Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: A Single Technology Appraisal

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Contributions of authors

Christopher Carroll and Duncan Chambers summarised and critiqued the clinical effectiveness data reported within the company's submission. Paul Tappenden and Rachid Rafia critiqued the health economic analysis submitted by the company. Mark Clowes critiqued the company's search strategies. Jean Sanderson critiqued the statistical analysis contained within the company's submission. Paul Durrington, Nadeem Qureshi and Anthony Wierzbicki provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

AAC	American College of Cardiology
ACS	Acute coronary syndrome
AE	Adverse event
AF	Atrial fibrillation
AHA	American Heart Association
AIC	Academic-in-confidence
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AWMSG	All Wales Medical Strategy Group
CAD	Coronary artery disease
CEAC	Cost-effectiveness acceptability curve
CHD	Coronary heart disease
CI	Confidence interval
CIC	Commercial-in-confidence
CG	Clinical guideline
CHD	Chronic Heart Disease
CHMP	Committee for Medicinal Products for Human Use
CMU	Commercial Medicines Unit
CPRD	Clinical Practice Research Datalink
CS	Company's submission
CTT	Cholesterol Treatment Trialists collaboration
CVD	Cardiovascular disease
DLCN	Dutch Lipid Clinic Network
EAS	European Atherosclerosis Society
ECVD	Established CVD
EQ-5D	EuroQol-5D
EMBASE	Excerpta Medica database
eMIT	Electronic market information tool
ERG	Evidence Review Group
ESC	European Society of Cardiology
FAS	Full analysis set
FH	Familial hypercholesterolaemia
GDG	Guideline Development Group
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HES	Hospital Episode Statistics
HF	Heart failure
HoFH	Homozygous familial hypercholesterolaemia
HRQoL	Health-related quality of life
HSE	Health Survey for England
HSSS	Highly Sensitive Search Strategy
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IC	Intermittent claudication
IPD	Individual patient data

IS	Ischaemic stroke
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
Lp(a)	Lipoprotein(a)
MEDLINE	Medical Literature Analysis and Retrieval System Online
MI	Myocardial infarction
mmol/L	millimole per litre
NCEP	National Cholesterol Education Program
NHS	National Health Service
NHS EED	National Health Service Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OD	Once daily
ONS	Office of National Statistics
PCSK9	Proprotein convertase subtilisin/kexintype 9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
Q2W	Every 2 weeks
QM	Monthly
RCT	Randomised controlled trial
REACH	REduction of Atherothrombosis for Continued Health
SAE	Serious adverse event
SBP	Systolic blood pressure
SmPC	Summary of product characteristics
SI	Statin intolerant
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SMR	Standardised mortality ratio
ST	Statin tolerant
TA	Technology Appraisal
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
TTO	Time trade-off
UA	Unstable angina
UKPDS	UK Prospective Diabetes Study
VLDL-C	Very low-density lipoprotein cholesterol
WTP	Willingness to pay

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

Cardiovascular disease (CVD) can have major health and economic implications for people and health services: it remains the most common cause of mortality in women in England and the second most common cause of mortality in men in England. Elevated cholesterol is predictive of CVD risk. Lipid-lowering therapies are recognised as being effective for reducing hypercholesterolaemia and also for reducing risk of CVD. Recent years have seen consistent increases in prescription rates for lipid-lowering therapies in England.

Hypercholesterolaemia, a type of hyperlipidaemia, specifically refers to the presence of high levels of cholesterol, including low-density lipoprotein cholesterol (LDL-C), in the blood. Primary hypercholesterolaemia can be familial or non-familial. Heterozygous familial hypercholesterolaemia (HeFH) is monogenic, i.e. related to a single genetic locus; the LDL-cholesterol is elevated from birth and can lead to life-long elevated LDL-C levels. LDL-C levels in people with HeFH are typically two to three times higher than normal. Homozygous familial hypercholesterolaemia (HoFH) is a more severe and rare form of hyperlipidaemia with defects in LDL-receptor genes inherited from both parents rather than one. Non-familial primary hypercholesterolaemia is polygenic: elevated LDL-C is produced by a combination of various genes and nutritional and lifestyle factors. However, the exact role of polygenic inheritance in producing LDL-C levels is unclear. This is the most common form of primary hypercholesterolaemia in the UK; approximately 70% of people with primary hypercholesterolaemia have this non-familial polygenic type. Mixed dyslipidaemia or "combined hyperlipidaemia" is characterised by elevated LDL-C and high triglycerides and/or reduced or elevated high-density lipoprotein cholesterol (HDL-C). It is a type of primary hypercholesterolaemia. Like primary non-familial hypercholesterolaemia, it is also relatively common; approximately 10% of people with primary hypercholesterolaemia in the UK have this type of "mixed dyslipidaemia."

The decision problem required an assessment of the clinical effectiveness and cost-effectiveness of evolocumab compared to ezetimibe in treating primary hypercholesterolaemia (familial and non-familial) in patients with inadequately-controlled LDL-C levels despite being on a maximum-tolerated dose of statins, or in patients for whom statins are inappropriate (due to intolerance or contraindication).

Evolocumab is a fully human monoclonal antibody that binds selectively to proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that regulates the recycling of LDL-receptors on the surface of liver cells and decreases the ability of the liver to clear LDL from the blood. By binding to PCSK9, evolocumab increases liver levels of LDL receptors, thereby reducing serum LDL-cholesterol levels.

It is indicated in adults aged 18 years or older with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, for those who have reached a maximum-tolerated dose on statins, or who are contraindicated for statins. It is also indicated for use in populations with homozygous familial hypercholesterolaemia (HoFH), although this population is not part of the final scope issued by the National Institute for Health and Care Excellence (NICE). Evolocumab is given as either one dose (140mg) every 2 weeks (Q2W) or three doses (420mg) every month (QM), administered by subcutaneous injection (s.c.) via a prefilled pen or syringe. The intervention is designed to be self-administered by the patient after proper training. The cost of evolocumab is £170.10 per 140 mg prefilled pen or syringe.

The population described in the clinical trial evidence was adult patients with primary hypercholesterolaemia (which includes mixed dyslipidaemia), for whom statins do not provide optimal control of their LDL-C levels and/or for whom statins are contraindicated or not tolerated. This was consistent with the decision problem. There was a single trial of evolocumab within a diagnosed HeFH subgroup population (RUTHERFORD-2). The populations in the clinical trial evidence and the scope are in keeping with the wording of the marketing authorisation for ezetimibe, which is the comparator specified within the decision problem. Clinical evidence was presented for each of the subgroups listed for consideration in the final NICE scope: presence of CVD or known risk factors for CVD; adults with HeFH; adults in whom two or more statins cannot be tolerated, or only the lowest dose can be tolerated; and groups with differing levels of severity of hypercholesterolaemia, which is defined by the company according to baseline LDL-C level. The trial populations were generally consistent with the decision problem, although it is unclear whether some of the populations in some of the included trials were currently receiving the maximum-tolerated dose of statins.

The decision problem required the consideration of evolocumab as monotherapy or in combination with a statin with or without ezetimibe, or in combination with ezetimibe (without statin therapy). The clinical evidence presented satisfied the majority of these principal combinations of interventions, although evidence was absent for certain subgroups that were to be considered: in particular, there were no trials of evolocumab in combination with ezetimibe in populations (both non-familial and HeFH) in whom statins could not be tolerated or were contraindicated.

The principal efficacy outcomes for consideration were plasma lipid and lipoprotein levels, including LDL-cholesterol, non-HDL-cholesterol, HDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB) and lipoprotein(a) (Lp(a)). These were reported in all randomised controlled trials (RCTs) included in the review of clinical efficacy (LAPLACE-2, GAUSS-2, DESCARTES and RUTHERFORD-2). The majority of the clinical evidence reported the required minimum 12-week

follow-up, with the exception of the DESCARTES trial (52 weeks). The use of LDL-C as a potential surrogate for CVD is generally accepted and the company provided evidence for the relationship between LDL-C reduction, due to statin therapy, and the reduction of CV events based on a meta-analysis of 26 trials by the Cholesterol Treatment Trialists' collaboration (CTT). CV events include myocardial infarction (MI) and unstable angina (collectively referred to as coronary heart disease [CHD]), stroke, transient ischaemic attacks (TIAs) and peripheral artery disease. However, this meta-analysis concerned statin therapies only.

The principal safety outcomes were all also considered and reported in the company's submission (CS). The short follow-up of most trials (12 weeks) prevented the reporting of meaningful numbers of fatal and non-fatal cardiovascular events, mortality data, apheresis (a type of 'extracorporeal' procedure to remove low density lipoprotein (LDL) cholesterol from the blood) or revascularisations. However, all available data were reported and additional safety data were also provided. Health-related quality of life (HRQoL) was not assessed or reported in any of the included trials. There were no reported equity issues, end of life criteria were not relevant to the submission and no PAS application was submitted. The Evidence Review Group (ERG) considers that the evidence presented in the submission was therefore generally consistent with the decision problem, with only minor discrepancies between the submission and the available evidence.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company submission (CS) consisted of three separate reviews: (i) a review of the clinical efficacy evidence from RCTs of evolocumab; (ii) a review of the evidence from non-randomised and non-controlled studies, and; (iii) a review of safety evidence from randomised and a non-randomised studies. The principal clinical efficacy review included four relevant RCTs: two trials comparing evolocumab with ezetimibe in adults with primary non-familial hypercholesterolaemia who were able to take statins (LAPLACE-2) or who were statin-intolerant (GAUSS-2); and two placebo-controlled trials, one in adults with primary non-familial hypercholesterolaemia (DESCARTES) and one in adults with HeFH (RUTHERFORD-2). Three RCTs evaluated both licensed doses of evolocumab (Q2W and QM) and one trial (DESCARTES) evaluated only the QM dose. All RCTs were found to be at a low risk of bias following quality assessment using a standard critical appraisal tool. The following results were presented for the primary efficacy outcome of LDL-C: mean percentage change from baseline, and mean percentage treatment difference, for a range of follow-ups: both the mean of the values at 10 and 12 weeks; and for 12 weeks alone (LAPLACE-2, GAUSS-2, RUTHERFORD-2) and for 12 and 52 weeks (DESCARTES). Detailed results were presented for all trial arms (based on the two licensed evolocumab doses and different background statins and comparator treatments). Detailed results were also provided in the main submission and appendices

for other lipid parameters and pre-specified and *post hoc* subgroup analyses based on key covariates. The submission reported that evolocumab provided consistent and intensive reductions in LDL-C compared to ezetimibe and placebo, regardless of patient population, dosing regimen, CVD risk, and presence and type of background lipid-lowering therapy. The results presented within the company's submission were based on the full analysis set (FAS) of the trials rather than the published data reported in the original publications.

The CS supplemented the main clinical efficacy review with additional efficacy evidence from two open-label extension trials, which included some slightly different populations in terms of baseline LDL-C and ethnicity (OSLER 1 and 2), and a single non-RCT (TAUSSIG) undertaken within the HeFH subgroup. The reported findings from these studies were consistent with the four key RCTs in terms of LDL-C reduction.

The review of the safety evidence included the four key RCTs, the supplementary studies from the efficacy review, and an integrated analysis set, which included a total of 14 RCTs. It was unclear how some of the evidence was identified and selected. The company's submission included extensive safety data on all adverse events (AEs), serious adverse events (SAEs), events leading to discontinuation, fatal and common AEs, as well as all-cause mortality and adjudicated cardiovascular events and non-coronary revascularisations, where such evidence was available. The submission concluded that the AEs were overall balanced between groups in all three periods of the integrated safety data set (12 weeks, year 1 and year 2), as well as across populations and therapeutic settings, and that most AEs were mild to moderate in severity, and SAEs and AEs leading to discontinuation of the intervention were infrequently reported and generally similar across treatment groups. A number of relevant ongoing trials were also listed.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The principal efficacy review represents a good quality systematic review of four relevant, good quality RCTs. The trials were generally consistent with the NICE scope. The primary efficacy outcome was mean percentage change in LDL-C from baseline, and mean treatment difference across trial arms, at follow-ups of 12 weeks (LAPLACE-2, GAUSS-2, DESCARTES and RUTHERFORD-2) and 52 weeks (DESCARTES).

In the LAPLACE-2 trial, at 12 weeks, patients with primary hypercholesterolaemia on background atorvastatin therapy (intensive and non-intensive doses) had a treatment difference in mean percentage change in LDL-C from baseline of -46.9 (95% CI, -53.0 to -40.7, $p<0.001$) and -42.5 (95%

confidence interval [CI], -47.9 to -37.0, $p<0.001$) for the Q2W and QM doses of evolocumab respectively, compared with ezetimibe (fixed effects model).
In the GAUSS-2 trial, at 12 weeks, patients with primary hypercholesterolaemia who were statin intolerant had a treatment difference in mean percentage change in LDL-C from baseline of -39.3 (95% CI, -45.0 to -33.5, $p<0.001$) and -38.1 (95% CI, -42.9 to -33.4, $p<0.001$) for the Q2W and QM doses of evolocumab compared with ezetimibe.

In the placebo-controlled RUTHERFORD-2 trial, at 12 weeks, patients with HeFH on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -62.7 (95% CI, -66.3 to -59.1) and -56.6 (95% CI, -60.9 to -52.3) for the Q2W and QM doses of evolocumab. The treatment difference in mean percentage change compared with placebo was -60.6 (95% CI, -66.7 to -54.5, $p<0.001$) and -60.3 (95% CI, -67.8, -52.9, $p<0.001$) for the Q2W and QM doses of evolocumab, respectively. The ERG received clinical advice that the HeFH population of the RUTHERFORD trial with a confirmed genetic mutation was higher than might be found in usual clinical practice in the UK, but the implications of this are unclear. The ERG also noted, following clinical advice, that the proportion of patients with Chronic Heart Disease (CHD) was higher in the intervention arms of the RUTHERFORD-2 trial (i.e. 30-36%) than would be expected in clinical practice in a HeFH population, and was higher than the prevalence reported for the other three trials (e.g. LAPLACE-2 trial arm populations ranged from 17% to 24% with CHD characteristics).

In the placebo-controlled DESCARTES trial, patients with primary hypercholesterolaemia on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -50.6 (95% CI, -53.2 to -48.0) for the QM dose of evolocumab at 52 weeks. The treatment difference in mean percentage change compared with placebo was -59.3 (95% CI, -63.8 to -54.9, $p<0.001$) at 52 weeks.

The results for other lipid parameters, such as non-HDL-cholesterol, HDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB) and lipoprotein(a) (Lp(a)), were consistent with the results for LDL-C, and pre-specified subgroup analyses demonstrated that these results were not sensitive to the different doses of evolocumab, or other key variables such as LDL-C baseline levels, severity of hypercholesterolaemia or CVD risk factors. The ERG noted that only 12-week evidence was available for the efficacy of the Q2W dose, whilst the QM dose had some data for 52 weeks. Additional clinical efficacy evidence was provided from a non-RCT study (TAUSSIG) and two open-label, extension studies (OSLER1 and 2). However, the extension studies included some trials with populations and/or comparators that were excluded from the principal review of the four RCTs and it is unclear how these trials and the non-RCT study were identified for inclusion in the company's review. The

inclusion of these studies was justified by the company on account of the longer-term evidence both from the extension studies and from TAUSSIG on the HeFH subgroup (36 weeks). A network meta-analysis (NMA) was not performed, although this might have been possible using particular trial evidence from both the primary non-familial hypercholesterolaemia population and the HeFH subgroup.

The clinical effectiveness review found that evolocumab is efficacious at lowering LDL-C, but in itself this is not a clinically important outcome: its importance is derived from it being a surrogate for CVD. Although there is an established relationship between statin-generated LDL-C reduction and reduced CV events, the impact of evolocumab on CVD has not been demonstrated: there is little or no direct evidence on this relationship. The ongoing FOURIER trial (clinicaltrials.gov identifier NCT02207634) aims to evaluate the impact of evolocumab on CVD outcomes, but only in people who have already had a CV event. The ERG also noted that there was no evidence on the relative efficacy of evolocumab versus ezetimibe in the familial hypercholesterolaemia subgroup, or for evolocumab in combination with ezetimibe in any population, and there was little or no direct trial evidence for evolocumab in terms of HRQoL or apheresis.

