Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Produced by Aberdeen HTA Group

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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.

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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.

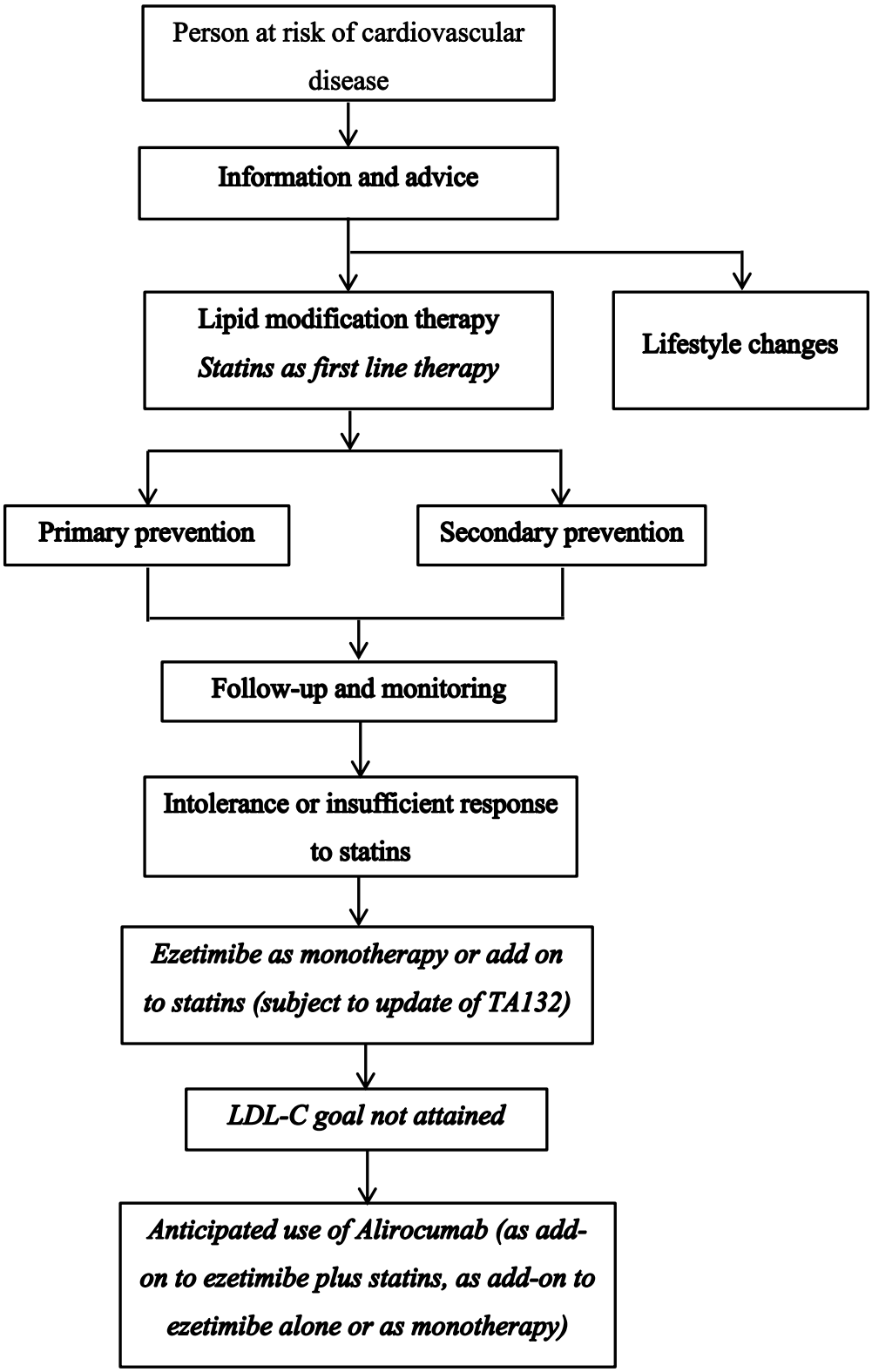


Figure 1 Pathway of clinical care for lipid modification therapy for the prevention of cardiovascular diseases (adapted from Cardiovascular disease prevention. NICE Pathway. London: National Institute for Health and Care Excellence, 2014[33])

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.

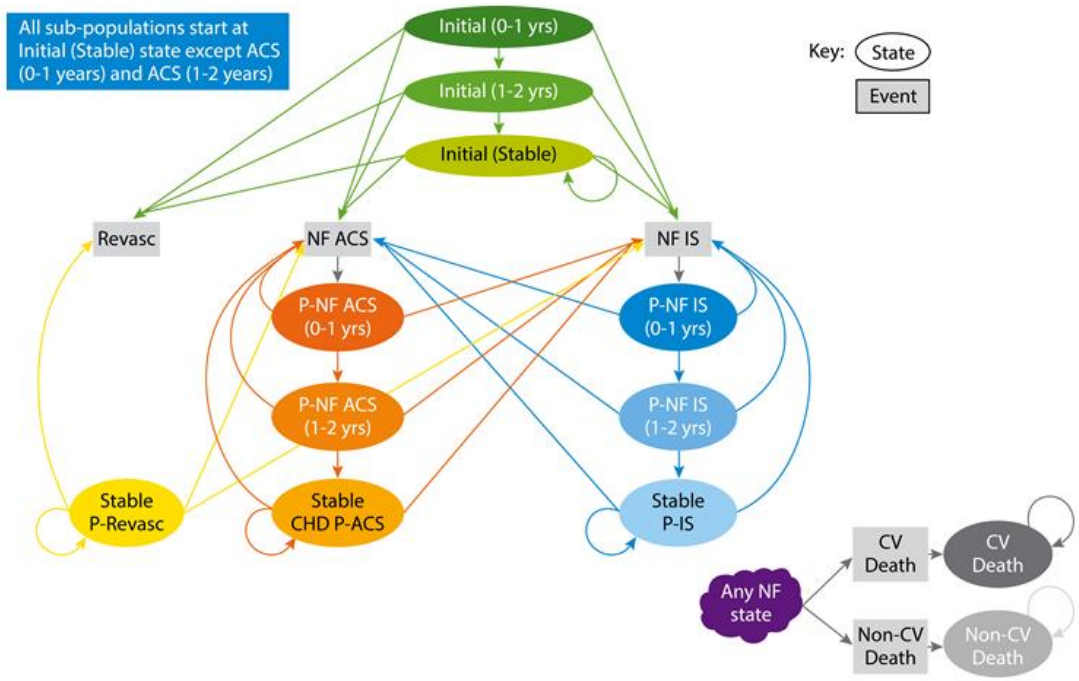


Figure 2 Model schematic (Source: Figure 30 of the company's submission)

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.

