproduced in Table 13 (deterministic) and 14 (probabilistic) below. A breakdown of the total and incremental costs and QALYs for each scenario was provided as an appendix to the company's response letter. This confirmed that it is only an increasing treatment cost in the alirocumab arm of the model (associated with increased non-PAS prescribing) that drives the observed increases in the ICERs.

The results indicate, as expected, that the ICER increases for each population as the the percentage of non-PAS uptake increases. By scenario 5, reflecting [redacted] non-PAS prescribing by year 5, the ICERs have increased by around £4000-£10,000. All subgroups, except the HeFH primary prevention (LDL-C ≥2.59 mmol/L) subgroup, have ICERs that remain below £25,000/QALY.

The probabilistic ICERs were found to be similar to the deterministic ICERs (Table 14). For scenario 5, alirocumab has a probability between [redacted] and [redacted] of being cost-effective at a WTP threshold of £30,000/QALY - excluding the HeFH primary prevention (LDL-C ≥2.59 mmol/L) population.

Table 13 Cost-effectiveness results for each scenario, by patient subgroup (breakdown provided in Appendix 2)

Patient population	Technology (and comparators)	Base case	Scenario 1 [redacted] by year 5 [start year 2)	Scenario 2 [redacted] by year 5 [start year 2)	Scenario 3 [redacted] by year 5 [start year 2)	Scenario 4 [redacted] by year 5 [start year 2)	Scenario 5 [redacted] by year 5 [start year 2)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	£36,793	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)						
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	£16,896	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)						
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	£19,751	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)						
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	£19,447	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)						

Table 14 Probabilistic cost-effectiveness results and estimated probability of being cost-effective at three WTP thresholds - Scenario 1 and Scenario 5

Patient population	Scenario 1 [redacted] by year 5 [start year 2) PSA ICER	Scenario 1 [redacted] by year 5 [start year 2) p(C/E @ 20K/Q)	Scenario 1 [redacted] by year 5 [start year 2) p(C/E @ 30K/Q)	Scenario 1 [redacted] by year 5 [start year 2) p(C/E @ 40K/Q)		Scenario 5 [redacted] by year 5 [start year 2) PSA ICER	Scenario 5 [redacted] by year 5 [start year 2) p(C/E @ 20K/Q)	Scenario 5 [redacted] by year 5 [start year 2) p(C/E @ 30K/Q)	Scenario 5 [redacted] by year 5 [start year 2) p(C/E @ 40K/Q)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	[redacted]	10.2%	33.0%	51.2%		[redacted]	0.00%	19.4%	36.6%
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	[redacted]	56.6%	79.2%	88.2%		[redacted]	39.6%	69.0%	83.0%
High risk CVD (LDL-C ≥3.36 mmol/L)	[redacted]	45.6%	78.6%	86.4%		[redacted]	21.8%	64.0%	78.6%
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	[redacted]	49.6%	77.0%	86.4%		[redacted]	25.8%	63.4%	82.2%

ERG's critique of the company's additional sensitivity analysis

The ERG reviewed the company's additional scenarios, and implemented the same changes to its modified version of the company's model. Thus the ERG can confirm that the described scenarios have been implemented as described, and the results have been exactly replicated.

In terms of justification for the scenarios explored, the ERG cannot suggest any better data sources to inform the input parameters. The company maintain that RA monoclonal antibodies provide the closest analogues for the proposed secondary/home care delivery model for alirocumab. However, they may not be necessarily the closest analogues in terms of the underlying nature of the condition being treated. For primary hypercholesterolemia patients who are being managed in secondary care because they are poorly controlled on statins alone, it might not be unreasonable to assume that similar rates of primary care prescribing (as observed for denosumab) could in theory be seen over time for alirocumab patients who do achieve control. However, if the counterfactual is that patients would otherwise remain uncontrolled without alirocumab, there might be a follow-up cost reduction (in terms of less frequent outpatient monitoring) which could partly counter the higher drug costs associated with the switch to primary care.