The submission of safety evidence was a non-systematic review of good quality RCTs, providing evidence for up to two years. There were no obvious safety concerns, with most AEs being balanced across evolocumab and comparator trial arms, and very small numbers of SAEs. However, the ERG noted that relatively higher 12-week AE rates were reported in patients who had HeFH or who had primary non-familial hypercholesterolaemia and were statin-intolerant. Similarly, these rates were also relatively higher for trials with a longer follow-up duration. This suggests that some patient subgroups might experience more frequent events and that all patients are at risk of AEs over time, though the rates are generally similar to comparators. The ERG noted also that the longer-term evidence presented was derived from some trials with populations who would not be eligible to receive evolocumab in clinical practice in the NHS (e.g. people who were not on maximum-tolerated doses of statins). Further long-term data are therefore needed in relevant UK populations, although it is not clear whether ongoing trials will address this.

1.4 Summary of cost effectiveness submitted evidence by the company

The CS includes a systematic review of economic evaluations of lipid lowering therapies together with a *de novo* model-based economic evaluation to assess the incremental cost-effectiveness of evolocumab versus ezetimibe (both with or without statins) for the treatment of patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia.

The company's systematic review included 108 previously published economic evaluations. One of the included studies is the model developed to inform NICE Clinical Guideline (CG) 181. None of these studies assessed the cost-effectiveness of evolocumab.

The company developed *a de novo* health economic model to assess evolocumab versus ezetimibe (both with and without statins) in three populations:

(i) Patients with non-familial primary hypercholesterolaemia who have no history of CVD (primary prevention);

(ii) Patients with non-familial primary hypercholesterolaemia who have existing CVD (secondary prevention), and;

(iii) Patients with HeFH, comprising a mix of patients who have no history of CVD and patients who have existing CVD (primary and secondary prevention).

For all three populations, separate analyses are presented for patients who are able to take statins (denoted ST) and for patients for whom statins are contraindicated or not tolerated (denoted SI). The company's base case analysis assesses evolocumab with/without statins; additional scenario analyses are presented in which evolocumab is used in combination with ezetimibe.

The company's base case model adopts a Markov approach and evaluates costs and health outcomes from the perspective of the NHS over a lifetime horizon. The model includes 24 mutually exclusive health states which include three individual "acute" event states (where patients remain for a maximum duration of one year unless they experience the same event during the next cycle), five individual "chronic" event states (including three "post-event" health states - post-acute coronary syndrome (ACS), post-ischaemic stroke (IS) and post-heart failure (HF), as well as no CVD and "established" CVD (ECVD), and thirteen composite CVD health states (including "acute" and "post-event" health states, which contain either two or three individual health states), and three death states (CHD death, stroke death and death due to other causes). The model is evaluated using an annual cycle length. Baseline characteristics for the non-familial primary prevention and secondary prevention populations were based on individual patient data (IPD) for a subset of patients from the LAPLACE-2 trial (those with LDL-C>2.5mmol/L), whilst baseline characteristics for the HeFH population were based on IPD from the modified intention-to-treat (ITT) population of the RUTHERFORD-2 trial. The model uses risk equations from the Framingham Heart Study and REduction of Atherothrombosis for Continued Health (REACH) Registry to predict CV risk and then adjusts these using calibration factors derived from an analysis of data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES), or using literature. For patients who are able to take statins, LDL-C treatment effects were based on the LAPLACE-2 trial. For patients for whom statins are contraindicated or not tolerated, treatment effects were based on the

GAUSS-2 trial. The impact of lowering lipid levels was modelled based on an assumed relationship between LDL-C reduction and CV event reduction. Health utilities were based on Euroqol 5-D (EQ-5D) and time trade-off (TTO) studies used in the NICE CG181 model. Costs were drawn from the NHS Drugs Tariff, NHS Reference Costs, the Personal Social Services Research Unit (PSSRU) and a CPRD/HES costing analysis.

The company's original base case model indicates the following results. Within the non-familial primary prevention statin tolerant (ST) population, the company's threshold analyses indicate that in patients with a baseline LDL-C of 3.5mmol/L, the incremental cost-effectiveness ratio (ICER) for evolocumab plus statins versus ezetimibe plus statins would be below £30,000 per QALY gained in patients with a 10-year CVD risk of 79% (or higher). The corresponding 10-year risk thresholds for patients with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 73% and 70%, respectively. Within the non-familial primary prevention statin intolerant (SI) population with a baseline LDL-C of 3.5mmol/L, the ICER for evolocumab versus ezetimibe would be below £30,000 per QALY gained in patients with a 10-year CVD risk of 81% (or higher). The corresponding 10-year risk thresholds for patients with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 75% and 71%, respectively. Within the non-familial secondary prevention ST population, the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.44 QALYs at an additional cost of £51,407 compared with ezetimibe plus statins; the resulting ICER is estimated to be £116,713 per QALY gained (probabilistic ICER=£119,012 per QALY gained). Within the non-familial secondary prevention SI population, the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.42 QALYs at an additional cost of £50,542 compared with ezetimibe monotherapy; the resulting ICER is estimated to be £119,971 per QALY gained (probabilistic ICER=£123,780 per QALY gained). Within the HeFH primary/secondary prevention ST population, the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.20 QALYs at an additional cost of £53,565 compared with ezetimibe plus statins; the resulting ICER is estimated to be £44,741 per QALY gained (probabilistic ICER=£46,412 per QALY gained). Within the HeFH primary/secondary prevention SI population, evolocumab monotherapy is expected to produce an additional 1.10 QALYs at an additional cost of £51,749 compared with ezetimibe monotherapy; the resulting ICER is estimated to be £47,193 per QALY gained (probabilistic ICER=£48,362 per QALY gained).

The ERG critically appraised the company's economic analysis and partially double-programmed the company's health economic model using transition probabilities taken directly from the company's model. Whilst the ERG's rebuild of the Markov component of the model did not identify any major problems, serious logic errors were identified in the transition probabilities used in the company's model whereby under certain combinations of parameter inputs, some of the model's transition

probabilities and hence health state populations became negative. The ERG requested that the company submit an amended model in which this problem was rectified. In response, the company acknowledged the problem and noted that their results for the non-familial primary prevention population were "invalid." The company also submitted an amended model and accompanying addendum which included an additional assumption which affects the risk predictions in the HeFH primary/secondary prevention population. The results for the non-familial secondary prevention population were unaffected by the company's amendments to the model.

The amendment to the company's model indicates the following results. Within the HeFH primary/secondary prevention ST population, the company's amended base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.15 QALYs at an additional cost of £73,620 compared with ezetimibe plus statins; the resulting ICER is estimated to be £47,195 per QALY gained (probabilistic ICER=£48,664 per QALY gained). Within the HeFH primary/secondary prevention SI population, evolocumab monotherapy is expected to produce an additional 1.05 QALYs at an additional cost of £52,486 compared with ezetimibe monotherapy; the resulting ICER is expected to be £49,900 per QALY gained (probabilistic ICER=£51,061 per QALY gained).

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG's critique of the company's model identified a number of matters of concern. These include: (i) deviations from the NICE Reference Case; (ii) concerns regarding the conceptualisation and implementation of the company's model structure and logic; (iii) concerns regarding the populations and baseline characteristics included in the company's analyses; (iv) issues regarding the use of CVD risk equations and the need for subsequent calibration; (v) concerns regarding the derivation of calibration factors to adjust the baseline risk of CVD for the raised LDL-C analysis; (vi) issues surrounding the derivation of the calibration factor to adjust the baseline risk of CVD for patients with HeFH; (vii) concerns regarding the appropriateness of treatment effects; (viii) issues regarding the relationship between LDL-C reduction and CVD events; (ix) the limited relevance of health utility estimates; (x) discrepancies in the cost parameters used in the company's model, and; (xi) errors in the interpretation and reporting of health economic results.

Whilst some of these issues reflect matters of subjective opinion, others reflect serious underlying problems regarding the conceptualisation and implementation of the model and the use of evidence to inform the model's parameters. These issues impact upon the credibility of the results presented within the CS and the subsequent addendum. The ERG notes that the amendments made to the company's model during the clarification process do not address the underlying issue, but merely

makes it less visible. Consequently, the ERG considers that all results presented by the company should be interpreted with caution.

1.6 ERG commentary on the robustness of evidence submitted by the company

The ERG considered the RCT evidence submitted by the company to be robust: it generally satisfied the requirements of the decision problem, with some minor exceptions, and should be considered to be good quality. The results were consistent across trials for both efficacy and safety outcomes.

1.6.1 Strengths

The ERG recognises that the submission included a good quality systematic review of the efficacy evidence and the four key RCTs were all good quality and at low risk of bias. The trials address most of the issues raised in the decision problem, their findings were generally consistent and appear to be unaffected by moderating variables.

The CS includes large reviews of existing economic evaluations, previous health utility studies, costing studies and CV risk equations. However, the relationship between these reviews and the structure and parameters used within the company's *de novo* health economic model are unclear.

1.6.2 Weaknesses and areas of uncertainty

The ERG noted that the principal areas of uncertainty in the clinical evidence concerned the absence of any direct evidence of the effectiveness of evolocumab compared with ezetimibe in HeFH populations and for evolocumab in combination with ezetimibe in any population. The ERG also noted uncertainty regarding the impact of evolocumab on CVD, apheresis and HRQoL because there was little or no direct evidence on these key outcomes. The safety evidence, though extensive, was derived in part from trial populations which do not reflect the patients likely to present in UK clinical practice, and AE rates appear to be higher in some subgroups: the provision of more long-term safety evidence in these populations would therefore be helpful. The ERG also notes that the longer-term efficacy and safety evidence from the placebo controlled trial DESCARTES relates only to the QM evolocumab dose: there are no equivalent data for the Q2W dose. Finally, it should be noted that, whilst LDL-C is an accepted surrogate outcome for CVD for statins, there is little or no direct evidence for the relationship between evolocumab and CV events. This is the reason for the current ongoing FOURIER trial, although this trial includes only people who have already had a CV event.

Serious logic errors were identified in the derivation of the transition probabilities within the company's model. Consequently, the ERG has serious doubts regarding the validity of the results presented within the CS and would advise considerable caution in their interpretation and use in

informing decision-making. Given the problems identified within the company's health economic model, the cost-effectiveness of evolocumab in any population remains unclear.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

As a consequence of multiple problems identified within the company's model, the ERG did not consider it appropriate or valuable to undertake additional exploratory analyses.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

Based on 2006 survey data, one third of adults aged 40-79 years in England are estimated to have high total serum cholesterol.[1] Elevated LDL-C is one of a number of factors that is predictive of the risk of CVD.[1,2] Estimates of the number of people in the UK in 2012/2013 who have CVD are based on around 2.3 million people suffering from CHD, 1.2 million people suffering from stroke, around one million from atrial fibrillation (AF) and just over 480,000 from HF.[3] There is variation in prevalence rates by gender, age and region.[3] The current management of elevated cholesterol levels includes dietary and lifestyle changes, such as smoking cessation, weight loss and increased physical activity. For individuals who still have elevated LDL-C, lipid-lowering therapies are recognised as being effective as first-line treatment for reducing LDL-C and also for reducing risk of CVD.[1] CVD can have major health and economic implications for people and health services: it remains the most common cause of mortality in women and the second most common cause of mortality in men in England.[3] Recent years have also seen consistent increases in prescription rates for lipid-lowering therapies in England.[3]

The populations referred to in the final NICE scope are people with primary hypercholesterolaemia and mixed dyslipidaemia.[4] Hypercholesterolaemia, a type of hyperlipidaemia, specifically refers to an excessive total plasma cholesterol concentration, especially LDL-C, in the blood. Hypercholesterolaemia has been defined as an elevated LDL-cholesterol of approximately $\geq$3mmol/l.[2] Hypercholesterolaemia might be secondary to a number of recognised conditions or factors, such as: nephrotic syndrome; type 2 diabetes mellitus; obesity; excessive alcohol consumption; and renal dialysis.[2] However, if these causes are excluded following clinical examination, then the hypercholesterolaemia is considered to be primary. Primary hypercholesterolaemia can be familial or non-familial. The former is defined as monogenic, i.e. related to a single genetic locus, in which the LDL-cholesterol is elevated from birth; it is characterised by a "dominant pattern of inheritance of premature coronary disease and/or tendon xanthomata."[5] In this population, one of the pair of LDL-receptor genes is defective or mutated and impairs the LDL cholesterol receptor activity leading to life-long elevated LDL-C levels.[2,5,6] This population is principally composed of the heterozygous familial hypercholesterolaemia (HeFH) subgroup specified in the final NICE scope and is most commonly diagnosed in the UK using the Simon Broome criteria,[7,8] although more novel molecular diagnosis tests are being developed.[9] The LDL-C levels in people with HeFH are typically two to three times higher than normal.[10,11] The prevalence of HeFH within primary hypercholesterolaemia in the UK is 0.2%,[2] with up to one in every 300 people affected worldwide.[12] Homozygous familial hypercholesterolaemia (HoFH) is a more severe and rare form of hyperlipidaemia with defects in LDL-receptor genes inherited from both parents rather than one.

Non-familial primary hypercholesterolaemia is elevated LDL-C produced by a combination of various genes and nutritional and lifestyle factors.[2] However, the exact role of genetic inheritance in producing LDL-C levels is unclear.[5] Non-familial hypercholesterolaemia is the most common form of primary hypercholesterolaemia in the UK: approximately 70% of people with primary hypercholesterolaemia have this non-familial type.[2]

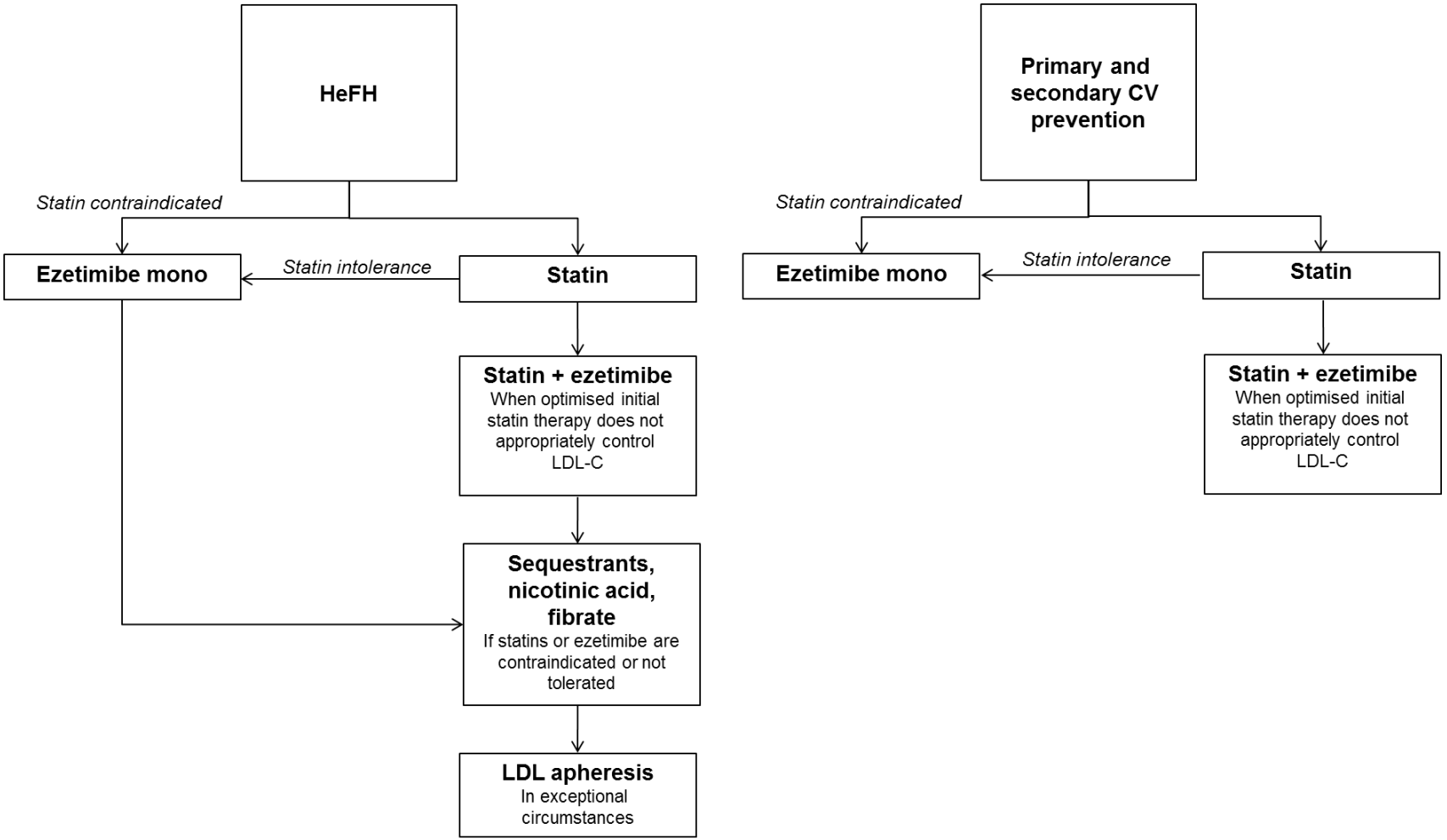
The second principal population referred to in the final NICE scope is people with "mixed dyslipidaemia." This is described in the literature also as "combined hyperlipidaemia", a disorder which is characterised by elevated LDL-C and high triglycerides and/or reduced or elevated HDL-C. It is a type of primary hypercholesterolaemia. Like primary non-familial hypercholesterolaemia, it is also relatively common: approximately 10% of people with primary hypercholesterolaemia in the UK have this type of "mixed dyslipidaemia".[2]

The CS provides a brief description of primary hypercholesterolaemia and mixed dyslipidaemia in accordance with the terminology used in the scope. The principal focus of the submission was a description of the relationship between elevated LDL-C and the risk of CVD and CV events (see CS,[13] pages 38-41).