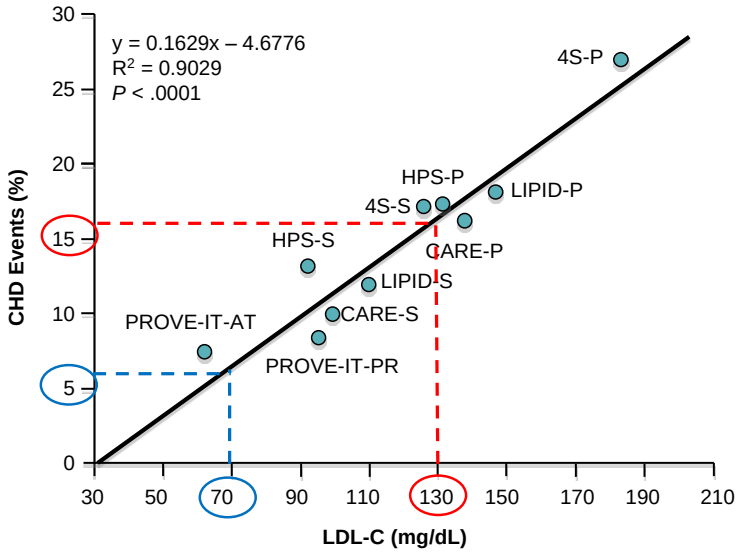


Figure 3 Relationship between LDL-C and CV event risk (Figure adapted from O'Keefe et al. 2004 - scale shown is in mg/dL; 70 mg/dL = 1.81mmol/L, 130 mg/dL = 3.36 mmol/L) (Source: Figure 29 of the company's submission)

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)

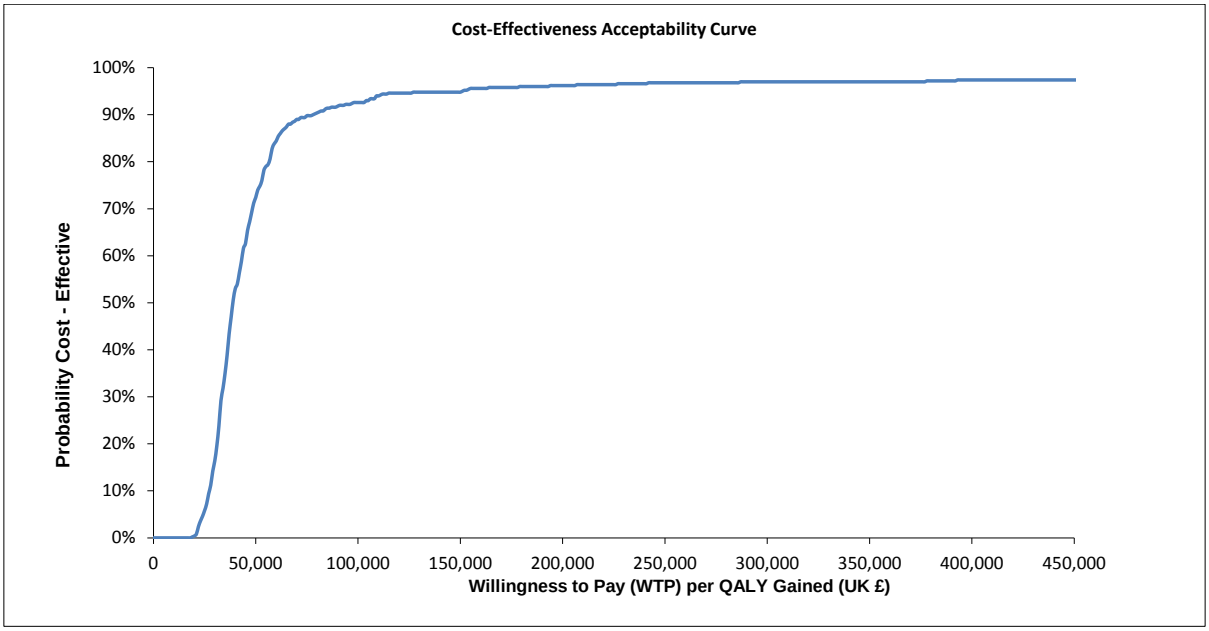
Variable	Distribution	Variation
Cohort characteristics		
Proportion with diabetes	Normal	SE from proportion of population with diabetes in THIN (1%)
Proportion of males	Normal	Standard error calculated as +/- 25% / 6
Baseline LDL-C	Log-Normal	Standard error calculated as +/- 25% / 6
Initial age	Normal	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.



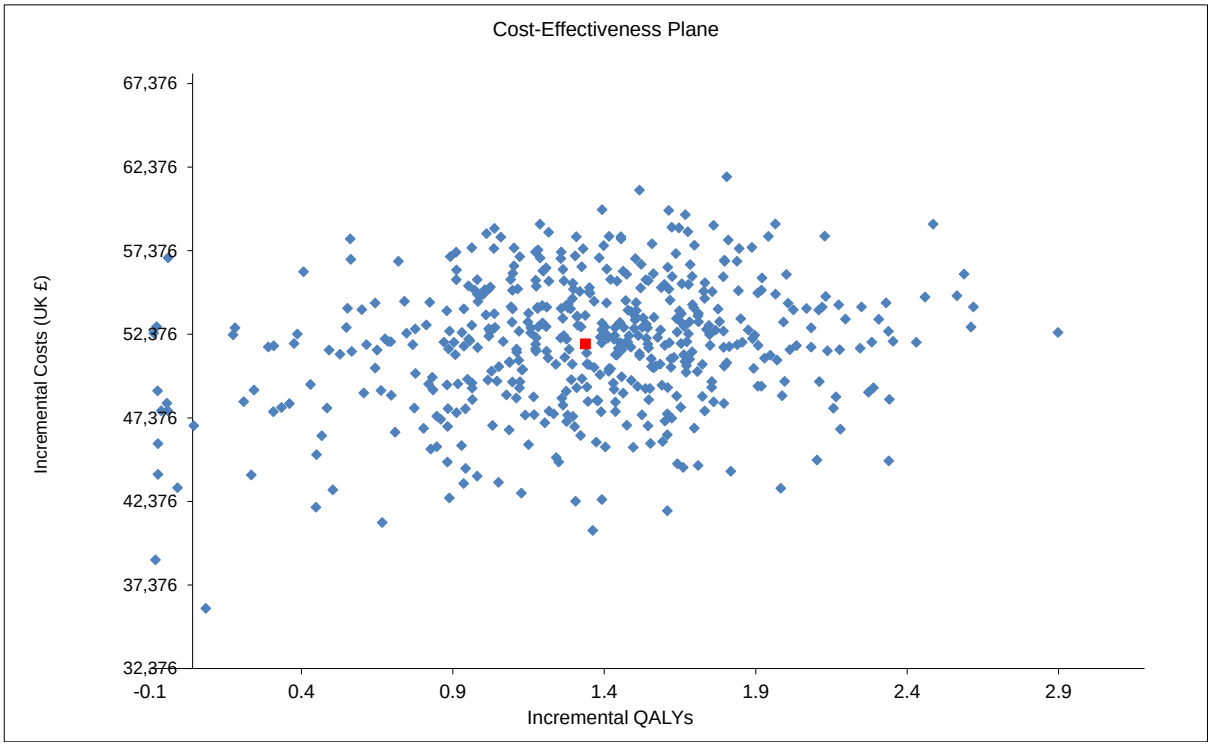


Figure 4 HeFH primary prevention, Scatter plot and CEAC with PAS (Source: Figure 1 of the company's PAS submission)