The ERG note that a similar discussion arose with respect to the proposed PAS for evolocumab during its recent NICE appraisal (http://www.nice.org.uk/guidance/indevelopment/gid-tag498), and the draft ACD states that *"The Committee agreed that up to 90% of people may have evolocumab through FP10 prescriptions in primary care after 2 years."* However, the company (Sanofi) provided a comment from a clinical expert stating: *"I would disagree with the statement that 'up to 90% of people' will be followed up in primary care. The reasons for this is that patients with FH are treated and followed up in lipid clinics in secondary care as referred to in NICE QS41 and CG71. Patients who have well documented intolerance to statins as referred to in NICE CG181 recommend specialist referral and these patients are subsequently managed in secondary care. Both these groups will be managed in secondary care because of the complexity of their lipid management and requirements for specialist risk assessment and intervention. These cohorts will potentially benefit from PCSK9 inhibition therapy."*

The ERG's clinical advisor is of the opinion that the proportion who will transit to primary care prescribing remains unknown. However, he suspects that, at least for the HeFH secondary prevention and recurrent CVD/polyvascular disease populations, the majority of patients would remain in secondary care, at least for the next few years. He also points out a potential reluctance of GPs to take on prescribing of these drugs (Dr William Simpson, NHS Grampian, personal communication; 07/12/2015).

In summary, the ERG accepts that there is potential for patients who achieve good control with alirocumab to be managed in primary care with FP10 prescribing. However, the proportion of patients who will make this transition is unknown and may vary between the modelled cohorts. It could perhaps be more likely for the HeFH primary prevention and high risk CVD cohorts who achieve target on alirocumab, and less likely for the HeFH secondary prevention and recurrent CVD/polyvascular disease cohorts who may require closer ongoing secondary care follow-up for other reasons.

Additional scenario analysis explored by the ERG

In light of the uncertainty surrounding the proportion of patients who might transit to primary care in each population, and the committee's stated position in the recent evolocumab appraisal, the ERG has extended the company's scenario analysis up to a maximum of [redacted] transiting to primary care by 5 years - otherwise applying the company's base case assumptions (Table 15). For completeness, the ERG also offer the same set of prescribing scenarios using their modified version of the company's model: i) retaining the scaled hazard ratios from Naverese et al. (Table 16); and ii) using the CTT meta-analysis to model all the effects of alirocumab (Table 17). Finally, to explore the impact of combining other scenario changes with the FP10 prescribing scenario, the ERG has reproduced the scenario analysis tables from the company's main submission with the company's maximum [redacted] transiting to primary care scenario (Tables 18-21).

Table 15 The ERG's extension of the company's non-PAS prescribing scenarios by patient population, up to 90% non-PAS primary care prescribing (otherwise applying the company's base case assumptions)

Patient population	Technology (and comparators)	Base case	Scenario 1 [redacted] by year 5 [start year 2)	Scenario 2 [redacted] by year 5 [start year 2)	Scenario 3 [redacted] by year 5 [start year 2)	Scenario 4 [redacted] by year 5 [start year 2)	Scenario 5 [redacted] by year 5 [start year 2)	Scenario 6 [redacted] by year 5 [start year 2)	Scenario 7 [redacted] by year 5 [start year 2)	Scenario 8 [redacted] by year 5 [start year 2)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	£36,793	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	£16,896	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	£19,751	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	£19,447	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									

Table 16 Cost-effectiveness results for non-PAS prescribing scenarios using the ERG's base case assumptions (with the rate ratios per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitors from Navarese et al. meta-analysis)-with different PAS scenarios

Patient population	Technology (and comparators)	Base case	Scenario 1 [redacted] by year 5 [start year 2)	Scenario 2 [redacted] by year 5 [start year 2)	Scenario 3 [redacted] by year 5 [start year 2)	Scenario 4 [redacted] by year 5 [start year 2)	Scenario 5 [redacted] by year 5 [start year 2)	Scenario 6 [redacted] by year 5 [start year 2)	Scenario 7 [redacted] by year 5 [start year 2)	Scenario 8 [redacted] by year 5 [start year 2)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	41,243	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	16,933	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	19,432	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	19,021	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									