2.2 Critique of manufacturer's overview of current service provision

The ERG and clinical advisors consider that the company's description of current service provision for the treatment of populations with primary hypercholesterolaemia and mixed dyslipidaemia (see CS,[13] pages 43-54) is mostly appropriate and relevant to the decision problem and that the recommendations of all relevant clinical guidelines have been taken into account. Figure 1 presents the company's view of the current UK clinical pathway of care for lipid-lowering therapy for primary hypercholesterolaemia, derived from relevant NICE guidelines and technology appraisals (TAs). The principal therapies prescribed for these populations are statins and, where relevant, ezetimibe and/or bile acid sequestrants, fibrates or high dose omega-3 fatty acids, which might be used if statins and/or ezetimibe are not appropriate.[14,15]

Figure 1: Summary of current UK clinical pathway of care for lipid-lowering therapy for primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia based on NICE clinical guidelines and technology appraisal guidance (reproduced from CS,[13] Figure 3-2, page 49)



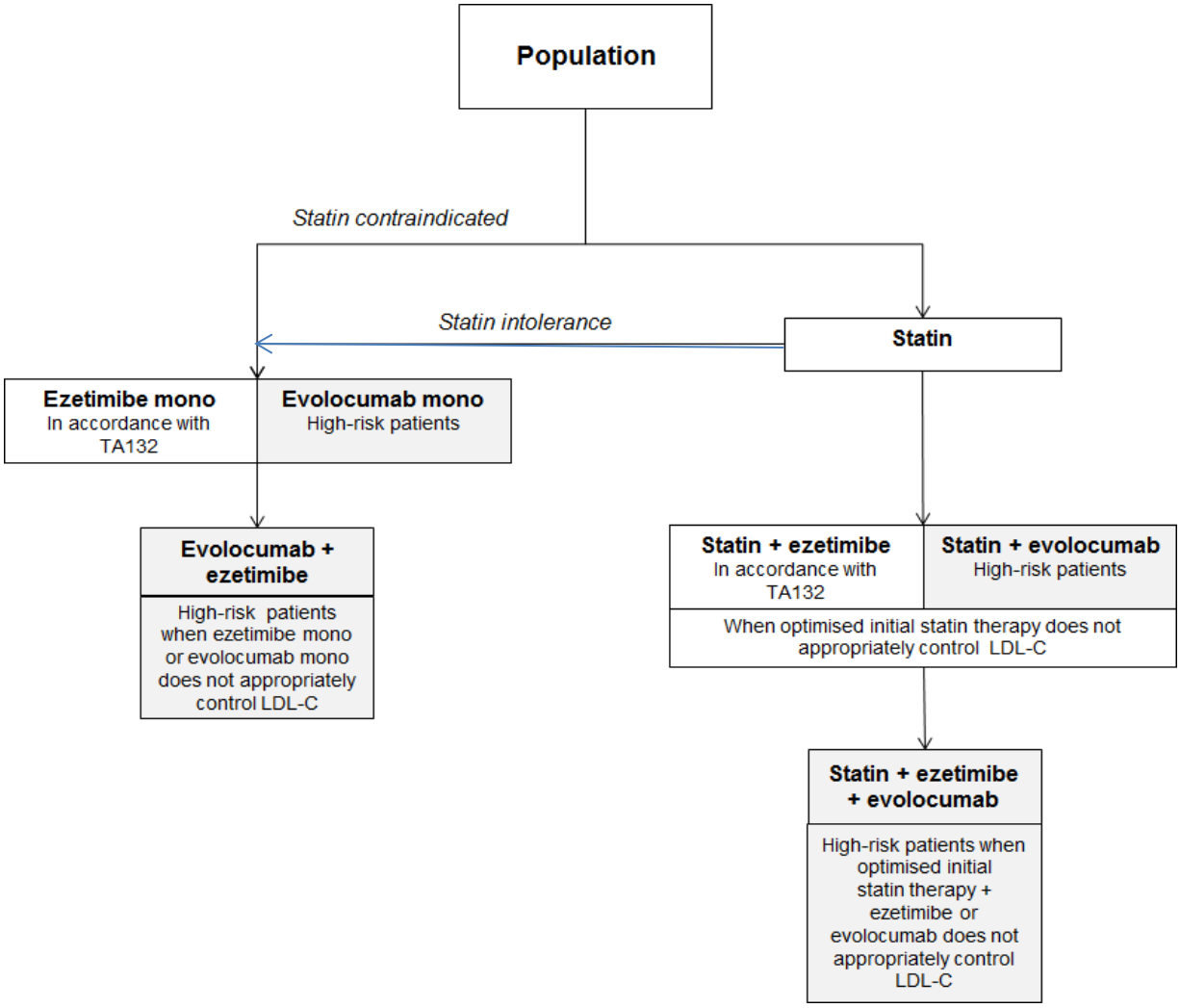
CV - cardiovascular; HeFH - heterozygous familial hypercholesterolaemia; LDL-C - low-density lipoprotein cholesterol; mono - monotherapy; NICE - National Institute for Health and Care Excellence

Figure 2 presents the company's view of the possible place of evolocumab in the pathway, with the different populations of Figure 1 possibly represented within the "high-risk patients" groups listed in Figure 2. As with ezetimibe, the company anticipates that evolocumab would only be prescribed in secondary care clinics. It would only be used after referral to specialist lipid clinics when initial statin therapy was considered to offer inadequate control of LDL-C or when patients were identified as being unable to take statins due to intolerance or contraindications. Statins are accepted as the first-line therapy for reducing LDL-C levels;[15] statin intolerance due to side effects, such as muscle-related symptoms (e.g. myalgia), might be encountered in between 5%[16] and 10%-20% of hypercholesterolemia patients.[17]

Clinical advisors to the ERG confirmed that the prescription of evolocumab only in secondary care clinics was appropriate. Advice from one clinician suggested that evolocumab might be used only when ezetimibe is inappropriate or ineffective rather than as an alternative to ezetimibe; this is because ezetimibe has longer-term safety data and evidence relating to its impact on CVD outcomes (e.g. the IMPROVE-IT trial[18]). The pathway fails to take account of the role of evolocumab relative to bile acid sequestrants, fibrates or high dose omega-3 fatty acids, which might be used if statins and/or ezetimibe are not appropriate.

Clinical advice received by the ERG confirmed that it was unlikely that there would be any requirement for additional tests or investigations for selection of patients appropriate for evolocumab, or any additional monitoring, over and above those which are part of routine clinical practice. The CS recommends using the Simon Broome criteria for diagnosing HeFH in accordance with NICE guidance.[19] However, the ERG noted, following clinical advice, that the accurate diagnosis of HeFH is potentially problematic in practice, especially in the absence of appropriate genetic testing.[9,20] It is worthy of note that in the trial of HeFH patients included in the submission (RUTHERFORD-2), between 17% and 24% of patients in any arm had a "possible" rather than a "definite" diagnosis of HeFH (CS, Table 4-8), and also that the proportion of participants who were tested and had a genetic mutation was much higher than in most studies.[21]

Figure 2: Proposed place of evolocumab in the treatment pathway (reproduced from CS,[13] Figure 3-3, page 55)



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

Currently available recommended therapies and their efficacy and safety are described in some detail in the CS, principally atorvastatin (dose based on risk of CVD, with a maximum dose of 80mg)[15] and ezetimibe (based on inadequate LDL-C control by statins or statin intolerance or contraindication).[14]

The CS proposes evolocumab as an alternative to ezetimibe as monotherapy for people in whom statins are contraindicated or are not tolerated, or in combination with statins if optimised statin therapy does not adequately control LDL-C levels. It is also proposed as a treatment, in combination with ezetimibe, when response to monotherapy is considered inadequate. Eligible patients are considered to be at high-risk of a CV event on account of inadequately-controlled LDL-C levels, one of a number of risk factors for CV events, due to the inappropriateness of statin therapy or the failure of a maximum-tolerated dose of statins to control LDL-C levels. This includes people with HeFH.

The CS claims that there is unmet need in these groups, who are at high risk of CV events. These high risk populations are defined in the CS (page 58) as:

- adults with primary non-familial hypercholesterolaemia who have not had a CVD event but have a greater than 10% 10-year risk of an event based on QRISK2,[22]
- adults with primary non-familial hypercholesterolaemia who have had a CVD event;
- adults with heterozygous familial hypercholesterolaemia (HeFH).

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The evidence presented within the CS was generally consistent with the decision problem, with only minor discrepancies between the submission and the available evidence. These are described in Sections 3.1-3.4 below. Table 1 summarises the populations, interventions and comparators specified within the company's decision problem.

Table 1: Decision problem in final NICE scope

Population	Intervention	Comparator
Primary hypercholesterolaemia and mixed dyslipidaemia	Evolocumab with statin	Ezetimibe with statin
Primary hypercholesterolaemia and mixed dyslipidaemia	Evolocumab with statin and ezetimibe	Ezetimibe with statin
Subgroups in NICE scope		
Primary hypercholesterolaemia, Statin intolerant	Evolocumab alone	Ezetimibe alone
Primary hypercholesterolaemia, Statin intolerant	Evolocumab with ezetimibe	Ezetimibe alone
HeFH	Evolocumab with statin	Ezetimibe with statin
HeFH	Evolocumab with statin and ezetimibe	Ezetimibe with statin
HeFH, statin intolerant	Evolocumab alone	Ezetimibe alone
HeFH, statin intolerant	Evolocumab with ezetimibe	Ezetimibe alone

HeFH - heterozygous familial hypercholesterolaemia

The clinical evidence focused on four RCTs: LAPLACE-2[23], GAUSS-2[24], RUTHERFORD-2[21] and DESCARTES.[25] Table 2 summarises the clinical trial evidence available for evolocumab in the treatment of hypercholesterolaemia.

Table 2: Clinical evidence presented within the CS

Population	**Intervention**	**Comparator**	**Trial evidence** (Acronym)
Primary hypercholesterolaemia	Evolocumab with statin	Ezetimibe with statin	LAPLACE-2, DESCARTES
Primary hypercholesterolaemia	Evolocumab with statin and ezetimibe	Ezetimibe with statin	DESCARTES (trial subgroup)
Subgroups in NICE scope			
Primary hypercholesterolaemia, Statin intolerant	Evolocumab alone	Ezetimibe alone	GAUSS-2
Primary hypercholesterolaemia, Statin intolerant	Evolocumab with ezetimibe	Ezetimibe alone	None
HeFH	Evolocumab with statin	Ezetimibe with statin	None
HeFH	Evolocumab with statin and ezetimibe	Ezetimibe with statin	RUTHERFORD-2
HeFH, statin intolerant	Evolocumab alone	Ezetimibe alone	None
HeFH, statin intolerant	Evolocumab with ezetimibe	Ezetimibe alone	None

HeFH - heterozygous familial hypercholesterolaemia

3.1 Population

Evolocumab is indicated for the treatment of adults aged 18 years or older with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, for those who have reached a maximum-tolerated dose on statins, or who are contraindicated for statins.[26]

It is also indicated for use in populations with homozygous familial hypercholesterolaemia (HoFH); this population is not covered by this appraisal.

The population described in the available clinical evidence is adult patients with primary hypercholesterolaemia (which includes mixed dyslipidaemia). This is consistent with the decision problem specified in the final NICE scope.[4] There is a single trial of evolocumab undertaken within a HeFH subgroup population.[21] The populations in the clinical evidence and the scope are largely consistent with the wording of the marketing authorisation for ezetimibe, which is the comparator required by the final NICE scope. Clinical evidence is presented for each of the subgroups listed for consideration in the scope: presence or risk of CVD (LAPLACE-2, DESCARTES); adults with HeFH (RUTHERFORD-2); adults in whom two or more statins cannot be tolerated, or only the lowest dose can be tolerated (GAUSS-2); and groups with differing levels of severity of hypercholesterolaemia (LAPLACE-2). The trial populations are generally consistent with the final NICE scope. One issue

concerns whether the populations in the trials where statin intolerance is not an issue were actually receiving the maximum-tolerated dose of statins, as required by the licence. For example, the LAPLACE-2 trial included patients on both moderate-intensity and high-intensity statin therapy; however, although data on the different statin groups were presented separately, the main comparison between evolocumab and ezetimibe did involve patients taking a higher dose of statin (atorvastatin 80 mg daily). DESCARTES also involved patients taking different doses of statin, including some on no statin or low-dose statin.

3.2 Intervention

The technology described is evolocumab (brand name: Repatha; AMG145) produced by Amgen. Evolocumab is a fully human monoclonal antibody that binds selectively to proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that affects the recycling of LDL-receptors on the surface of liver cells and decreases the ability of the liver to clear LDL from the blood.[26] By binding to PCSK9, evolocumab increases liver levels of LDL receptors, thereby reducing serum LDL-cholesterol levels. The benefits of evolocumab are its ability to reduce the level of serum LDL-cholesterol in patients who are unable to control their cholesterol despite taking a maximum tolerated dose of statins, or in patients who cannot take statins. The most common side effects are: nasopharyngitis, upper respiratory tract infection, headache and back pain. Evolocumab received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) regarding marketing authorisation within the EU on 22nd May 2015. Full marketing authorisation was granted in July 2015. The marketing authorisation states that evolocumab "is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated."

Evolocumab is given as either one dose (140mg) every two weeks (Q2W) or three doses (420mg) every month (QM), administered by subcutaneous injection (s.c.) via a prefilled pen or syringe. The intervention is designed to be self-administered by the patient after proper training.

The final NICE scope required the consideration of evolocumab as monotherapy or in combination with a statin with or without ezetimibe, or in combination with ezetimibe (without statin). The clinical evidence presented satisfied the majority of these principal combinations of interventions, although data on the combination of evolocumab with statin therapy and ezetimibe in primary non-familial

(DESCARTES trial subgroup) and familial (RUTHERFORD-2) hypercholesterolaemia populations were from trial subgroups only, and then only with ezetimibe as background therapy. Evidence was also absent for certain subgroups that were to be considered, in particular there were no head-to-head trials of evolocumab in combination with ezetimibe in populations in whom statins could not be tolerated or were contraindicated in either the non-familial or HeFH populations.

3.3 Comparators

The decision problem required the consideration of evolocumab (with or without statins and with or without ezetimibe) versus ezetimibe (with or without statins). The clinical evidence presented satisfied the majority of these principal combinations of interventions and comparators. The appraisal focused on evolocumab and ezetimibe and does not consider other lipid-lowering therapies, such as bile acid sequestrants, fibrates and nicotinic acid.[27]

3.4 Outcomes

The principal efficacy outcomes for consideration were plasma lipid and lipoprotein levels, including LDL-cholesterol, non-HDL-cholesterol, HDL-cholesterol, TG, triglycerides (TG), apolipoprotein B (ApoB) and lipoprotein(a) (Lp(a)). These were reported in all RCTs included in the company's review of clinical efficacy. The majority of the clinical evidence reported follow-up for 12-weeks. The exception was the DESCARTES trial, which reported data for 12 weeks and 52 weeks. The use of LDL-C as a surrogate for CVD is generally accepted for statin therapies and the company provided evidence for the relationship between LDL-C reduction and the reduction of CV events, citing the meta-analyses of the CTTC, which have recently found that a reduction of 1mmol/L might lead to 22% reduced risk of CV events.[18,28-30] CV events include MI and unstable angina (collectively referred to as CHD) stroke, TIAs and peripheral artery disease.[31] However, the optimal LDL-C level to minimise risk of CVD is not known and only long-term data can provide robust evidence of the efficacy of evolocumab on CVD outcomes, as well as its long-term safety. These issues are being addressed in part in ongoing trials, such as the FOURIER trial (NCT01764633) for CV events in a hypercholesterolaemia population with existing CVD[32] and the long-term, open-label extension studies OSLER 1 and OSLER-2.[33]

The principal safety outcomes were all also considered and reported in the submission. However, the short follow-up of most trials (12 weeks) prevented the reporting of meaningful numbers of fatal and non-fatal cardiovascular events, all-cause mortality data, apheresis or revascularisations. However, all available data were reported and additional safety data were also provided. For example, coronary and non-coronary revascularisations were not reported from the four clinical efficacy trials, but were reported from other sources (see CS,[13] Table 4-27, pages 145-146). In order to address the required outcome of apheresis, the results of a non-RCT assessing efficacy in LDL-C reduction at 36 weeks in

people with familial hypercholesterolaemia currently receiving apheresis were also reported (see CS,[13] Section 4.11).