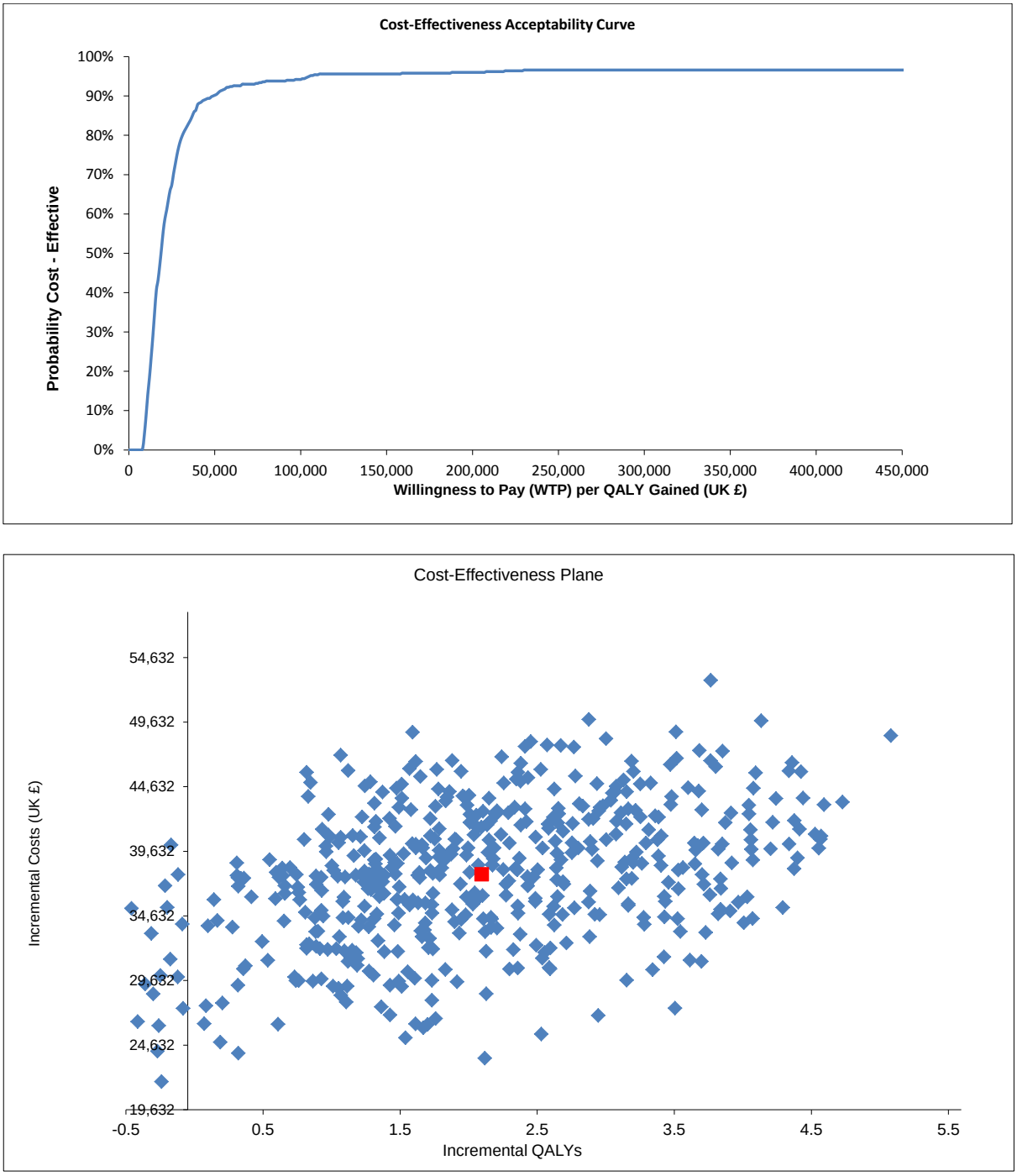
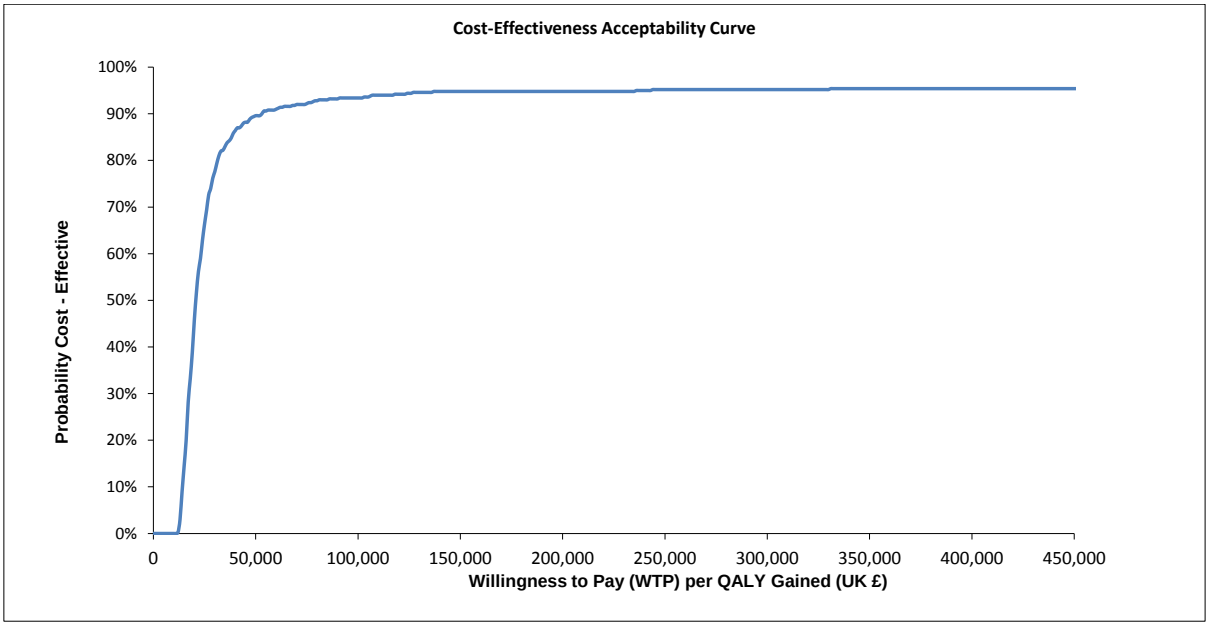


Figure 5 HeFH secondary prevention, Scatter plot and CEAC with PAS

(Source: Figure 2 of the company's PAS submission)



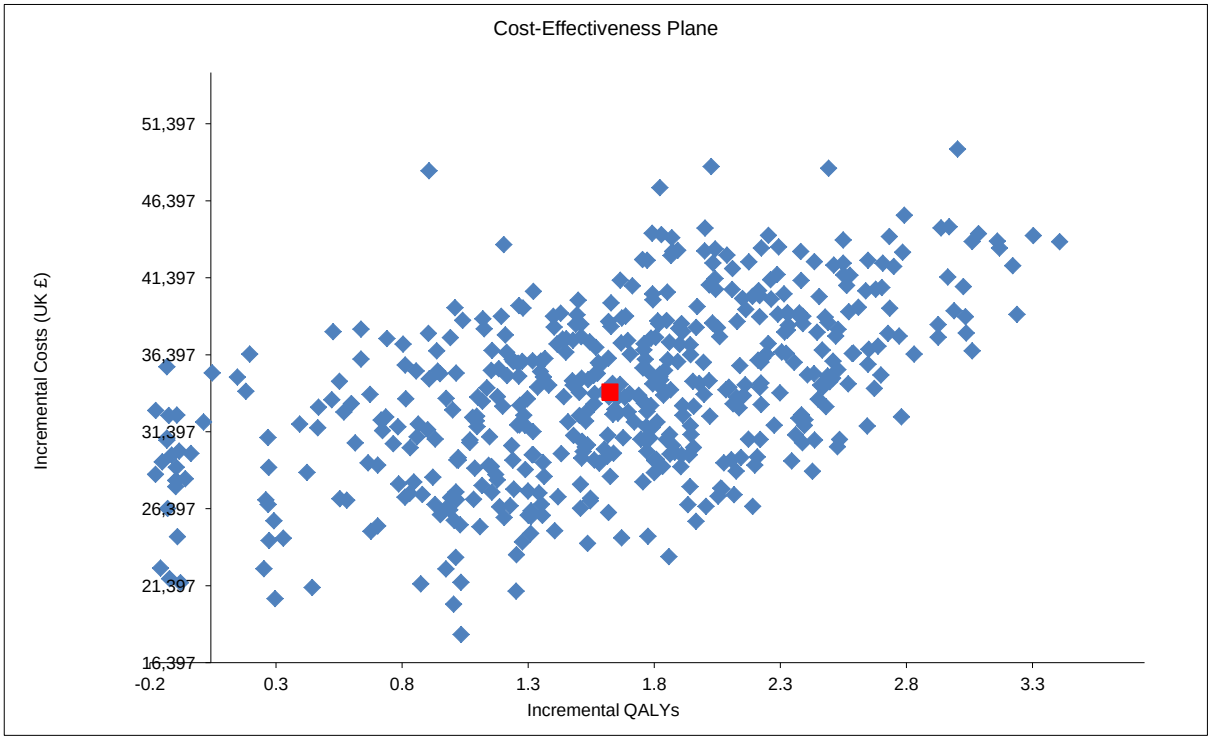
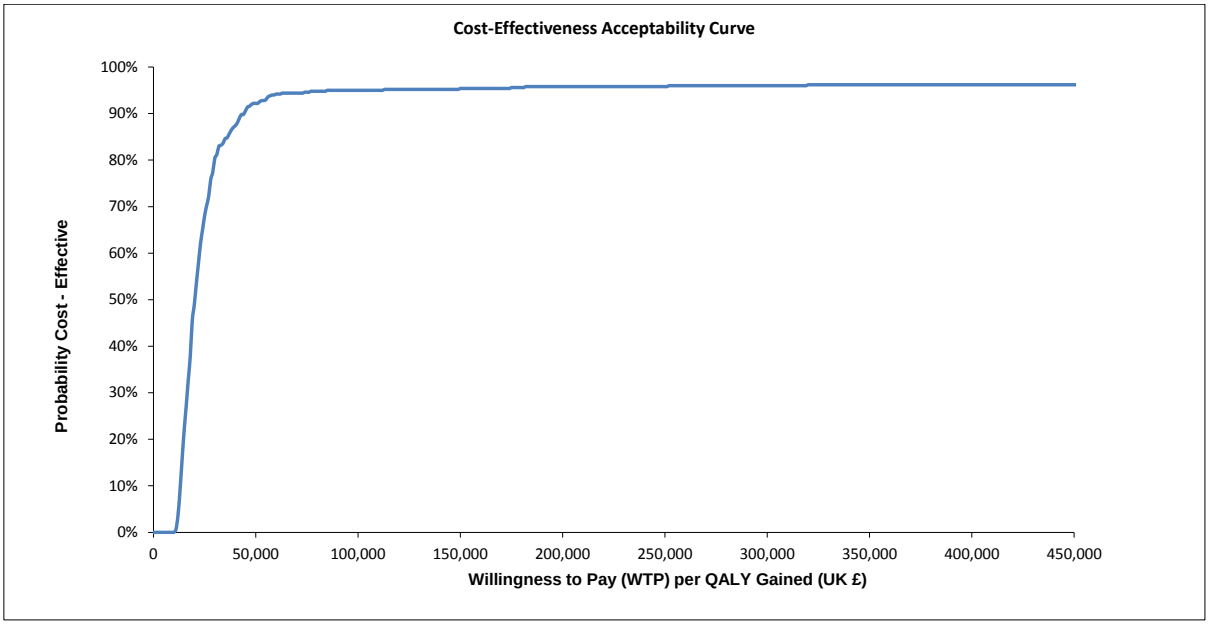