Table 17 Cost-effectiveness results for non-PAS prescribing scenarios using the ERG's assumptions (with rate ratios per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis)-with different PAS scenarios

Patient population	Technology (and comparators)	Base case	Scenario 1 [redacted] by year 5 [start year 2)	Scenario 2 [redacted] by year 5 [start year 2)	Scenario 3 [redacted] by year 5 [start year 2)	Scenario 4 [redacted] by year 5 [start year 2)	Scenario 5 [redacted] by year 5 [start year 2)	Scenario 6 [redacted] by year 5 [start year 2)	Scenario 7 [redacted] by year 5 [start year 2)	Scenario 8 [redacted] by year 5 [start year 2)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	67,215	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	33,339	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	42,131	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	44,759	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									

Table 18 HeFH primary prevention (LDL-C ≥ 2.59 mmol/L), alirocumab plus statins plus ezetimibe versus statins plus ezetimibe) - scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with new PAS policy**			[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.50%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non fatal; QALY, quality-adjusted life-year

Table 19 HeFH secondary prevention (LDL-C ≥ 2.59 mmol/L), alirocumab plus statins plus ezetimibe versus statins plus ezetimibe – scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with new PAS policy**			[redacted]
Baseline risk data	As per Mohrschladt 2004	As per THIN	[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.5%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; HSE; Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non-fatal

Table 20 High Risk CVD (LDL-C ≥ 3.36 mmol/L), alirocumab plus statins versus statins) - scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with new PAS policy**			[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.5%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; CVD, cardiovascular disease; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P-NF, post-non-fatal

Table 21 Recurrent events/polyvascular disease (LDL-C ≥ 2.59 mmol/L), alirocumab plus statins versus statins – scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with new PAS policy**			[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.5%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P -NF, post-non-fatal

Impact on the ICERs the non-PAS primary care prescribing

- The company's scenarios (up to [redacted] non-PAS prescribing by 5 years) indicate that when modelling the effects of alirocumab through the scaled hazard ratios of Navarese et al., the ICERs for alirocumab remain below £25,000 in all but the HeFH primary prevention cohort.
- Applying the same scenarios using the ERG modified base case assumptions, and continuing to model the effects of alirocumab on ACS events and CV deaths using the scaled hazard ratios from Navarese et al., the findings are similar. Further extending the proportion of patients

transitioning to primary care to [redacted] by 5 years raises the ICERs further. However, they remain below £30,000 – in all but the HeFH primary prevention population.

- Applying the non-PAS prescribing scenarios with the effects of alirocumab modelled through the CTT meta-analysis, the ICERs as expected increase further above base levels above £30,000.
- Combining the company's [redacted] non-PAS prescribing scenario with other uncertain scenarios, shows that from this alternative reference point; the ICERs remain reasonably robust (in terms of crossing thresholds) to changes assessed – apart from the source of hazard ratios per unit reduction in LDL-C

References

1. Mohrschladt MF, Westendorp RGJ, Gevers Leuven JA, et al. Cardiovascular disease and mortality in statin-treated patients with familial hypercholesterolemia. Atherosclerosis 2004;172(2):329-35

2. 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 Int Med 2015;**163**(1):40-51.

3. Moriaty P, Thompson P, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE Q1 randomized trial. J Clin Lipidol 2015: doi.org/10.1016/j.jacl.2015.08.006.

4. NICE QS41 Familial hypercholesterolaemiaNICE quality standard [QS41] Published date: August 2013: https://www.nice.org.uk/guidance/qs41

5. Identification and management of familial hypercholesterolaemia (FH). NICE CG71. London: National Institute for Health and Care Excellence, 2008

6. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of acrdiovascular disease. NICE CG181. London: National Institute for Health and Care Excellence, 2014. URL: http://www.nice.org.uk/guidance/cg181 [accessed December 2015]