Health-related quality of life (HRQoL) was not assessed or reported in any of the included trials. The company's *de novo* model used other published evidence for HRQoL based on studies used to inform NICE CG181.[15]

3.5 Other relevant factors

There were no reported equity issues, end of life criteria were not relevant to the submission and no PAS application was submitted.

4. CLINICAL EFFECTIVENES

This section presents a summary and critique of the reviews submitted by the company on the efficacy and safety of evolocumab in the relevant populations. The critique was performed following the principles of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and checklist.[34]

4.1 Critique of the methods of review(s)

The CS reports three separate reviews:

- a review of the efficacy evidence from RCTs (see CS,[13] Sections 4.1-4.10);
- a review of the efficacy and safety evidence from non-randomised and non-controlled studies (see CS,[13] Section 4.11), and;
- a review of safety evidence from RCTs and a non-randomised study (see CS, Section 4.12).[13]

Each review appears to have applied different inclusion criteria. However, only the criteria for the first review of clinical efficacy evidence from RCTs were described within the CS. Following a request for clarification regarding certain process elements (the searching, study selection, data extraction and quality assessment processes and descriptive synthesis), this efficacy review of RCT evidence was considered by the ERG to be generally robust (see clarification response,[35] questions A1, A9 and A12). The review of the efficacy and safety evidence from non-randomised and non-controlled studies was limited to a single two-arm Phase II/III trial of a severe familial hypercholesterolaemia (FH) population (TAUSSIG). This was not considered to be a systematic review because it was unclear how the evidence was identified, selected and extracted, no inclusion or exclusion criteria were provided, no list of excluded studies was provided, and no quality assessment of the included study was performed by the company. The review of the safety evidence is also not considered to be a systematic review because it was unclear from the original submission how some of the evidence was identified and selected; no detailed inclusion or exclusion criteria were provided, no list of excluded studies was provided, and no quality assessment was performed on the majority of included studies. However, in response to a request for clarification by the ERG (see clarification response,[35] question A12), the company conducted a quality assessment of the studies included in the safety evidence review.

4.1.1 Searches

Searches to identify evidence of clinical effectiveness and safety were conducted in March 2015 and were reproduced in full in the appendices to the CS. The searches were well structured, based on an appropriate PICO analysis of the key concepts specified in the review question and, by searching for a

range of comparators in addition to evolocumab, allowed for the possibility of identifying relevant studies for indirect as well as direct comparisons of effectiveness. Subject headings and free text terms (including a range of synonyms) have been used appropriately. The search terms used are consistent with the topic of the appraisal. Terms for "mixed dyslipidaemia" were not included among the indications in the search strategy, but this was corrected in a supplementary search conducted by the company at the request of the ERG (see clarification response,[35] question A1) and no additional relevant studies were identified. There were also some minor errors in the company's searches, including redundant repetition (e.g. fluvastatin or fluvastatin sodium) and some minor typographical errors (e.g. ".tn." is not a valid index in MEDLINE). There was also some inconsistency in the use of field tags, with some terms only being searched for in specific fields, whilst others were searched for in all fields.

Searches were conducted across a range of relevant databases (including MEDLINE, EMBASE and the Cochrane Library) and were accurately translated to the different requirements of these platforms (for example, choosing the correct subject headings available in each database). PubMed was not among the sources searched; had it been included, there would have been an additional opportunity to find recent studies not yet indexed in MEDLINE or MEDLINE In-Process. No limits were applied to these searches, except for an RCT filter, based on Cochrane's Highly Sensitive Search Strategy (HSSS) for identifying randomised controlled trials.[36] The ERG notes that the company's searches made several minor alterations to this filter without explanation; these were later clarified by the company and the search was not adversely affected (see clarification response,[35] question A2). The ERG also questioned how non-RCT evidence was identified, given that this was explicitly excluded by the use of an RCT filter; the company responded that non-RCT evidence was not identified using systematic review methods (see clarification response,[35] question A3).

Additional searches of several relevant trials registers and conference proceedings were also conducted, and there is some mention of hand-searching of reference lists, which did not include forward tracking of citations. On re-running a sample of searches, the numbers of results were consistent with those reported in the PRISMA diagram and search histories (see CS, p.66 and Appendix 3). Despite the caveats noted above, the ERG is broadly satisfied with the comprehensiveness of the company's search strategy.

4.1.2 Inclusion criteria

The inclusion criteria for the reviews are described in Table 4-1 of the CS (see Table 3). However, these criteria can only relate to the reviews of RCT evidence assessing clinical efficacy and safety because non-randomised studies are explicitly excluded (and an RCT study filter is applied in the reported searches). The criteria also specifically include populations with HoFH, although these

studies, as well as studies of Japanese populations,[37] are then correctly excluded using additional inclusion/exclusion criteria described later in the CS. The intervention should have also included evolocumab in combination with ezetimibe in accordance with the decision problem specified in the final NICE scope.

The review of RCT evidence of clinical efficacy also included evidence from a non-RCT study, TAUSSIG,[38] which should have been excluded based on the reported inclusion criteria, and the OSLER 1 and 2 trials,[33] which included participants from trials excluded from the principal clinical efficacy review because the populations and comparators did not satisfy the criteria outlined in the company submission (see CS, Table 4-1[13] and Table 3), for example, the studies involving Japanese patients and varying standards of care. This was acknowledged in the CS, but the trials were all retained with the justification that they provided longer-term evaluation data.

The review of the efficacy and safety evidence from non-randomised and non-controlled studies did not specify any inclusion criteria. This review reported a single study of severe FH patients who were allocated to a trial arm depending on whether or not they were also receiving apheresis (TAUSSIG). The inclusion of this study was justified in the submission on account of having included populations (FH and apheresis) which were relevant to the decision problem and on account of having longer-term efficacy evidence than RUTHERFORD-2 (36 weeks versus 12 weeks).

The inclusion criteria for the review of safety evidence from both RCTs and non-randomised studies were not specified. This review initially included the four RCTs from the clinical efficacy review, as well as the OSLER 1 and 2 trials, and the TAUSSIG study from the review of non-randomised and non-controlled studies. However, as noted above, the methods by which these additional studies were identified and the criteria by which they were selected, and others were excluded, are not clear. A set of integrated analyses of safety data were then presented that contained additional randomised and non-randomised studies which were excluded from the clinical efficacy review (see CS, Section 4.12).[13]

Table 3: Inclusion and exclusion criteria for the broad clinical efficacy/safety systematic literature review (reproduced from CS,[13] Table 4-1, page 63)

	Inclusion criteria	Exclusion criteria
Population	• Studies in adults (≥ 18 years old) with primary hypercholesterolaemia (including familial and non-familial) who are candidates for treatment of elevated lipid levels (hyperlipidaemia) and consequent reduction in CV events. For patients with HoFH, studies including patients ≥ 12 years old were also included • Where available, data were identified and reported for two specific groups of patients: ▪ Patients whose condition is not adequately controlled or is unlikely to be adequately controlled (according to European lipid targets) with a statin alone ▪ Patients in whom a statin is considered inappropriate or is only tolerated at low dose/intensity. • Data relevant to the following subgroups were identified: ▪ Patients with HeFH; patients with HoFH; patients with IHD, CVD, or PAD; and patients with diabetes mellitus type 2 • Data were also recorded for subgroups defined by gender, age (< 65, ≥ 65 years), and race (white, non-white) where reported	• Studies including patients with organ transplantations and infectious diseases (e.g. HIV) were excluded. In addition, studies including patients with significant heart failure (NYHA grade III-IV) or significant renal dysfunction (Stage 4-5), which are considered to be major confounding comorbidities, were also excluded
Intervention	• Evolocumab used in combination with moderate- or high-dose statins where cholesterol is insufficiently controlled with statin therapy alone and as monotherapy (in for example statin-intolerant patients). The following doses of evolocumab evaluated will be eligible for inclusion: ▪ 140 mg SC Q2W (1 prefilled AI/pen injection) ▪ 420 mg SC QM (3 prefilled AI/pen injections or 1 personal injector injection)	• Studies that do not include either the included intervention or comparator agents as one of their treatment arms
Comparators[a]	<u>Patients whose condition is not adequately controlled with a statin alone</u> • Alternative moderate- to high-intensity statin monotherapies (daily dose lowers LDL-C on average, by approximately ≥ 30%): atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin • Or alternatively, statins in combination with any of the following alternative lipid-lowering therapies such as: other alternative PCSK9 inhibitor monotherapies; cholesterol absorption inhibitors; nicotinic acids; fibrates; cholesteryl ester transfer proteins; and lomitapide, mipomersen, and apheresis (for HoFH) <u>Patients in whom a statin is considered inappropriate or is not tolerated</u>	

	Inclusion criteria	Exclusion criteria
	• No treatment/placebo; other alternative PCSK9 inhibitor monotherapies; cholesterol absorption inhibitors; bile acid resins; fibrates; cholesteryl ester transfer proteins; and lomitapide, mipomersen, and apheresis (for HoFH)	
Outcomes	<u>Clinical outcomes</u> • Overall survival; incidence of CV death; incidence of non-CV death; incidence of fatal and non-fatal CV events (composite and individual outcomes) e.g. CV death, MI, ischaemic stroke, TIA, hospitalisation for unstable angina, hospitalisation for worsening heart failure, symptomatic PAD, CHD and coronary revascularisation; time to fatal or non-fatal CV events (composite and individual outcomes) <u>Lipid-related outcomes (absolute values and change from baseline):</u> • LDL-C; triglycerides; HDL-C; VLDL-C; total cholesterol; total cholesterol/ HDL-C ratio; non-HDL-C; ApoB; ApoB/ApoA1 ratio; Lp(a); and incidence of apheresis (HoFH only). <u>Safety outcomes</u> • Incidence of treatment-related adverse events (any event, serious events, and specific individual events such as hepatic events, gastrointestinal events, headaches, muscle-related events, etc.) <u>Patient-reported outcomes (absolute values and change from baseline)</u> • HRQoL	• RCTs that do not assess one of the included outcomes
Study design	RCTs (including randomised dose finding and formulation studies with either a control or active control arm) were eligible for inclusion, if they were of ≥ 12 weeks' duration. This reflects regulatory guidance on the minimum duration of studies to demonstrate the lipid-lowering effects of investigational agents. It is also in line with previous recommendations included in NICE TA132 (ezetimibe for the treatment of hypercholesterolaemia). This STA reported that trials of shorter duration were considered 'unlikely to inform on survival, CVD events, adverse events or HRQoL' and were also 'excluded to allow for the tachyphylaxis effects'.	• Non-randomised studies • Studies < 12 weeks' duration or with < 10 participants per arm • Pre-clinical, phase 1, and animal studies
Language	Searches were not limited by language.	N/A

[a]A more detailed list of specific comparator agents was provided in CS, Appendix 3.AI, autoinjector; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; HIV, human immunodeficiency virus; HoFH, homozygous familial hypercholesterolaemia; HRQoL, health-related quality of life; IHD, ischaemic heart disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); MI, myocardial infarction; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; QM, monthly; RCT, randomised controlled trial; SC, subcutaneous; STA, single technology appraisal; TIA, transient ischaemic attack; VLDL-C, very low-density lipoprotein cholesterol

4.1.3 Critique of study selection and data extraction

No information was given in any of the reviews regarding the data extraction process (for example, the number of reviewers involved, actions taken to minimise error), but this was addressed in response to clarification requests (see clarification response,[35] question A9). Following standard systematic review processes, trials were independently selected for inclusion by two reviewers, with any discrepancies between reviewers resolved through discussion or the intervention of a third reviewer. Data extraction was performed by one reviewer and independently checked for errors against the original trial report by a second reviewer. Any discrepancies were resolved through discussion or through the intervention of a third reviewer. An error in the PRISMA flowchart was acknowledged and addressed by the company in response to a clarification request from the ERG (see clarification response,[35] question A10).

4.1.4 Quality assessment

For the review of clinical efficacy, the company undertook a thorough critical appraisal of the four included trials using a standard risk of bias assessment tool (see CS,[13] Section 4.6). The submission reported that the trials were at low risk of bias across all domains. Critical appraisal of the four trials was also conducted by the ERG and the assessments reported by the company were found to be generally reasonable based on data presented in the trial protocols, published journal articles and clinical study reports. It should be noted that the 52-week DESCARTES trial had greater scope for bias in the potential moderating effects of co-interventions regarding maintenance of diet, exercise and other lipid-lowering regimens, but the principal caveat is that the data in all trials were analysed using a 'modified intention-to-treat (ITT)' approach (all patients who received at least one dose of study drug included in the analysis) rather than a true ITT analysis (including all randomised patients in the groups to which they were assigned). This approach can result in bias: trials using a modified ITT analysis tend to report larger treatment effects than those that use a true ITT approach.[39] Numbers of patients who were excluded from the analysis after randomisation were as follows: 3/1899 in LAPLACE-2; 1/307 in GAUSS-2; 4/905 in DESCARTES; and 2/331 in RUTHERFORD-2. These data suggest that bias introduced by deviation from a true ITT analysis is unlikely to have had a major impact on the results of these trials.

For the non-randomised evidence, a single additional, non-RCT study was identified and its findings were presented, but a quality assessment was not performed for this study. The risk of bias affecting this study is therefore uncertain.

For the review of the safety evidence (see CS,[13] Section 4.12), data from fourteen studies, RCTs and one non-RCT were presented, but other than the four trials also included in the clinical effectiveness

review, no quality assessment of these studies was performed within the CS. However, this was addressed by the company in response to a clarification request from the ERG (see clarification response,[35] question A12). The ERG accepts that the included studies are likely to be at low risk of bias.

4.1.5 Evidence synthesis

The synthesis for the review of clinical efficacy was a basic descriptive summary of the evidence from the four included trials. A meta-analysis was not performed and there was no discussion of heterogeneity in treatment effects between studies.

Following a request from the ERG, the company provided a justification for not conducting an network meta-analysis (NMA); the company argued that such an analysis was not necessary due to the availability of relevant head-to-head trials for the principal population: "*Given the availability of robust RCTs that provide head-to-head efficacy data for the intervention versus relevant comparators for patients with primary hypercholesterolaemia and mixed dyslipidaemia, a network meta-analysis was not considered to be necessary*" (clarification response,[35] question A14). The submission justified not undertaking an NMA within the HeFH subgroup on account of baseline differences between the identified studies in terms of background lipid-lowering therapy; the ERG considered this to be reasonable.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Review of clinical efficacy (RCT evidence)

The submission provides a very detailed, extensive description of four included trials (see Table 4). Two RCTs were presented as relevant interventions versus relevant comparators for the decision problem: LAPLACE-2 and GAUSS-2. These two trials compared evolocumab with ezetimibe in people with primary hypercholesterolaemia whose LDL-C was uncontrolled on statins (LAPLACE-2) or who were statin intolerant (GAUSS-2). Two further trials included in the CS were placebo-controlled, but were included because: they provided longer-term data (DESCARTES, 52 weeks); because pre-specified stratification factor and covariate subgroup analyses provided relevant comparative data (DESCARTES); or because they provided comparative data on a recognised subgroup of interest (HeFH) (RUTHERFORD-2).

Table 4: Included RCTs: Basic characteristics

Study (Acronym)	Population	Intervention	Comparator
LAPLACE-2	Primary hypercholesterolaemia	Evolocumab with statin	Ezetimibe with statin
GAUSS-2	Primary hypercholesterolaemia, intolerant to at least 2 statins or able to tolerate only the smallest dose because of muscle-related side-effects	Evolocumab alone	Ezetimibe alone
DESCARTES	Primary hypercholesterolaemia	Evolocumab with statin and ezetimibe	Ezetimibe with statin
RUTHERFORD-2	HeFH	Evolocumab with statin	Placebo and statin

HeFH - heterozygous familial hypercholesterolaemia

The LAPLACE-2 trial recruited people who have non-familial primary hypercholesterolaemia. The trial directly compared evolocumab in its two licensed doses with ezetimibe (10mg once daily (OD)) in people also taking a statin. The trial directly compared evolocumab in combination with three statins at five doses: an intensive statin dose (atorvastatin 80mg and rovustatin 40mg) and a non-intensive dose (atorvastatin 10mg, simvastatin 40mg and rovustatin 5mg). The trial measured change in LDL-C from baseline to 12 weeks.