Figure 6 High Risk CVD, scatter plot and CEAC with PAS (Source: Figure 3 of the company's PAS submission)



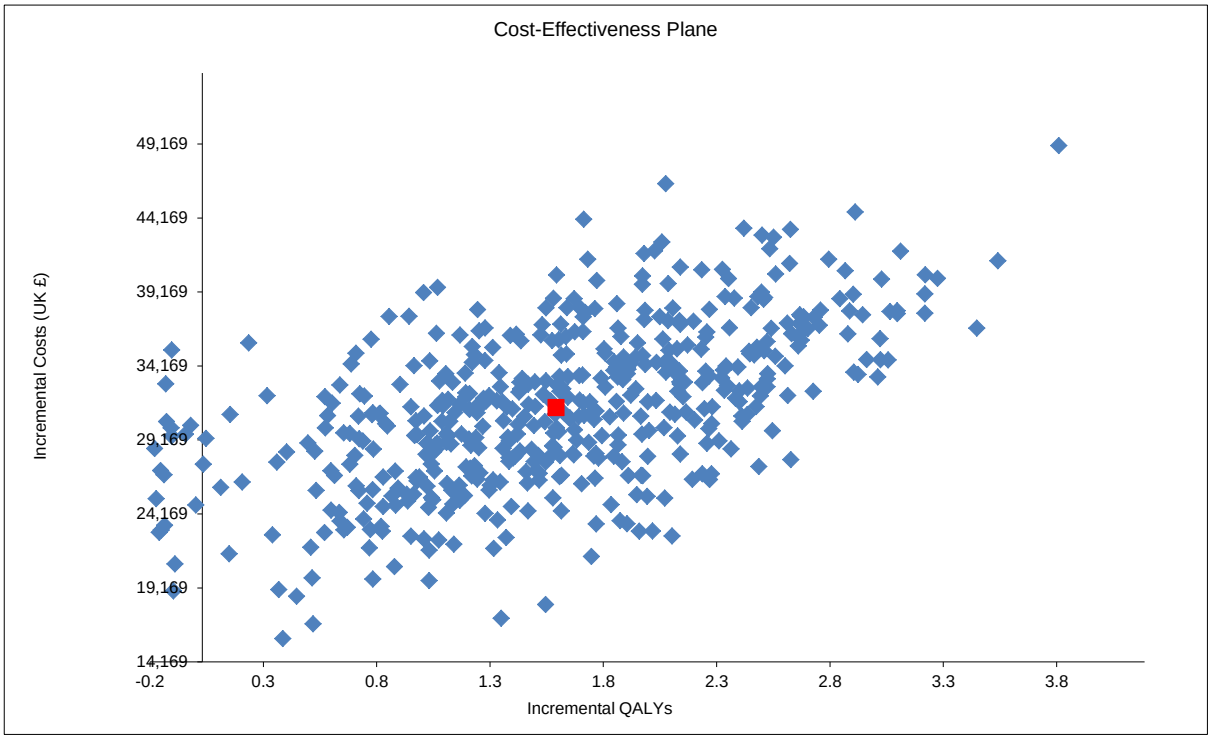


Figure 7 Polyvascular, scatter plot and CEAC with PAS (Source: Figure 4 of the company's PAS submission)

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

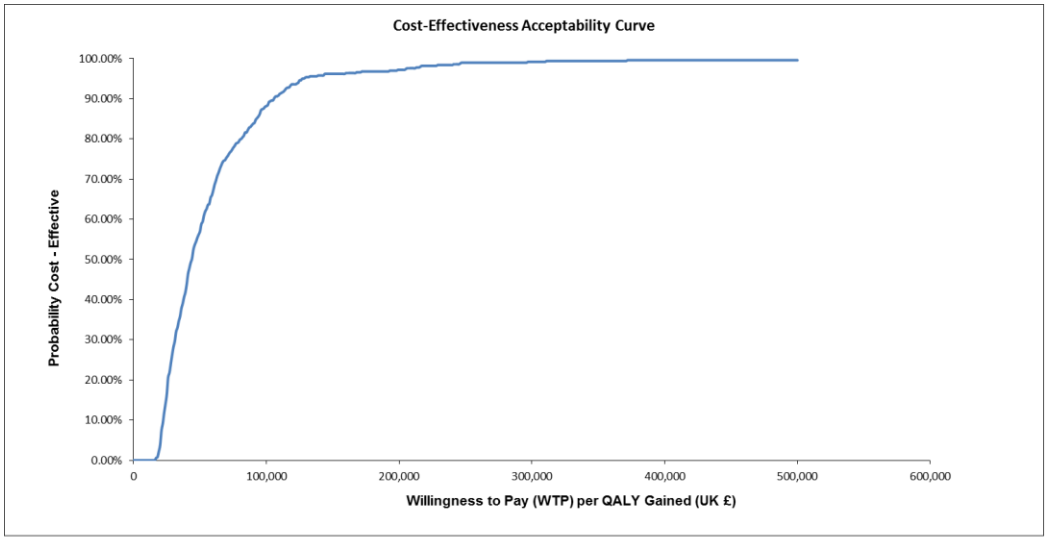
Table 56 and Figures 8 to 11 summarise the results from the ERGs updated base case when running the model probabilistically. All these comparisons are for alirocumab as an adjunct to maximally tolerated statin (+/- ezetimibe) in the respective populations. The findings are generally consistent with the 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