The GAUSS-2 trial recruited people who have non-familial primary hypercholesterolaemia but in whom two or more statins could not be tolerated, or only the smallest dose could be tolerated. The trial directly compared evolocumab in its two licensed doses with ezetimibe (10mg OD) in the absence of statin therapy. The trial measured change in LDL-C from baseline to 12 weeks.

The DESCARTES trial recruited people who have non-familial primary hypercholesterolaemia. The trial directly compared evolocumab, at the QM dose only, with placebo in the presence of background lipid-lowering therapy. The trial measured change in LDL-C from baseline to both 12 weeks and 52 weeks. The trial was included on account of its longer-term data. However, the trial did not compare evolocumab with ezetimibe, and included people who did not receive statins or received only low intensity statins (10mg atorvastatin), who were neither statin intolerant nor on a maximum-tolerated dose of a statin. It was therefore not wholly consistent with the decision problem specified in the final NICE scope.[4] The trial also had a subgroup of patients who received ezetimibe as background therapy.

The RUTHERFORD-2 trial recruited patients with HeFH. The trial directly compared evolocumab in its two licensed doses with placebo in patients receiving stable lipid-lowering therapy at baseline. The trial measured change in LDL-C from baseline to 12 weeks. The ERG received clinical advice that the HeFH population of the RUTHERFORD trial with a confirmed genetic mutation was higher than might be found in usual clinical practice in the UK,[40] but the implications of this are unclear. The ERG also noted, following clinical advice, that the proportion of patients with CHD was higher in the intervention arms of the RUTHERFORD-2 trial (i.e. 30-36%) than would be expected in clinical practice in a HeFH population, and was higher than the prevalence reported for the other three trials (e.g. LAPLACE-2 trial arm populations ranged from 17% to 24% with CHD characteristics).

A list of excluded studies, with reasons, was provided by the company (see CS,[13] Section 4.1 and Appendix 3). The principal reasons for excluding studies that otherwise satisfied the inclusion criteria for the review (for example, a number of relevant Phase II trials) were the publication of an identical, subsequent, larger Phase III trial (e.g. LAPLACE-1, GAUSS-1, RUTHERFORD-1), the absence of statins in a cohort who were eligible for statins, as required by the marketing authorisation for evolocumab,[41,42] or the absence of a relevant comparator.[43,44]

All four included trials were international and multicentre. The populations of three of the included trials are reported in the submission as having "primary hypercholesterolaemia and mixed dyslipidaemia" (LAPLACE-2, GAUSS-2, DESCARTES, see Table 5). The final selection of four included trials for the clinical effectiveness review was therefore considered by the ERG to be reasonable. However, the appearance of two new, open-label extension trials, OSLER 1 and OSLER 2,[33] within the results section of the CS (see CS,[13] Section 4.10, Table 4-10) was neither justified nor appropriate. Efficacy results are provided from these "Supplementary ongoing, randomised, controlled, open-label LTE studies" (see CS, pages 120-121), but these trials contain mixed populations from Phase II and other RCTs that were otherwise explicitly excluded from the clinical effectiveness review, as described above. It was acknowledged in the CS that this population might not reflect the population that would receive evolocumab in clinical practice in England. This evidence is therefore arguably not relevant to this appraisal.

Patient characteristics were generally well-balanced across arms in all trials. It should also be noted that people with type 1 diabetes mellitus or newly-diagnosed or poorly-controlled type 2 diabetes mellitus were excluded from the four key trials. This group represent a cohort of patients who are highly likely to present with hypercholestorelaemia[45] and who are at a high risk of CVD events.

Table 5: Included RCTs: Populations

Study (Acronym)	Design	Population	Inclusion criteria	Exclusion criteria
Non-familial primary hypercholesterolaemia				
LAPLACE-2	International, multi-centre, Phase III, parallel-group, double-blind RCT	Patients with "primary hypercholesterolaemia and mixed dyslipidaemia" treated with background moderate- to high-intensity statin therapy	• Informed consent • Male or female ≥ 18 to ≤ 80 years of age • Fasting LDL-C ≥ 2.1 mmol/L (taking an intensive statin at screening), ≥ 2.6 mmol/L (taking a non-intensive statin at screening), or ≥ 4.5 mmol/L (not taking a statin at screening) at screening • Fasting TG ≤ 4.5 mmol/L at screening • Negative pregnancy test, AST and ALT ≤ 2 times ULN, CK ≤ 3 x ULN as determined by central laboratory at the end of the lipid stabilisation period	• Use of other lipid-lowering therapy other than statin or ezetimibe in previous 6 weeks • NYHA class III/IV HF or LVEF < 30% • Uncontrolled cardiac arrhythmia within 3 months • MI, UA, PCI, CABG, or stroke within 6 months • Planned cardiac surgery or revascularisation • Type 1 diabetes or newly diagnosed or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction
GAUSS-2	International, multi-centre, Phase III, parallel-group, double-blind RCT	Patients with "primary hypercholesterolaemia and mixed dyslipidaemia" with statin intolerance	• Informed consent • Male or female ≥ 18 to ≤ 80 years of age • No or low-dose statin at baseline • Fasting LDL-C at screening based on NCEP ATP III risk category goals ▪ LDL-C ≥ 2.6 mmol/L for those with CHD or CHD risk equivalents ▪ LDL-C ≥ 3.4 mmol/L for patients without diagnosed	• NYHA class III/IV HF or LVEF < 30% • Uncontrolled cardiac arrhythmia in the prior 3 months • MI, UA, PCI, CABG, or stroke within 3 months • Planned cardiac surgery or revascularisation • Type 1 or 2 diabetes or newly diagnosed

Study (Acronym)	Design	Population	Inclusion criteria	Exclusion criteria
Non-familial primary hypercholesterolaemia				
			CHD or risk equivalent but with ≥ 2 risk factors ▪ LDL-C ≥ 4.1 mmol/L for patients without diagnosed CHD or risk equivalent but with 1 risk factor ▪ LDL-C ≥ 4.9 mmol/L for patients without diagnosed CHD or risk equivalent and no risk factors • Statin intolerant (history of intolerance to ≥ 2 statins) ▪ Inability to tolerate any dose or increase above a maximum dose[b] because of intolerable muscle-related side effects; AND ▪ Symptoms resolved or improved when statin dose was decreased or discontinued • Stable lipid-lowering therapy for ≥ 4 weeks before screening if on statin and/or bile acid sequestrant and/or stanol; if on ezetimibe at screening, ezetimibe must be discontinued for ≥ 4 weeks before LDL-C screening • Fasting TG ≤ 4.5 mmol/L at screening	or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction
DESCARTES	International, multi-centre, Phase III, parallel-group, double-blind RCT	Patients with "primary hypercholesterolaemia and mixed dyslipidaemia" treated with background lipid-lowering therapy	• Informed consent • Male or female ≥ 18 to ≤ 75 years of age • Fasting LDL-C ≥ 2.0 mmol/L and fasting TG ≤ 4.5 mmol/L at screening • Fasting LDL-C after 4-week lipid stabilisation period with one of four background lipid-lowering therapy regimens based on NCEP ATP III risk category goals	• CHD or CHD risk equivalent and not receiving statin with LDL-C at screening ≤ 2.6 mmol/L • NYHA class II/III/IV HF or LVEF < 30% • Uncontrolled cardiac arrhythmia within 3 months prior to randomisation

Study (Acronym)	Design	Population	Inclusion criteria	Exclusion criteria
Non-familial primary hypercholesterolaemia				
			▪ LDL-C ≥ 2.0 mmol/L and < 2.6 mmol/L for those with CHD or CHD risk equivalents; ▪ LDL-C ≥ 2.0 mmol/L and < 3.4 mmol/L in patients without CHD or risk equivalent; ▪ OR for patients on maximal background lipid-lowering therapy (diet + atorvastatin 80 mg + ezetimibe), LDL-C ≥ 2.0 mmol/L	• MI, UA, PCI, CABG, or stroke within 3 months prior to randomisation • Planned cardiac surgery or revascularisation • Type 1 diabetes or newly diagnosed or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction
Familial primary hypercholesterolaemia: HeFH				
RUTHER-FORD-2	International, multi-centre, Phase III, parallel-group, double-blind RCT	Patients with HeFH treated with stable background lipid-lowering therapy (statin ± other lipid-lowering therapy)	• Informed consent • Male or female ≥ 18 to ≤ 80 years of age • Diagnosis of HeFH by Simon Broome criteria • On a stable dose of an approved statin ± other allowed lipid-lowering therapy (e.g. ezetimibe, resins, stanols, or niacin) for ≥ 4 weeks before screening and, in the opinion of the investigator, not requiring uptitration • Fasting LDL-C ≥ 2.6 mmol/L at screening • Fasting TG ≤ 4.5 mmol/L at screening	• HoFH • LDL or plasma apheresis within 4 months • NYHA class III/IV HF or LVEF < 30% • Uncontrolled cardiac arrhythmia within 3 months • MI, UA, PCI, CABG, or stroke within 3 months • Planned cardiac surgery or revascularisation • Type 1 diabetes or newly diagnosed or poorly controlled type 2 diabetes • Major haematologic, renal, metabolic, GI, or endocrine dysfunction

The three RCTs that assessed a general primary non-familial hypercholesterolaemia population included more than 3,000 participants. Three of the RCTs had a follow-up of 12 weeks; one trial reported data for 12 and 52 weeks (DESCARTES, see Table 6). The intervention was administered using both licensed doses of evolocumab in separate arms in all trials, with the exception of the 52-week DESCARTES trial, which only used the QM regime of 3 doses per month (420mg). The doses of ezetimibe (10mg OD) and background statin therapy were generally in accordance with NICE guidance.[14,15] The ERG noted that there is a lack of evidence on the effectiveness of evolocumab in combination with ezetimibe (all populations). This was provided in subgroups for the RUTHERFORD and DESCARTES trials, but with ezetimibe only as part of the background therapy (in a comparison with placebo).

Table 6: Included RCTs: Interventions and comparators

Study (Acronym)	Numbers randomised	Follow-up	Intervention	Comparator
Non-familial primary hypercholesterolaemia				
LAPLACE-2	n=1899	12 weeks	• Evolocumab 420 mg QM + Placebo OD oral (n = 562) • Evolocumab 140 mg Q2W + Placebo OD oral (n = 557)	• Placebo QM + Placebo OD oral (n = 278) • Ezetimibe 10 mg OD oral + Placebo QM (n = 109) • Ezetimibe 10 mg OD oral + Placebo Q2W (n = 112) • Placebo Q2W + Placebo OD oral (n = 281)
GAUSS-2	n=307	12 weeks	• Evolocumab 140 mg Q2W + Placebo OD oral (n = 103) • Evolocumab 420 mg QM + Placebo OD oral (n = 102)	• Ezetimibe 10 mg OD oral + Placebo Q2W (n = 51) • Ezetimibe 10 mg OD oral + Placebo QM (n = 51)
DESCARTES	n=905	52 weeks	• Evolocumab 420 mg QM (n = 602)	• Placebo QM (n = 303)
Familial primary hypercholesterolaemia: HeFH				
RUTHER-FORD-2	n=331	12 weeks	• Evolocumab 420 mg QM (n = 110) • Evolocumab 140 mg Q2W (n = 111)	• Placebo QM (n = 55) • Placebo Q2W (n = 55)

HeFH - heterozygous familial hypercholesterolaemia; OD – once daily; Q2W - every 2 weeks; QM - monthly

The majority of the clinical evidence reported 12-week follow-up (the minimum required duration to demonstrate lipid-lowering effects of investigational agents[15]), with the exception of the DESCARTES trial (52 weeks). The principal efficacy outcomes for consideration were plasma lipid

and lipoprotein levels, including LDL-cholesterol, non-HDL-cholesterol, apolipoprotein B and lipoprotein(a). These were reported in all RCTs. Only the mean percentage change from baseline in calculated LDL-C and treatment differences are reported here. The results for non-HDL-cholesterol, apolipoprotein B and lipoprotein(a) were detailed in Appendix 5 of the CS.[13] Separate, pre-specified subgroup analyses were reported that assessed whether there was any difference in treatment effect based on trial stratification factors, such as background lipid-lowering therapy and severity of hypercholesterolaemia, as well as other covariates, such as evolocumab dose (Q2W versus QM), age, gender, baseline LDL-C level, and CHD risk factors (see Table 7).

Table 7: Included RCTs: Outcomes

Study (Acronym)	**LAPLACE-2**	**GAUSS-2**	**DESCARTES**	**RUTHERFORD-2**
Primary efficacy outcome	• Percent change from baseline in LDL-C at week 12 • Percent change from baseline in LDL-C at the mean of weeks 10/12	• Percent change from baseline in LDL-C at week 12 • Percent change from baseline in LDL-C at the mean of weeks 10/12	• Percent change from baseline in LDL-C at week 52	• Percent change from baseline in LDL-C at week 12 • Percent change from baseline in LDL-C at the mean of weeks 10/12
Pre-specified subgroups	<u>Stratification factors</u> • Entry statin therapy • Simvastatin contraindicated therapy usage for first randomisation <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2, region, family history of premature CHD, baseline PCSK9, baseline TG, and NCEP high risk	<u>Stratification factors</u> • Screening LDL-C < 4.7 mmol/L vs. ≥ 4.7 mmol/L • Baseline statin use <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2, region, family history of premature CHD, baseline PCSK9, baseline TG, NCEP high risk, intolerance to statin, and background lipid-modifying therapy	<u>Stratification factors</u> • Background lipid-lowering therapy <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2, region, family history of premature CHD, baseline PCSK9, baseline TG, and NCEP high risk	<u>Stratification factors</u> • Screening LDL-C < 4.2 mmol/L vs. ≥ 4.2 mmol/L • Ezetimibe use at baseline <u>Covariates</u> Age, sex, race, baseline LDL-C, BMI, glucose tolerance status, hypertension, current smoker, baseline CHD factors ≥ 2, region, family history of premature CHD, baseline PCSK9, baseline TG, NCEP high risk, HeFH status, and background lipid-modifying therapy

4.2.2 Results

Results for the primary outcome - the mean percentage change in calculated LDL-C from baseline to follow-up – for all four trials were reported in the CS. In within-trial pooled analyses, data were reported for all trial arms, all follow-ups, and for all pre-specified and *post hoc* subgroups. For LAPLACE-2, within-trial pooled analyses for evolocumab trial arms were reported using both fixed and random effects models.

Across all four trials, evolocumab at both licensed doses (Q2W and QM) in primary hypercholesterolaemia populations (for whom statins were and were not appropriate) was associated with reductions, and statistically significant treatment differences ($p<0.001$), compared with ezetimibe or placebo in mean percentage change in LDL-C from baseline at the mean follow-ups of weeks 10/12 and week 12 (LAPLACE-2, GAUSS-2) and at weeks 12 and 52 (DESCARTES). Similar results were found versus placebo for the HeFH population (RUTHERFORD-2).

Tables 8 to 16 summarise the main results of the four key evolocumab trials included in the CS for the outcome of LDL-C. The results presented here are those considered most relevant to the decision problem specified in the final NICE scope,[4] particularly those comparing treatment regimens involving evolocumab with regimens involving ezetimibe. All the results are expressed as the least-squares mean percentage change from baseline in LDL-C, with associated 95% Confidence Intervals (CIs). Most results are reported at two time points: a mean of the values for weeks 10 and 12, and the mean value for the results for week 12; the exception is the DESCARTES trial, which measured outcomes at 12 and 52 weeks. *P*-values with associated 95% CIs are only reported for treatment difference in mean percentage change from baseline in calculated LDL-C.

LAPLACE-2

This trial allows a comparison to be made between evolocumab and ezetimibe (10mg OD) in patients also taking a statin. The trial compared both doses of evolocumab in combination with three statins at five doses: an intensive statin dose (atorvastatin 80mg and rovustatin 40mg) and a non-intensive dose (atorvastatin 10mg, simvastatin 40mg and rovustatin 5mg). For the purposes of this appraisal, the results for atorvastatin (both doses versus ezetimibe) and all statins (combined) are reported here: these are the focus of the appraisal and were used in the company's health economic model (see Section 5.2).