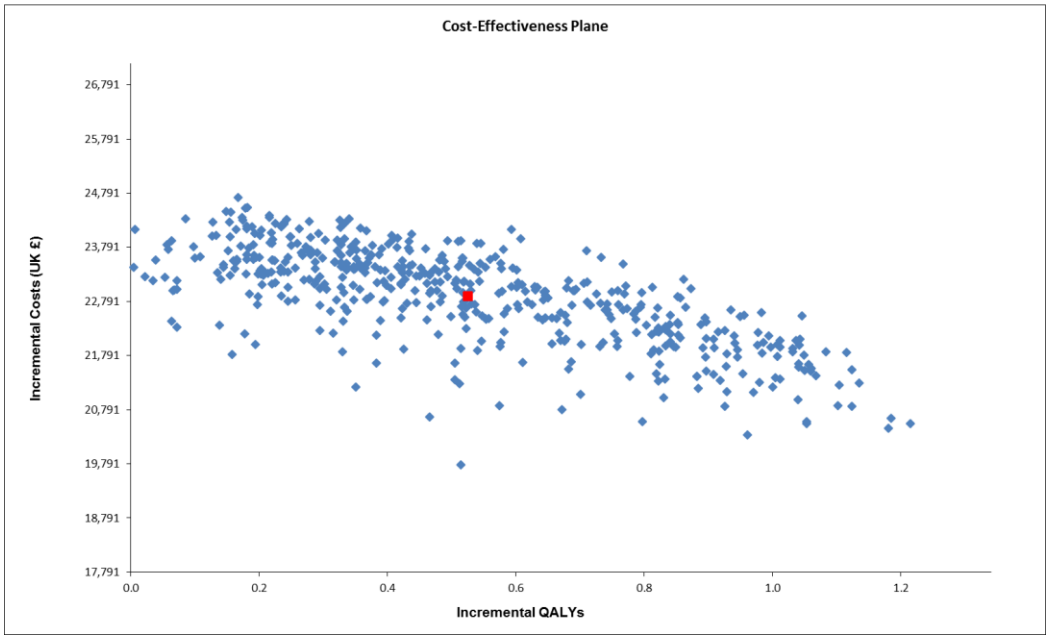
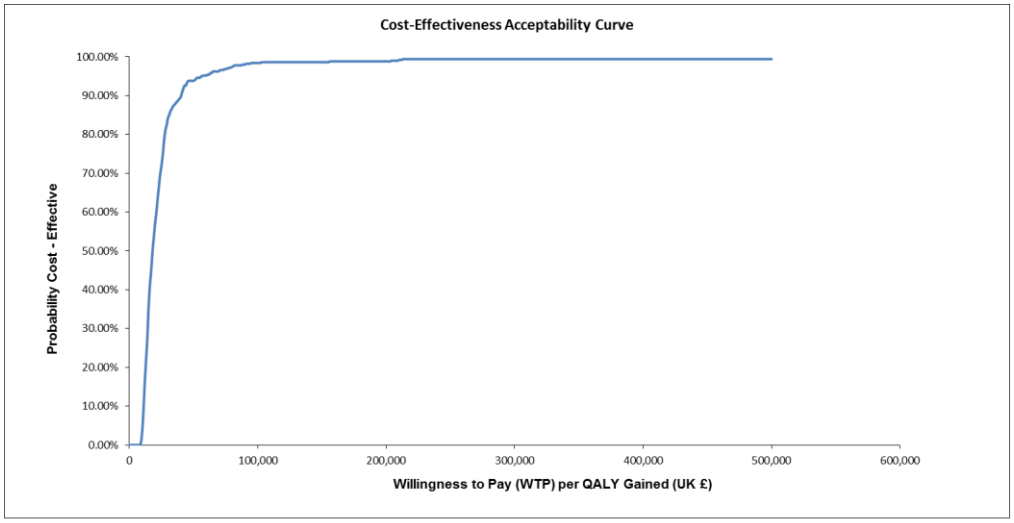


Figure 8 Cost-effectiveness acceptability curve and scatter plot: HeFH primary prevention - with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitor from Navarese et al.'s meta-analysis (alirocumab + statins + ezetimibe vs. statins + ezetimibe)



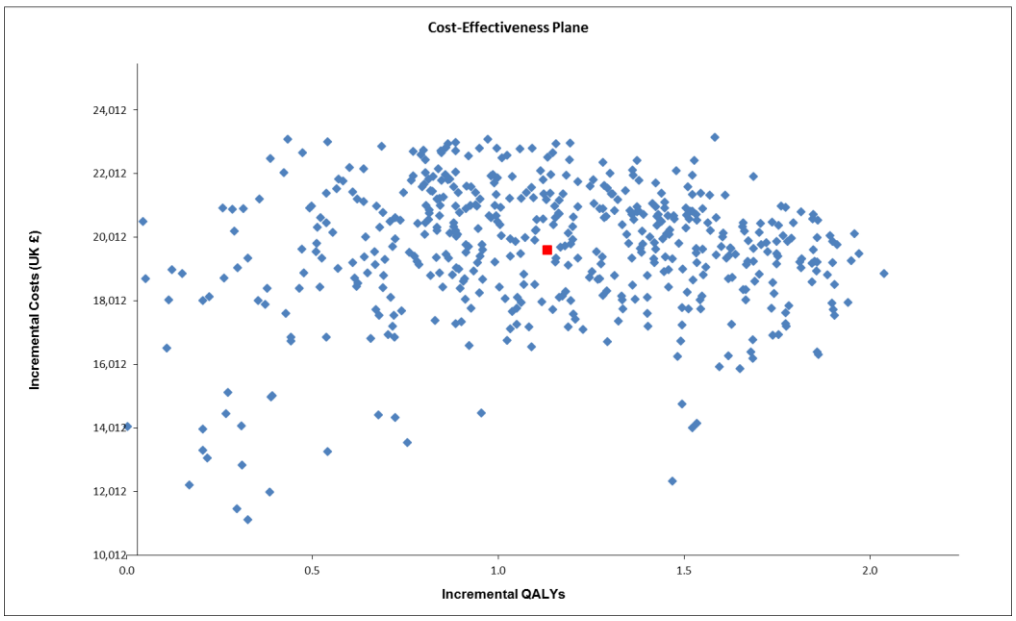
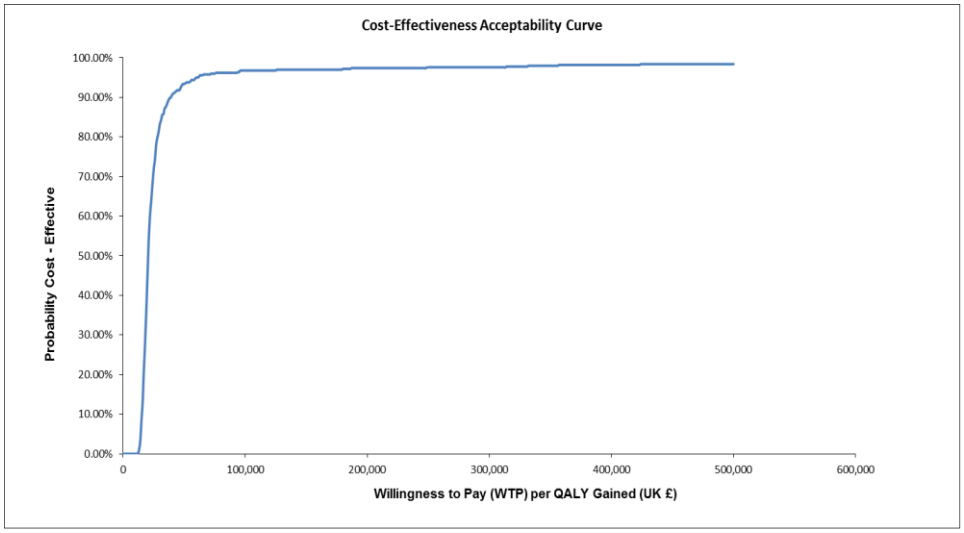