The results for mean percentage change (and 95% CIs) in LDL-C from baseline to week 12 in the atorvastatin groups are reported in Table 8. In the atorvastatin (10mg) groups, the mean percentage change in LDL-C from baseline to week 12 was -20.9 (95% CI, -26.4 to -15.5) and -17.1 (95% CI, -22.7 to -11.4) for ezetimibe, compared with -64.6 (95% CI, -68.3 to -60.8) for evolocumab Q2W and

-60.1 (95% CI, -64.1 to -56.0) for evolocumab QM. For the atorvastatin (80mg) groups, the mean percentage change in LDL-C from baseline to week 12 was -15.0 (95% CI, -24.3 to -5.8) and -21.1 (95% CI, -28.7 to -13.4) for ezetimibe compared with -64.9 (95% CI, -71.5 to -59.5) for evolocumab Q2W and -62.4 (95% CI, -67.9 to -57.0) for evolocumab QM.

Table 8: Mean percentage change from baseline (and 95% CIs) in calculated LDL-C in LAPLACE-2: evolocumab versus ezetimibe arms

Timepoint	Ezetimibe 10 mg OD + placebo Q2W	Evolocumab 140 mg Q2W + placebo OD	Ezetimibe 10 mg OD + placebo QM	Evolocumab 420 mg QM + placebo OD
Atorvastatin 10 mg cohort				
Mean of weeks 10/12	-23.4 (-28.3 to -18.5)	-64.1 (-67.5 to -60.8)	-18.8 (-24.0 to -13.6)	-64.1 (-67.7 to -60.4)
Week 12	-20.9 (-26.4 to -15.5)	-64.6 (-68.3 to -60.8)	-17.1 (-22.7 to -11.4)	-60.1 (-64.1 to -56.0)
Atorvastatin 80 mg cohort				
Mean of weeks 10/12	-17.3 (-25.3 to -9.3)	-65.3 (-71.0 to -59.5)	-22.1 (-29.0 to -15.2)	-68.1 (-72.9 to -63.2)
Week 12	-15.0 (-24.3 to -5.8)	-64.9 (-71.5 to -58.4)	-21.1 (-28.7 to -13.4)	-62.4 (-67.9 to -57.0)

OD - once daily, LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

The results for the treatment difference in mean percentage change (and 95% CIs) in LDL-C from baseline to week 12 in the atorvastatin groups are reported in Table 9. For the atorvastatin (10mg) groups, the treatment difference in the mean percentage change in LDL-C from baseline to week 12 was -43.6 (95% CI, -50.2 to -37.1) for evolocumab Q2W compared to ezetimibe, and -43.0 (95% CI, -49.9 to -36.1, $p<0.001$) for evolocumab QM compared with ezetimibe. For the atorvastatin (80mg) groups, the treatment difference in the mean percentage change in LDL-C from baseline to week 12 was -49.9 (95% CI, -61.2 to -38.7) for evolocumab Q2W compared with ezetimibe, and -41.4 (95% CI, -50.8 to -31.9, $p<0.001$) for evolocumab QM compared with ezetimibe.

Table 9: Treatment difference in mean percentage change (and 95% CIs) in calculated LDL-C from baseline in LAPLACE-2: evolocumab versus ezetimibe arms

Timepoint	Evolocumab 140 mg Q2W vs. Ezetimibe 10 mg OD		Evolocumab 420 mg QM vs. Ezetimibe 10 mg OD	
	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort	Atorvastatin 10 mg cohort	Atorvastatin 80 mg cohort
Mean of weeks 10/12	-40.8 (-46.7 to -34.9)	-48.0 (-57.8 to -38.1)	-45.2 (-51.6 to -38.9)	-46.0 (-54.4 to -37.5)
Week 12	-43.6 (-50.2 to -37.1)	-49.9 (-61.2 to -38.7)	-43.0 (-49.9 to -36.1)	-41.4 (-50.8 to -31.9)

OD - once daily; LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

The results for the mean percentage change from baseline, and treatment difference, in LDL-C from baseline to week 12 across all of the statin groups are reported in Table 10. In the pooled analysis across all statin groups, both doses of evolocumab were significantly superior to placebo at 12 weeks both in terms of mean change from baseline and treatment difference ($p<0.001$), regardless of whether fixed or random effects models were used.

Table 10: Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C in LAPLACE-2: pooled analysis across all statin cohorts

Timepoint	Outcome	Placebo Q2W (N = 281)	Evolocumab 140 mg Q2W (N = 555)	Placebo QM (N = 277)	Evolocumab 420 mg QM (N = 562)
Mean of weeks 10/12	Mean percentage change from baseline (95% CI)	7.9 (5.4 to 10.5)	-64.3 (-66.1 to -62.5)	4.6 (1.7 to 7.4)	-65.1 (-67.0 to -63.1)
	Fixed effect treatment difference (95% CI)		-72.3 (-75.4 to -69.1)		-69.6 (-73.1to -66.1)
	Random effects treatment difference (95% CI)		-71.8 (-74.7 to -68.9)		-69.1 (-73.5 to -64.8)
Week 12	Mean percentage change from baseline (95% CI)	9.5 (6.6 to 12.4)	-64.3 (-66.4 to -62.3)	5.6 (2.4, 8.7)	-59.1 (-61.3 to -56.8)
	Fixed effect treatment difference (95% CI)		-73.8 (-77.4 to -70.3)		-64.6 (-68.5 to -60.8)
	Random effects treatment difference (95% CI)		-73.3 (-76.6 to -70.0)		-64.4 (-69.2 to -59.6)

OD - once daily; LDL-C, low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

The results for the mean percentage change from baseline, and treatment difference, in LDL-C from baseline to week 12 across all of the atorvastatin groups are reported in Table 11. For this pooled

analysis of the atorvastatin (10mg and 80mg) groups, the findings were similar to and consistent with the findings for separate atorvastatin cohorts, both in terms of mean percentage change from baseline and statistically significant treatment difference (p<0.001), regardless of whether fixed or random effects models were used.

Table 11: Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C in LAPLACE-2: pooled analysis across atorvastatin cohorts

Timepoint	Outcome	Placebo Q2W + ezetimibe 10 mg OD (N = 112)	Evolocumab 140 mg Q2W (N = 219)	Placebo QM + ezetimibe 10 mg OD (N = 109)	Evolocumab 420 mg QM (N = 220)
Mean of weeks 10/12	Mean percentage change from baseline (95% CI)	-20.2 (-24.6 to -15.8)	-64.7 (-67.8 to -61.6)	-20.4 (-24.5 to [-]16.3)	-66.2 (-69.1 to -63.3)
	Fixed effect treatment difference (95% CI)		-44.5 (-49.9 to -39.2)		-45.8 (-50.8 to -40.8)
	Random effects treatment difference (95% CI)		-43.3 (-50.0 to -36.5)		-45.5 (-50.5 to -40.5)
Week 12	Mean percentage change from baseline (95% CI)	-17.9 (-23.0 to -12.8)	-64.8 (-68.3 to -61.2)	-18.9 (-23.4 to -14.5)	-61.4 (-64.6 to -58.2)
	Fixed effect treatment difference (95% CI)		-46.9 (-53.0 to -40.7)		-42.5 (-47.9 to -37.0)
	Random effects treatment difference (95% CI)		-45.2 (-50.8 to -39.6)		-42.4 (-48.0 to -36.9)

OD - once daily; LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

GAUSS-2

The GAUSS-2 trial recruited people in whom two or more statins could not be tolerated or only the smallest dose could be tolerated, and so directly compared evolocumab and ezetimibe in the absence of statin therapy. The main results are summarised in Table 12. At week 12, a mean percentage change in LDL-C from baseline of -18.2 (95% CI, -23.2 to -13.1) and -14.9 (95% CI, -19.2 to -10.5) was reported for ezetimibe across the two cohorts, compared with -57.4 (95% CI, -61.3 to -51.6) and -53.0 (95% CI, -56.2 to -49.8) for evolocumab Q2W and QM, respectively. At week 12, the treatment

difference for mean percentage change in LDL-C from baseline was -39.3 (95% CI, -45.0 to -33.5, $p<0.001$) and -38.1 (95% CI, -42.9 to -33.4, $p<0.001$) for evolocumab Q2W and QM, respectively, compared with the two ezetimibe cohorts.

The ERG noted that the results presented in the CS are for the Full analysis Set (FAS) and report greater efficacy than the results reported in the original publication.[24] At week 12, the treatment difference for mean percentage change in LDL-C from baseline was -38.1 (95% CI, -43.7 to -32.4) and -37.6 (95% CI, -42.2 to -32.9) in the original publication for evolocumab Q2W and QM versus the two ezetimibe cohorts, compared with -39.3 (95% CI, -45.0 to -33.5) and -38.1 (95% CI, -42.9 to -33.4) in the CS. The *p*-value for these comparisons in both the CS and journal publications was the same ($p<0.001$). All of the Week 12 results were consistent with the findings for Weeks 10/12.

Table 12: Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C from baseline in GAUSS-2

Outcome	Placebo Q2W + ezetimibe 10 mg OD (N = 51)	Evolocumab 140 mg Q2W + placebo OD (N = 103)	Placebo QM + ezetimibe 10 mg OD (N = 51)	Evolocumab 420 mg QM + placebo OD (N = 102)
Mean of weeks 10/12 mean percentage change from baseline	-19.0 (-23.9 to -14.1)	-57.1 (-60.8 to -53.4)	-16.6 (-20.7 to -12.5)	-55.8 (-58.9 to -52.8)
Mean of weeks 10/12 treatment difference		-38.1 (-43.6 to -32.6)		-39.2 (-43.7 to -34.8)
Week 12 mean percentage change from baseline	-18.2 (-23.2 to -13.1)	-57.4 (-61.3 to -53.6)	-14.9 (-19.2 to -10.5)	-53.0 (-56.2 to -49.8)
Week 12 treatment difference		-39.3 (-45.0 to -33.5)		-38.1 (-42.9 to -33.4)

OD - once daily; LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

DESCARTES

The DESCARTES trial measured change in LDL-C from baseline to both 12 weeks and 52 weeks in people with primary hypercholesterolaemia. The main results comparing evolocumab, at the QM dose only, with placebo in the presence of background lipid-lowering therapy are summarised in Table 13. The comparison with placebo is not in line with the final NICE scope (although this is used in the model), partly because ezetimibe is not a comparator, but also because the trial included people who did not receive statins or received only low intensity statins (10mg atorvastatin), who were therefore neither statin intolerant nor on a maximum-tolerated dose of a statin, as required by the decision problem specified in the final NICE scope[4] and the marketing authorisation for evolocumab. The results are reproduced here briefly only for comparison with the 12 week results of the LAPLACE-2 and GAUSS-2 trials, and for comparison with the 52-week results, which represent the longest relevant follow-up of efficacy data for evolocumab.

At week 52, the mean percentage change in LDL-C from baseline was -50.6 (95% CI, -53.2 to -48.0) for evolocumab at the QM dose compared with 8.7 (95% CI, 5.1 to 12.4) for the placebo group, producing a treatment difference of -59.3 (-95% CI, -63.8 to -54.9) (p<0.001).

Table 13: Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C from baseline in DESCARTES

Outcome	Placebo QM (N = 302)	Evolocumab 420 mg QM (N = 599)
Week 12 mean percentage change from baseline	4.4 (1.7 to 7.0)	-56.7 (-58.7 to -57.8)†
Week 12 treatment difference		-61.1 (-64.3 to -57.9)†
Week 52 mean percentage change from baseline	8.7 (5.1 to 12.4)	-50.6 (-53.2 to -48.0)
Week 52 treatment difference		-59.3 (-63.8 to -54.9)

LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly
† It should be noted that the CS reported erroneous data for mean change from baseline at week 12, which also affect the treatment difference. These data are clearly in error because the mean is outside of the 95% CI: -56.7 (-58.7 to -57.8). Alternative data for this outcome measurement were not available.

However, this trial also had a subgroup of people on high-dose statins (atorvastatin 80mg) plus ezetimibe. The results for this subgroup are presented in Table 14. This analysis compares placebo plus diet plus statin plus ezetimibe with evolocumab plus diet plus statin plus ezetimibe (described in the CS[13] [page 152] as a "relevant intervention and comparator").

At week 52, the mean percentage change in LDL-C from baseline was -47.1 (95% CI, -52.9 to -41.2) for evolocumab QM compared with 2.3 (95% CI, -6.1 to 10.6) for the placebo group, producing a treatment difference of -49.3 (95% CI,-59.5 to -39.1, p<0.001).

Table 14: Subgroup analysis of mean percentage change and treatment difference in ultracentrifugation LDL-C from baseline in DESCARTES for patients using ezetimibe at baseline (from DESCARTES study report Table 14-4.7.1)

Outcome	Placebo QM	Evolocumab 420 mg QM
Number in subgroup	55	115
Week 52 mean percentage change from baseline	2.3 (-6.1 to 10.6)	-47.1 (-52.9 to -41.2)
Week 52 treatment difference		-49.3 (-59.5 to -39.1)

OD - once daily; LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly

RUTHERFORD-2

RUTHERFORD-2 recruited patients with HeFH. This was a placebo-controlled trial in patients receiving stable lipid-lowering therapy at baseline. Table 15 presents the results of the main analysis. A subgroup analysis of patients receiving ezetimibe at baseline allows a comparison of statin plus ezetimibe versus evolocumab plus statin plus ezetimibe (see Table 15). The ERG received clinical advice that the HeFH population of the RUTHERFORD trial with a confirmed genetic mutation was higher than might be found in usual clinical practice in the UK, but the implications of this are unclear. The ERG also noted, following clinical advice, that the proportion of patients with CHD was higher in the intervention arms of the RUTHERFORD-2 trial (i.e. 30-36%) than would be expected in clinical practice in a HeFH population, and were higher than the prevalence reported for the other three trials (e.g. LAPLACE-2 trial arm populations ranged from 17% to 24% with CHD characteristics).

At week 12, the mean percentage change in LDL-C from baseline was -62.7 (95% CI,-66.3 to -59.1) for evolocumab Q2W compared with -2.1 (95% CI,-7.2 to 3.0) for the placebo group, producing a treatment difference of -60.6 (95% CI, -66.7 to -54.5, $p<0.001$). At week 12, the mean percentage change in LDL-C from baseline was -56.6 (95% CI,-60.9 to -52.3) for evolocumab QM compared with 3.8 (95% CI,-2.5 to 10.0) for the placebo group, resulting in a treatment difference of -60.3 (95% CI, -67.8 to -52.9, $p<0.001$).

The ERG noted that the data presented in the submission are from the FAS and report greater treatment differences than in the original publication.[21] For example, for the mean of the results for weeks 10/12, the mean percentage change in LDL-C from baseline for the evolocumab Q2W dose was -61.2 (95% CI,-64.6 to -57.9) in the original publication, rather than -62.7 (95% CI,-66.3 to -59.1) in the CS and, for placebo, it was -1.1 (95% CI,-5.8 to 3.7) rather than -1.4 (95% CI,-6.3 to 3.6), resulting in a treatment difference of -60.2 (95% CI,-65.8 to -54.5) rather than the -61.3 (95% CI,-67.2 to -55.4) in the company submission. For weeks 10/12, the mean percentage change in LDL-C from baseline for the evolocumab QM dose was -63.3 (95% CI,-66.6 to -59.9) in the original publication, rather than 64.7 (95% CI,-68.1 to -61.4) in the CS and, for placebo, was 2.3 (95% CI, -2.5 to 7.1) rather than 1.5 (95% CI, -3.2 to 6.2), resulting in a treatment difference of -65.6 (95% CI,-71.3 to -59.8) rather than -66.2 (95% CI,-71.9 to -60.6). However, the *p*-values for treatment differences between both evolocumab doses and placebo in both the company submission and the journal publications all remain the same ($p<0.001$).