Figure 9 Cost-effectiveness acceptability curve and scatter plot: HeFH secondary prevention (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9 - inhibitor from Navarese et al.'s meta-analysis) (alirocumab + statins + ezetimibe vs. statins + ezetimibe)



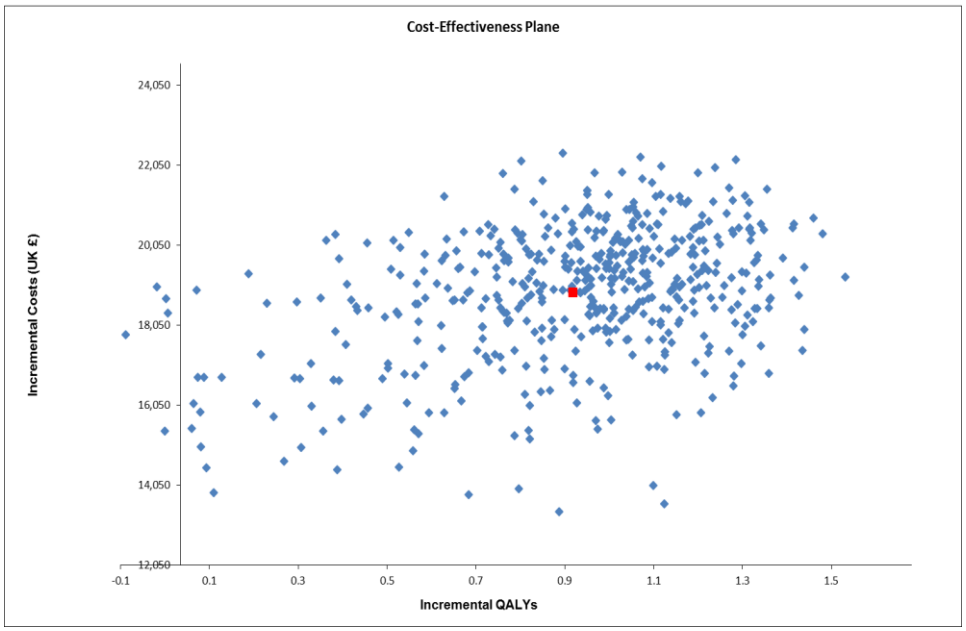


Figure 10 Cost-effectiveness acceptability curve and scatter plot: High risk CVD (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9 - inhibitor from Navarese et al.'s meta-analysis) (alirocumab + statins vs. statins)

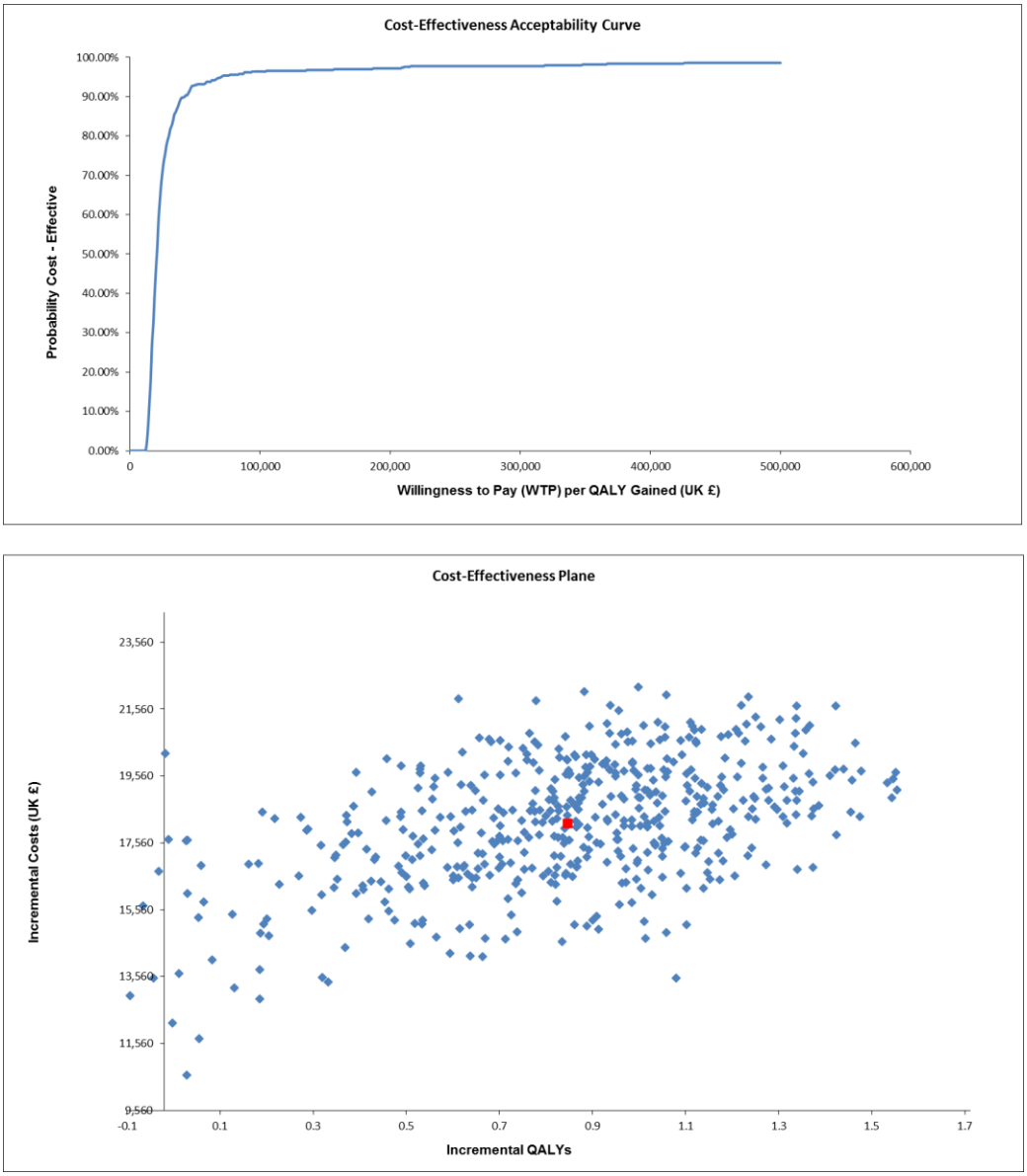
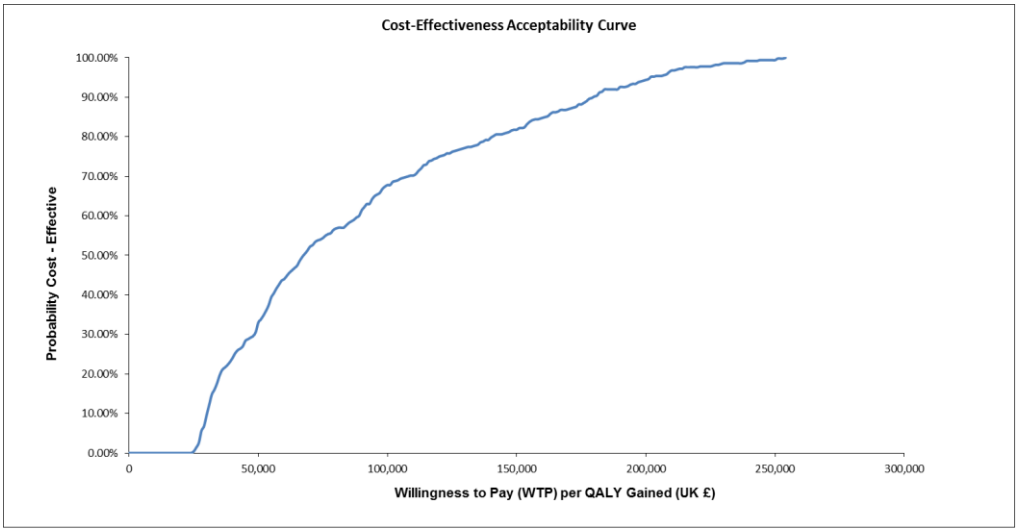