Table 15: Mean percentage change from baseline and mean percentage treatment difference (and 95% CIs) in calculated LDL-C from baseline in RUTHERFORD-2 (patients with heterozygous familial hypercholesterolaemia, based on CS,[13] Table 4.15 and Figure 4-8*)

Outcome	Placebo Q2W	Evolocumab 140 mg Q2W	Placebo QM	Evolocumab 420 mg QM
Mean of weeks 10/12 mean percentage change from baseline	-1.4 (-6.3 to 3.6)	-62.7 (-66.2 to -59.2)	1.5 (-3.2 to 6.2)	-64.7 (-68.1 to -61.4)
Mean of weeks 10/12 treatment difference		-61.3 (-67.2 to -55.4)		-66.2 (-71.9 to -60.6)
Week 12 mean percentage change from baseline	-2.1 (-7.2 to 3.0**)	-62.7 (-66.3 to -59.1)	3.8 (-2.5 to 10.0)	-56.6 (-60.9 to -52.3)
Week 12 treatment difference		-60.6 (-66.7 to -54.5)		-60.3 (-67.8, -52.9)

LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly
**Minor discrepancies between figure and table; data from table have been extracted **-3.0 in submission seems incorrect. Comparison is stable LLT vs. evolocumab + LLT. OD:*

As with the ezetimibe subgroup in DESCARTES, at week 12, the mean percentage change in LDL-C from baseline was -58.6 (95% CI,-63.6 to -53.6) for background ezetimibe and evolocumab at the Q2W dose compared with -0.2 (95% CI,-7.3 to 6.9) for the background ezetimibe and placebo group, producing a treatment difference of -58.4 (95% CI,-67.1 to -49.7, p<0.001). At week 12, the mean percentage change in LDL-C from baseline was -56.2 (95% CI,-62.1 to -50.4) for ezetimibe and evolocumab at the QM dose compared with 4.6 (95% CI, -3.6 to 12.9) for the ezetimibe and placebo group, producing a treatment difference of -60.9 (95% CI,-71.0 to -50.8, p<0.001).

Table 16: Subgroup analysis of mean percentage change and treatment difference (and 95% CIs) in calculated LDL-C from baseline in RUTHERFORD-2 for patients using ezetimibe at baseline (from study report Table 14-4.4.2)

Outcome	Placebo Q2W	Evolocumab 140 mg Q2W	Placebo QM	Evolocumab 420 mg QM
Number in subgroup	33	67	35	67
Mean of weeks 10/12 mean percentage change from baseline*	0.2 (-6.7 to 7.1)	-59.0 (-63.8 to -54.1)	0.6 (-5.5 to 6.7)	-64.6 (-68.9 to -60.2)
Mean of weeks 10/12 treatment difference		-59.2 (-67.6 to -50.8)		-65.2 (-72.7 to -57.7)
Number in subgroup	32	64	32	65
Week 12 mean percentage change from baseline*	-0.2 (-7.3 to 6.9)	-58.6 (-63.6 to -53.6)	4.6 (-3.6 to 12.9)	-56.2 (-62.1 to -50.4)
Week 12 treatment difference		-58.4 (-67.1 to -49.7)		-60.9 (-71.0 to -50.8)

LDL-C - low-density lipoprotein cholesterol; Q2W - every 2 weeks; QM - monthly
** Least squares mean as in other tables.*

Other lipid parameters

Across all four trials, statistically significant reductions were also reported for evolocumab versus placebo or ezetimibe for all other lipid parameters for weeks 10/12, week 12 and, in DESCARTES, for week 52: HDL-C, non-HDL-C, ApoB and Lp(a), triglycerides (TG) and very low-density lipoprotein cholesterol (VLDL-C). These results are not reported here but were provided in Appendix 5 of the CS. The *p*-values were between $p<0.001$ and $p<0.05$ depending on the parameter.

Pre-specified subgroups

The subgroup analyses were extensive and were presented in detail, with forest plots provided in Appendix 6 of the CS for all stratification factors and relevant covariates for each trial.[13] The conclusion that there were no significant differences between the two evolocumab dose regimens (which appear to be clinically equivalent), baseline lipid-lowering therapies, severity of hypercholesterolaemia, LDL-C level, statin use, CHD risk factors etc. appears sound, based on the results submitted for these trials. Analyses were also conducted on the following pre-specified high-risk subgroups, with no notable differences between groups:

From LAPLACE-2 and DESCARTES:

- CHD or CHD-risk equivalent with baseline LDL-C > 2.6 mmol/L, treated with statin;
- Statin-treated subjects with a history of MI or ischaemic stroke and baseline LDL-C > 1.8 mmol/L, >2.6 mmol/L, or >3.4 mmol/L

From RUTHERFORD and GAUSS-2:

- CHD risk equivalent

From RUTHERFORD:

- High risk HeFH (defined as any of the following: history of CV event; presence of xanthomas or premature arcus cornea; LDL-C > 4.1 mmol/L; ≥ 1 CV risk factors (e.g. smoking, diabetes): Lp(a) > 125 nmol/L, with subgroups (LDL-C >3.4 mmol/L and > 5.2 mmol/L)

From all trials:

- Very high risk according to ESC/EAS guidelines.

Evolocumab at both licensed doses, and in patients who could and who could not have statins, was therefore consistently effective relative to placebo and to ezetimibe in lowering LDL-C (mean percentage change from baseline at the mean of weeks 10/12 and at week 12 [RUTHERFORD-2, LAPLACE-2, GAUSS-2] or at week 52 [DESCARTES]) in all stratification factor and baseline covariate subgroups in each study.

4.2.3 Review of clinical efficacy and safety (non-randomised and non-controlled evidence)

The CS presents findings from a single non-randomised study: TAUSSIG (see CS,[13] Section 4.11). This is an ongoing long-term, open-label Phase II/III study, which recruited patients with severe familial hypercholesterolaemia. The study reported findings for up to 36 weeks. As noted above, however, it is not clear how this study was identified. It should also be noted that the study is unpublished (and cannot be appraised for risk of bias) and the population includes people with HeFH and HoFH; the latter group are excluded from the final scope for this appraisal. The ERG assumes, though this is not specified, that the interim FAS results presented are for the HeFH group alone. The study was considered relevant by the company because of the relative lack of data on evolocumab in the HeFH subgroup and in patients receiving apheresis, an outcome of relevance to the decision problem. However, the 16 patients receiving apheresis also received an unlicensed dose of evolocumab (420mg Q2W). For these reasons, the full results data are not reproduced here. The results reported that mean percentage change of LDL-C from baseline for evolocumab QM by week 36 in the severe FH, non-apheresis group (n=126) was -50.5 (standard error [SE]=3.6).

4.2.4 Review of safety (randomised and non-randomised trial evidence)

The submitted review of the safety evidence was extensive with all key adverse events covered and particular events addressed in detail. The principal omission was the failure to provide discrete data for each of the two licensed doses. The submission stated that there was no difference between doses, but the data were not clearly presented. Given that the two doses appear to be equivalent in terms of efficacy, the ERG considered that it therefore made sense to assess whether they are also equivalent in terms of safety. For this reason, the ERG has provided these data, where available from the original trial publications and submission appendices, in addition to the combined evidence for both doses, which was provided in the CS (see Tables 17-24). These data are not provided for all safety outcomes, but only for the principal outcomes of interest, as articulated in the literature and the CS: all AEs; SAEs; events leading to discontinuation of the study drug; nasopharyngitis; headache; back pain; neurocognitive events and upper respiratory tract infection.

Whilst the company's review appears to be sound, the ERG notes that it is not a systematic review of the safety evidence. The inclusion criteria for this review were not specified. CS Section 4.12 initially summarised the evidence from the four principal RCTs included in the efficacy review, as well as the OSLER 1 and 2 trials, and the TAUSSIG trial from the review of non-randomised and non-controlled studies (see CS,[13] Table 4-23, page 136). A set of integrated analyses of safety data from 14 randomised studies (11 studies of approximately 12 weeks in duration and three longer-term studies (one 52-week completed study and two ongoing extension studies, with unpublished data) are also presented. This is the "integrated parent analysis set", which includes the four principal RCTs but also many studies that were excluded from the clinical efficacy review. Reasons for exclusion from the

efficacy review included the level and appropriateness of the background lipid-lowering therapy used/not used, the inclusion of certain population groups, and the comparison being assessed. Consequently, the ERG notes that this population might not reflect the population that would receive evolocumab in clinical practice in England. Further, as noted above, the methods by which all of these studies were identified, in addition to the four trials included in the efficacy review, and the criteria by which they were selected, and others excluded, are not reported. However, in response to a request for clarification from the ERG (see clarification response,[35] question A12), the company provided a complete quality assessment of the included studies, all of which appear to be at low risk of bias. The data presented here are for the four principal RCTs, the integrated parent analysis set, and separate integrated data for year 1 and year 2 of the long-term, open-label extension studies, which include cumulative data to a 1st July 2014 cut-off date.

Table 17: Percentage rates of all AEs (from submission FAS, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338	12	36.3	36.3	36.3	40.3	
GAUSS-2	307	12	61	71	66	73	
DESCARTES	901	52		74.8			74.2
RUTHERFORD-2	329	12	55	57			49
OSLER 1, 2: Yr 1	4465				65.4 (69.2)†		61.1 (64.8) †
OSLER 1, 2: Yr 2	1675				[redacted]		
Integrated parent analysis set	6026	12, 52*			51.1	[redacted]	[redacted]

Evo = evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks; FAS - full analysis set

11 RCTs have 12 weeks, 1 RCT has 52 weeks. †Sabatine et al[33]

Table 18: Percentage rates of SAEs (from submission FAS, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338 555/562	12	2.3	1.7	2.1	0.9	
GAUSS-2	307	12	5	1	3	4	
DESCARTES	901	52		5.5			4.3
RUTHERFORD-2	329	12	3	4			4
OSLER 1, 2: Yr 1	4465				6.6 (7.5)†		6.7 (7.5)†
OSLER 1, 2: Yr 2	1675				[redacted]		
Integrated parent analysis set	6026	12, 52*			2.8	[redacted]	[redacted]

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks. †Sabatine et al[33]

Table 19: Percentage rates of AEs leading to discontinuation (from submission FAS, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338 555/562	12	2.3	1.7	1.9	1.8	
GAUSS-2	307	12	6	11	8	13	
DESCARTES	901	52		2.2			1.0
RUTHERFORD-2	329	12	0	0			0
OSLER 1, 2: Yr 1	4465				2.1 (2.4) †		NA
OSLER 1, 2: Yr 2	1675				[redacted]		
Integrated analysis set	6026	12, 52*			1.9	[redacted]	[redacted]

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks. † Sabatine et al[33]

Table 20: Percentage rates of nasopharyngitis (from submission FAS, Appendix 7, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	881	12			0.7	1.8	2.3
GAUSS-2	307	12	4.9	2.0	3.2	2.9	
DESCARTES	901	52		10.5			9.6
RUTHERFORD-2	329	12	7	10			4.8
Integrated analysis set	6026	12, 52*			5.9	[redacted]	[redacted]

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks.

Table 21: Percentage rates of headache (from submission FAS, Appendix 7, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338 555/562	12	1.3	2.1	1.7	2.3	
GAUSS-2	307	12	3.9	11.2	7.8	8.8	
DESCARTES	901	52		4.0			3.6
RUTHERFORD-2	329	12	4	5			3.6
OSLER 1, 2†	4465	52			3.6		2.1
Integrated analysis set	6026	12, 52*			3.0	[redacted]	[redacted]

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks

11 RCTs have 12 weeks, 1 RCT has 52 weeks. † Sabatine et al[33]

Table 22: Percentage rates of back pain (from submission FAS, Appendix 7, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338 555/562	12	2.5	1.1	1.8	3.2	
GAUSS-2	307	12					
DESCARTES	901	52		6.2			5.6
RUTHERFORD-2	329	12	2	5			0.9
Integrated analysis set	6026	12, 52*			3.0	[redacted]	[redacted]

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks
11 RCTs have 12 weeks, 1 RCT has 52 weeks.

Table 23: Percentage rates of neurocognition AEs (from submission FAS, Appendix 7, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	1338 555/562	12			0.1	1.4	
GAUSS-2	307	12					
DESCARTES	901	52					
RUTHERFORD-2	329	12	0	0			0
OSLER 1, 2†	4465				0.9		0.3
Integrated analysis set	6026	12, 52*					

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks
11 RCTs have 12 weeks, 1 RCT has 52 weeks. † Sabatine et al[33]

Table 24: Percentage rates of upper respiratory tract infection (from submission FAS, Appendix 7, Table 4-25 and 4-26 and original trial publications)

	Number	Follow-Up (weeks)	EvoQ2W	EvoQM	Any Evo	Eze	Pbo or SoC
LAPLACE-2	881	12			1.4	1.4	0.9
GAUSS-2	307	12					
DESCARTES	901	52		9.3			6.3
RUTHERFORD-2	329	12			3.2		2.8
Integrated analysis set	6026	12, 52*			3.2	[redacted]	[redacted]

Evo - evolocumab; Eze - ezetimibe; Pbo - placebo; SoC - standard of care; QM - monthly; Q2W - every 2 weeks
11 RCTs have 12 weeks, 1 RCT has 52 weeks.

The incidence of overall AEs appears to be quite high for evolocumab with a range of 36% to 74%, depending on the trial population, with the higher rates in the statin-intolerant and HeFH trial cohorts. However, the rates of SAEs are relatively low, at around 1-2%, and neither the overall nor serious event rates appear to be dissimilar to ezetimibe. There do not appear to be any AEs for evolocumab that are substantially higher than those found for ezetimibe. [redacted]

[redacted] The higher incidence of neurocognitive events (delirium, confusion, cognitive and attention disorders and disturbances, dementia, amnesia, disturbances in thinking and perception) in the evolocumab arms relative to the comparator arms (0.9 vs 0.3) reported in the OSLER 1 and 2 open-label extension studies appears to be associated with people who were at high risk of such events.[33] The ERG notes that a sub-study of the ongoing FOURIER outcomes study, EBBINGHAUS, includes an assessment of cognitive function in this group.[46]

There is also no consistent trend in relative frequency of AEs for the higher QM dose compared with the Q2W dose of evolocumab. For example, for the higher dose, the data from GAUSS-2 indicate much higher incidence rates of AEs leading to discontinuation, and a higher reported frequency of headache, but this is not reflected across other trials and the comparisons with ezetimibe are generally favourable. Across both doses of evolocumab, there also appears to be a slightly higher incidence of events at 12 weeks in the GAUSS and RUTHERFORD trials compared to ezetimibe or placebo, respectively. This might suggest that the statin intolerant and HeFH subgroups are at a slightly higher risk. The key finding is that AE rates are clearly higher for the DESCARTES trial across all of the safety outcomes reported here. The DESCARTES trial included only the higher QM dose of evolocumab. Given that the definition of AEs does not appear to differ between trials, the higher incidence of these events in the DESCARTES trial is almost certainly due to the longer follow-up (52 weeks compared with 12 weeks across most trials), as noted in the CS. This is also suggested by the data from the OSLER 1 and 2 open-label extension studies, which also report relatively higher rates of overall AEs and SAEs. In DESCARTES, event rates were, unsurprisingly, always higher for the evolocumab group than for the placebo group, with some rates as much as twice those found in the placebo group (e.g. events leading to discontinuation, 2.2% vs 1.0%). This suggests that long-term safety might be an issue. Greater clarity needs to be provided on the relative safety of both licensed doses compared to therapies such as ezetimibe in the long-term. None of the highlighted differences in safety outcomes have been assessed for statistical significance.

The CS reported that the number of deaths and positively adjudicated CV events (including revascularisation procedures) was small and similar between evolocumab and controls as reported from the larger integrated safety analysis and extension studies (see CS,[13] Table 4-27, page 145). It also noted that the preliminary empirical evidence from safety analyses suggested that long-term use of evolocumab to lower LDL-C may be associated with reduced risk of CV events (including revascularisation procedures). However, the CS acknowledged that these data are preliminary, the trials are not powered to detect a difference in major CV events, and the incidence is typically 0.5% or less for most positively adjudicated cardiovascular events and outcomes. The ongoing, longer-term

FOURIER trial is seeking to test this potential relationship in people who have had a CV event, with CVD as an efficacy rather than a safety outcome (clinicaltrials.gov identifier NCT01764633). This is an area of uncertainty in the evidence base.

The following additional safety outcomes are reported in the CS: injection site reactions; muscle and creatine kinase levels; incidence of liver function test abnormalities; Hepatitis C; immunogenicity and diabetes events. Frequency of hypersensitivity and injection site reactions was between 2% and 4% for evolocumab, with a higher incidence over time. Across these outcomes, events were infrequent and generally balanced between arms and between the parent and extension studies. Event rates also appear to be unaffected by baseline level of LDL-C. The presence of diabetes events was considered infrequent, but it should be noted that type 1 and newly-diagnosed or poorly-controlled type 2 diabetes mellitus was an exclusion criterion of the four key trials: LAPLACE-2; GAUSS-2; DESCARTES and RUTHERFORD-2 (see Table 4).

Evolocumab therefore appears to have an acceptable safety profile. However, longer-term data are required to determine whether reported frequency rates are maintained, whether or not certain subgroups of patients are at higher risk of certain events, and to confirm whether or not there are any differences between the two licensed doses of evolocumab.