Figure 11 Cost-effectiveness acceptability curve and scatter plot - Recurrent events/ polyvascular disease (with rate ratio per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitor from Navarese et al.'s meta-analysis) (alirocumab + statins vs. statins)

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



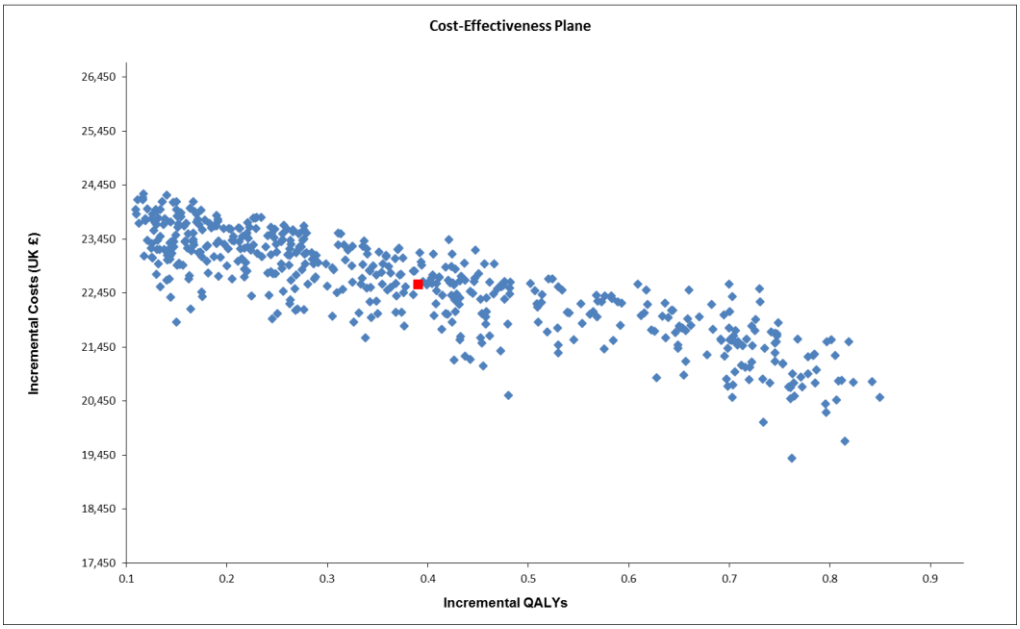
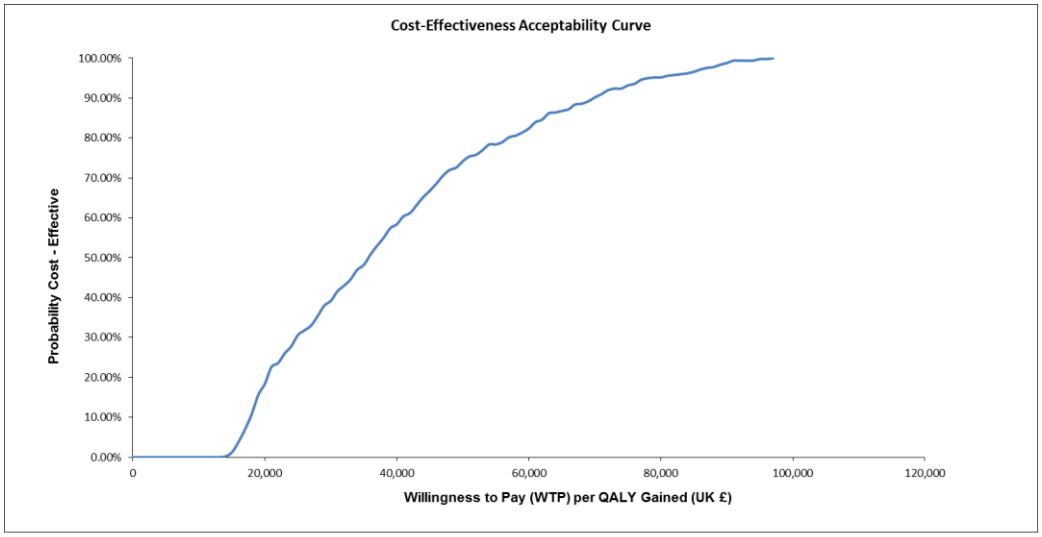


Figure 12 Cost-effectiveness acceptability curve and scatter plot: HeFH primary prevention - with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis (alirocumab + statins + ezetimibe vs. statins + ezetimibe)



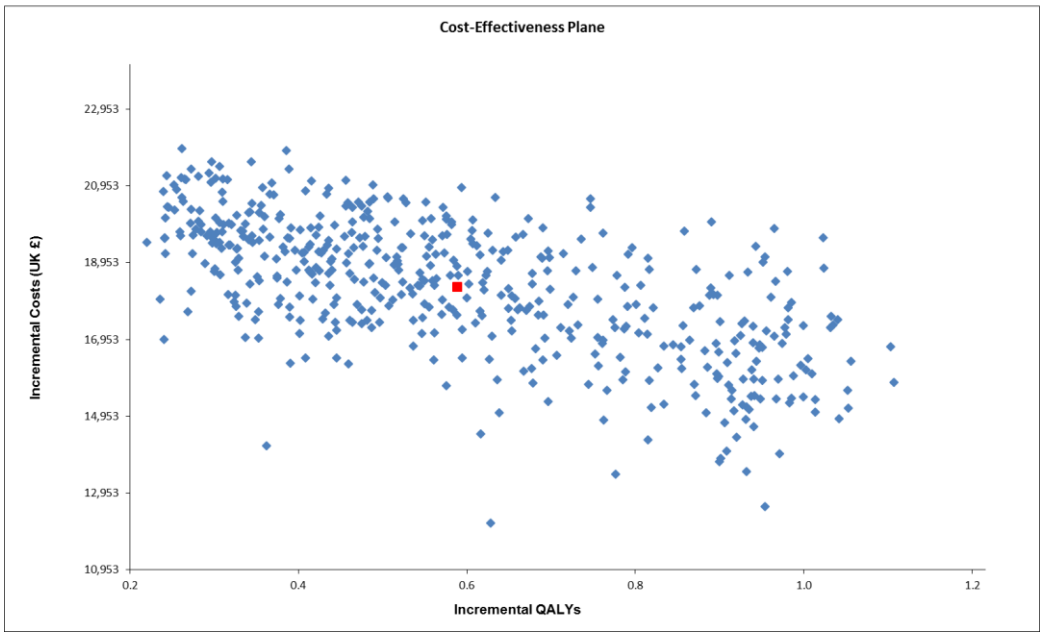
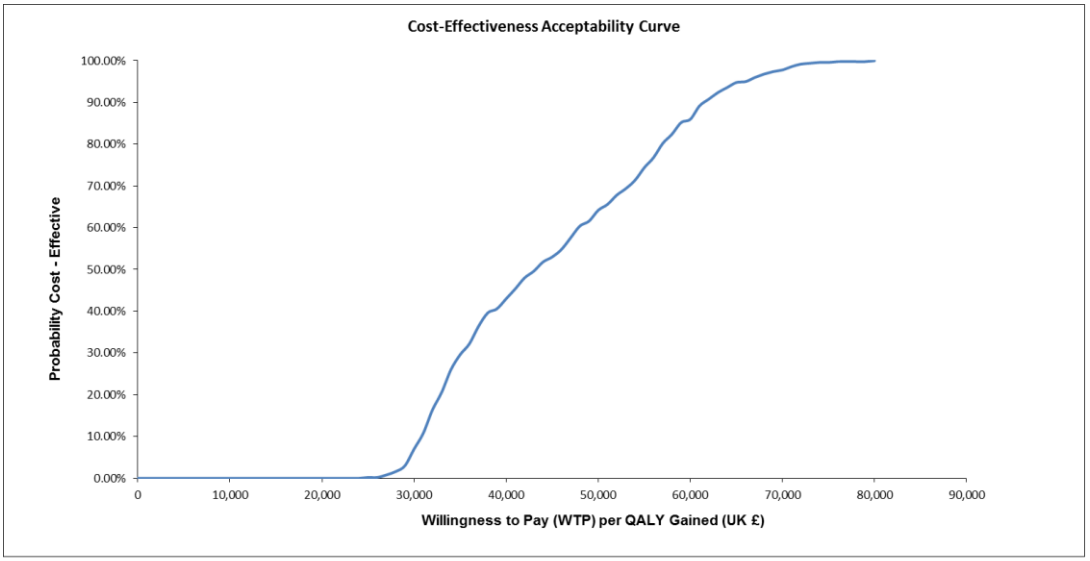


Figure 13 Cost-effectiveness acceptability curve and scatter plot: HeFH secondary prevention - with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis (alirocumab + statins + ezetimibe vs. statins + ezetimibe)



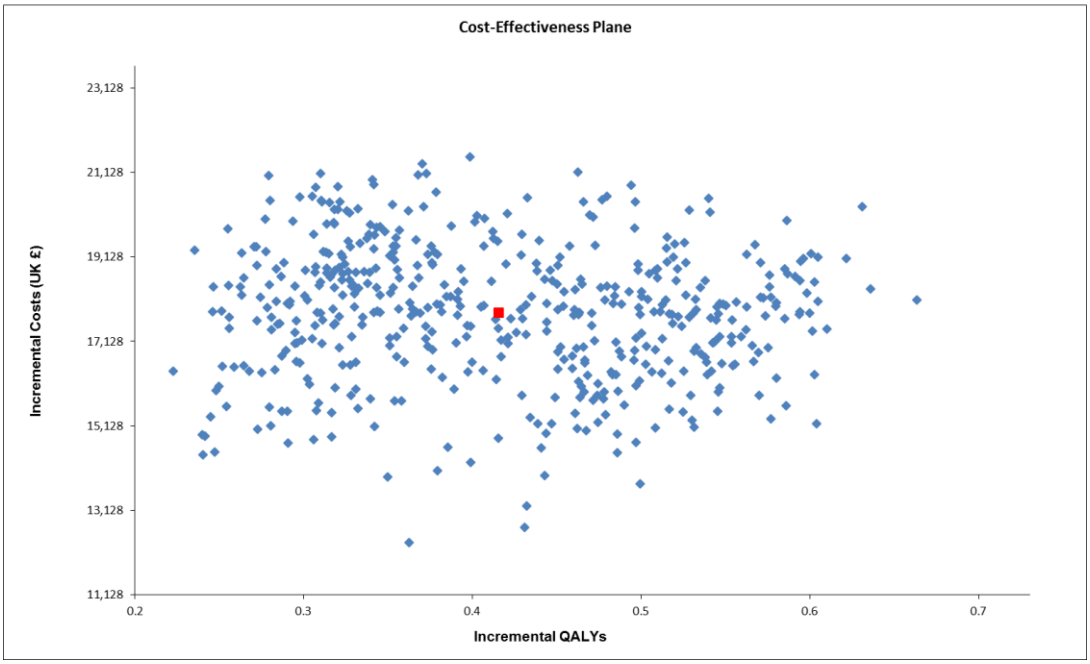


Figure 14 Cost-effectiveness acceptability curve and scatter plot: High risk CVD - with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis (alirocumab + statins vs. statins)

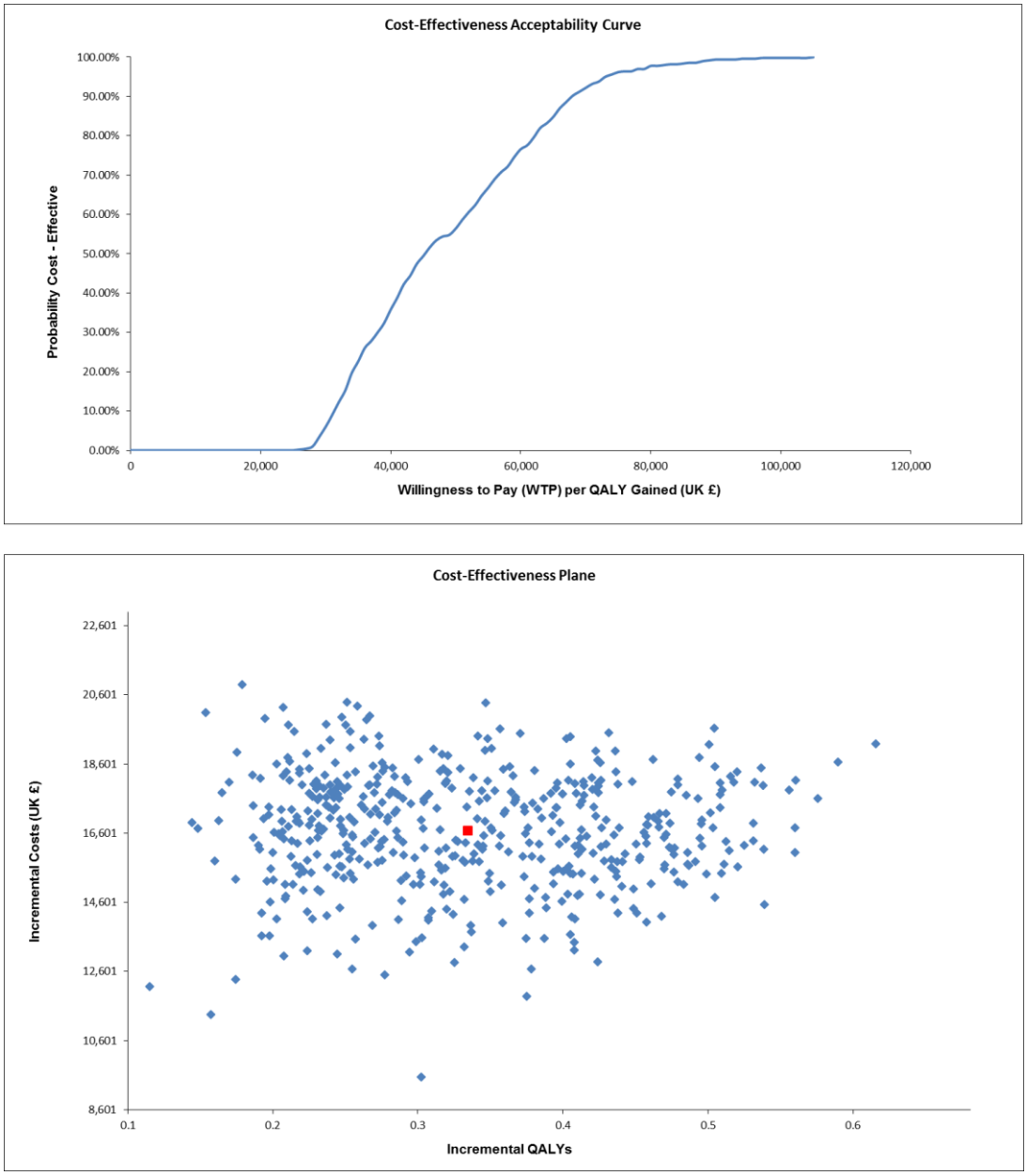


Figure 15 Cost-effectiveness acceptability curve and scatter plot: Recurrent events/ polyvascular disease - with rate ratio per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis (alirocumab + statins versus statins)

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).

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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		