4.2.5 Ongoing studies

The submission detailed a number of ongoing studies of evolocumab. The most relevant of these studies are listed in Table 25. For key efficacy outcomes, the most important trials are the Phase III RCTs FOURIER and GAUSS-3. FOURIER seeks to evaluate the effectiveness of evolocumab (both doses) on CVD outcomes in a population with CVD; GAUSS-3 is seeking to assess mean percentage change from baseline LDL-C at weeks 22 and 24 for people who are statin-intolerant (after a statin re-challenge). For safety outcomes, the most important trials are the ongoing OSLER 1 and 2 trials, and the EBBINGHAUS[46] subset from the FOURIER trial,[32] which has a particular focus on neurocognitive events (cognitive function).

These trials will provide important direct evidence of the relationship between evolocumab and CV events for people with CVD, longer-term efficacy evidence for people who are statin-intolerant, and some longer-term safety evidence, albeit with the caveats expressed above regarding the OLSER 1 and 2 trial populations. The FOURIER trial will therefore test the assumption that LDL-C is a viable surrogate for CV events for evolocumab for one subset of the relevant population; this is a key area of uncertainty in the current evidence base.

Table 25: Relevant ongoing studies of evolocumab (as of 1st July 2015, adapted from CS, Table 0-1)

Study	Description	Interventions	No. of patients	Primary outcome measure	Estimated completion dates
Efficacy outcomes					
FOURIER	Multicentre, international, Phase 3, RCT	• Placebo Q2W • Evolocumab 140 mg Q2W • Placebo QM • Evolocumab 420 mg QM	27,564	Time to CV death, MI, stroke, hospitalisation for UA, or coronary revascularisation, whichever occurs first	Completion date: February 2018 Primary completion date[a]: October 2017
GAUSS-3	Multicentre, international, Phase 3, RCT	<u>Part A – Cross-over statin rechallenge</u> • Placebo OD • Atorvastatin 20 mg OD <u>Part B – Comparison of evolocumab and ezetimibe</u> • Placebo QM + ezetimibe OD • Evolocumab 420 mg QM + Placebo OD <u>Part C – open-label extension</u> • Evolocumab 420 mg QM or 140 mg Q2W	519	Mean percent change from baseline in LDL-C at weeks 22 and 24 and mean percent change from baseline in LDL-C at week 24 in part B	Completion date: November 2017 Primary completion date[a]: October 2015
Safety outcomes					
OSLER-1	Phase 2, open-label extension	• SoC[b] • Evolocumab 420 mg QM + SoC[b]	1,324	Patient incidence of treatment emergent AEs (timeframe: approximately 1 year)	Completion date: July 2016 Primary completion date[a]: July 2016
OSLER-2	Phase 3, open-label extension	• SoC[b] • Evolocumab 140 mg Q2W or 420 mg QM + SoC[b]	4,428 (estimated)	Patient incidence of AEs (timeframe: 156 weeks)	Completion date: May 2018 Primary completion date[a]: May 2018

Study	Description	Interventions	No. of patients	Primary outcome measure	Estimated completion dates
EBBINGHAUS[c]	Multicentre, international, Phase 3, RCT	• Evolocumab Q2W or QM + effective statin dose • Placebo Q2W or QM + effective statin dose	4,000 (estimated)	Mean change from baseline over time in spatial working memory index of executive function	Completion date: February 2018 Primary completion date[a]: October 2017

[a]Final data collection date for primary outcome measure. [b]SoC (standard of care) therapy as per local practices. This could include prescribed therapies and/or dietary/exercise regimens. [c]EBBINGHAUS evaluates the effect of evolocumab on cognitive function in a subset of patients enrolled in FOURIER.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Two studies were identified as being potentially useful for synthesising comparative efficacy data for evolocumab plus statins compared with ezetimibe plus statins in patients with HeFH. One of the two included studies was the previously identified RUTHERFORD-2 study which assessed evolocumab Q2W plus lipid-lowering therapy and evolocumab QM plus lipid-lowering therapy (interventions) versus lipid-lowering therapy alone (comparator). Patients were receiving lipid lowering therapy prior to baseline measurement.

The additional identified study was ENHANCE,[47] which assessed ezetimibe plus statin (intervention) versus statin alone (comparator). In ENHANCE, patients were washed out of prior lipid-lowering therapy before the randomisation and then randomised to either statins and placebo, or statins and ezetimibe. The percentage change from baseline therefore reflects the treatment effect against a baseline of no lipid lowering therapy. This is different from the RUTHERFORD-2 study, which assesses the percentage change against a baseline of lipid-lowering therapy. The CS (page 130) therefore states that the percentage change from baseline within each patient is not comparable between ENHANCE and RUTHERFORD-2. For this reason, an indirect comparison was not performed.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The CS considered the use of an NMA only for the HeFH population. In this population, the CS asserts (page 130) that since the percentage change from baseline within each patient was not comparable between ENHANCE and RUTHERFORD-2, an NMA was "neither appropriate nor feasible." The ERG considers this conclusion to be appropriate.

Although an NMA was deemed inappropriate for the HeFH population, the ERG considers that it may have been useful for the company to consider undertaking an NMA for the primary non-familial hypercholesterolaemia population (LAPLACE-2, DESCARTES) and generate the joint posterior distribution of treatment effect for these studies. The treatment effect in LDL-C for evolocumab QM versus placebo was: -69.1 (95% CI, -73.5,-64.8) in LAPLACE-2 and -61.1 (95% CI, -64.3,-57.9) in DESCARTES, with the non-overlapping 95% confidence intervals suggesting heterogeneity in the treatment effects between studies (p=0.004 for difference between means).

The purpose of an NMA is primarily to estimate relative efficacy. However, it is also used to quantify uncertainty associated with the treatment effects as required for subsequent health economic analyses. In the presence of heterogeneity, the predictive distribution, rather than the distribution of the mean treatment effect, would better represent uncertainty about the treatment effect in a future study.

In the absence of head-to-head data in HeFH for evolocumab plus statins versus ezetimibe plus statins, the CS states (page 193) that treatment effects from the primary non-familial hypercholesterolaemia population are generalisable to the HeFH population. If this assertion is indeed true, the ERG considers that it would have been useful to perform an NMA over both populations: the hypercholesterolaemia population (LAPLACE-2, DESCARTES) and the HeFH population (RUTHERFORD-2) so that the clinical evidence from the HeFH population contributes to the utilised treatment effect, rather than simply replacing the required measure with that from the primary non-familial hypercholesterolaemia population. The treatment effect for evolocumab Q2M versus placebo was -71.8 (95% CI, -74.7,-68.9) in LAPLACE-2 and -61.3 (95% CI, -67.2,-55.4) in RUTHERFORD-2 (p=0.002 for difference between means). The use of only LAPLACE-2 to inform the treatment effect for the HeFH population therefore under-represents the true uncertainty in this treatment effect, and potentially over-estimates the magnitude of the treatment effect also.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG did not undertake any additional analyses for the clinical effectiveness review.

4.6 Conclusions of the clinical effectiveness section

The principal efficacy review represents a good quality systematic review of four relevant, good quality RCTs. The trials were generally consistent with the final NICE scope. The primary efficacy outcome was mean percentage change in LDL-C from baseline, and mean treatment difference across trial arms, at follow-ups of 12 weeks (LAPLACE-2, GAUSS-2, DESCARTES and RUTHERFORD-2) and 52 weeks (DESCARTES).

In the LAPLACE-2 trial, at 12 weeks, patients with primary hypercholesterolaemia on background atorvastatin therapy (intensive and non-intensive doses) had a treatment difference in mean percentage change in LDL-C from baseline of -46.9 (95% CI, -53.0 to -40.7, $p<0.001$) and -42.5 (95% CI, -47.9 to -37.0, $p<0.001$) for the Q2W and QM doses of evolocumab respectively, compared with ezetimibe (fixed effects model).

In the GAUSS-2 trial, at 12 weeks, patients with primary hypercholesterolaemia who were statin intolerant had a treatment difference in mean percentage change in LDL-C from baseline of -39.3 (95% CI, -45.0 to -33.5, $p<0.001$) and -38.1 (95% CI, -42.9 to -33.4, $p<0.001$) for the Q2W and QM doses of evolocumab compared with ezetimibe.

In the placebo-controlled RUTHERFORD-2 trial, at 12 weeks, patients with HeFH on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -62.7 (95% CI, -66.3 to -59.1) and -56.6 (95% CI, -60.9 to -52.3) for the Q2W and QM doses of evolocumab. The treatment difference in mean percentage change compared with placebo was -60.6 (95% CI, -66.7 to -54.5, $p<0.001$) and -60.3 (95% CI, -67.8, -52.9, $p<0.001$) for the Q2W and QM doses of evolocumab respectively. The ERG received clinical advice that the HeFH population of the RUTHERFORD trial with a confirmed genetic mutation was higher than might be found in usual clinical practice in the UK, but the implications of this are unclear. The ERG also noted, following clinical advice, that the proportion of patients with CHD was higher in the intervention arms of the RUTHERFORD-2 trial (i.e. 30-36%) than would be expected in clinical practice in a HeFH population, and was higher than the prevalence reported for the other three trials (e.g. LAPLACE-2 trial arm populations ranged from 17% to 24% with CHD characteristics).

In the placebo-controlled DESCARTES trial, patients with primary hypercholesterolaemia on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -50.6 (95% CI, -53.2 to -48.0) for the QM dose of evolocumab at 52 weeks. The treatment difference in mean percentage change compared with placebo was -59.3 (95% CI, -63.8 to -54.9, $p<0.001$) at 52 weeks.

The results for other lipid parameters, such as non-HDL-cholesterol, HDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB) and lipoprotein(a) (Lp(a)), were consistent with the results for LDL-C, and pre-specified subgroup analyses demonstrated that these results were not sensitive to the different doses of evolocumab, or other key variables, such as LDL-C baseline levels, severity of hypercholesterolaemia or CVD risk factors. The ERG noted that only 12-week evidence was available for the efficacy of the Q2W dose, whilst the QM dose had some data for 52 weeks. Additional clinical efficacy evidence was provided from a non-RCT study (TAUSSIG) and two open-label, extension

trials (OSLER 1 and 2). However, the extension studies included some trials with populations and/or comparators that were excluded from the principal review of four RCTs and it is unclear how these trials and the non-RCT study were identified for inclusion in the company's review. The inclusion of these studies was justified by the company on account of the longer-term evidence both from the extension studies and from TAUSSIG on the HeFH subgroup (36 weeks). An NMA was not performed, although this might have been possible using particular trial evidence from both the primary non-familial hypercholesterolaemia population and the HeFH subgroup.

The clinical effectiveness review found that evolocumab is efficacious at lowering LDL-C, but in itself this is not a clinically important outcome: its importance is derived from it being a surrogate for CVD. Although there is an established relationship between statin-generated LDL-C reduction and reduced CV events, the impact of evolocumab on CVD has not been demonstrated: there is little or no direct evidence on this relationship. The ongoing FOURIER trial (clinicaltrials.gov identifier NCT02207634) aims to evaluate the impact of evolocumab on CVD outcomes, but only in people who have already had a CV event. The ERG also noted that there was no evidence on the relative efficacy of evolocumab versus ezetimibe in the familial hypercholesterolaemia subgroup, or for evolocumab in combination with ezetimibe in any population, and there was little or no direct trial evidence for evolocumab in terms of HRQoL or apheresis.

The submission of safety evidence was a non-systematic review of good quality RCTs, providing evidence for up to two years. There were no obvious safety concerns, with most AEs being balanced across evolocumab and comparator trial arms, and very small numbers of SAEs were reported. However, the ERG noted that relatively higher 12-week AE rates were reported in patients who had HeFH or who had primary non-familial hypercholesterolaemia and were statin-intolerant. Similarly, these rates were also relatively higher for trials with a longer follow-up duration. This suggests that some patient subgroups might experience more frequent events and that all patients are at risk of AEs over time, though the rates are generally similar to comparators. The ERG noted also that the longer-term evidence presented was derived from some trials with populations who would not be eligible to receive evolocumab in clinical practice in the NHS (e.g. people who were not on maximum-tolerated doses of statins). More long-term data are therefore needed in relevant UK populations, although it is not clear whether ongoing trials will address this.

5 COST EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the company's review of published economic evaluations and the *de novo* health economic analysis presented within the CS.[13]

5.1 ERG comment on the company's systematic review of cost-effectiveness evidence

5.1.1 Description of company's systematic review of cost-effectiveness evidence

The CS[13] presents the methods and results of a systematic review of existing health economic evaluations of lipid-lowering drug therapies for the treatment of hypercholesterolaemia. According to the CS, the purpose of the review was *"to systematically identify, critically review, and summarise studies evaluating the cost-effectiveness of evolocumab, statins, and ezetimibe for LDL-C reduction in adults with hypercholesterolaemia"* (see CS,[13] page 161). The CS states that the review was undertaken to inform the *de novo* model developed as part of the submission.

Search strategy

The company undertook electronic searches within the following electronic databases:

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

Searches were limited to articles with abstracts written in English and published during the period 2000 to 2014.

In addition to the electronic searches, conference abstracts published between 2013 and 2014 from the following congresses were reviewed:

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

The CS states that the conference abstract search used the same strategy as the EMBASE search. The websites of the conferences not indexed by EMBASE (ESC 2014 and EAS 2014) were searched manually for relevant abstracts.

In addition, HTA documents assessing economic evaluations of lipid-lowering drug therapies were identified through a manual search of the health technology assessment (HTA) websites in a variety of countries including the UK (NICE, the All Wales Medical Strategy Group [AWMSG], and the Scottish Medicines Consortium [SMC]), Spain, Sweden, France, Australia, Canada, Netherlands, Belgium, Austria, Ireland, Portugal, Poland, Hungary, Slovenia, Mexico, and Brazil. As with the electronic searches, HTA websites were searched for studies reported during the period 2000-2014.

The reference sections of review articles identified in search results were hand-searched for original relevant articles which met the review inclusion criteria.

Inclusion and exclusion criteria

The inclusion and exclusion criteria adopted within the company's review are summarised in Box 1.

Box 1: Inclusion and exclusion criteria for company's review of cost-effectiveness studies

Inclusion criteria

- Full economic evaluations undertaken in adults with LDL hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies would be considered
- Studies assessing evolocumab, ezetimibe and/or statins
- Studies reporting on: cardiovascular event reduction; treatment costs; QALYs / quality of life measures; cost-effectiveness and/or cost-utility results for the interventions of interest (i.e. ICERs)

Exclusion criteria

- Studies undertaken in children only (<18 years of age)
- Studies undertaken in non-humans
- Studies evaluating surgical procedures, lifestyle interventions and/or dietary modification
- Models which do not involve economic evaluations
- Studies that assess only cost, utilisation or efficacy
- Studies that do not present cost-effectiveness measures
- Studies in which no abstract is available
- Studies not reported in English
- Studies published before the year 2000

Study selection and quality assessment

The CS[13] (page 164) states that study selection followed a 3-stage process involving the assessment of titles and abstracts of potentially relevant studies against the inclusion/exclusion criteria, followed by re-assessment of full texts of potentially includable studies against the criteria. Included studies were

assessed using the checklist reported by Drummond and Jefferson.[48] The CS notes that studies were not selected or excluded from the review based on quality assessment.

Results of the company's review of cost-effectiveness evidence

The company's electronic searches yielded 775 potentially relevant unique citations. Of these, 645 studies were excluded at the title/abstract stage. One additional study was identified through hand-searching, leading to 131 potentially includable studies. Following a review of the full texts of these studies, 35 were excluded. The conference proceedings search in EMBASE yielded 33 potentially includable studies; all but one of these was excluded as they did not evaluate at least one intervention of interest. The conference proceedings search for studies not yet indexed in EMBASE yielded 184 potentially includable abstracts, however all of these were excluded. The company's manual search of HTA websites identified 11 HTA reports that contained details of cost-effectiveness models that were deemed relevant to the decision problem.

A total of 108 studies were included in the review. The CS notes that 28 of these studies were UK-focussed, 66 adopted a Markov approach and 53 adopted a lifetime horizon. None of the identified studies evaluated evolocumab. The CS[13] (Table 5-2, page 176) presents a summary of 14 UK-based studies which presented a Markov model with a lifetime time horizon.

5.1.2 ERG critique of company's systematic review of cost-effectiveness evidence

The searches undertaken by the company were of a reasonable quality. Search terms were drawn from NICE CG181[15] and appropriate subject headings and syntax were used for each database. The ERG did however identify some problems. In particular, there is a risk of missing relevant foreign language studies by imposing a restriction to include only English language studies. Furthermore, the company appears to have developed their own filter for identifying economic evaluations; this was tailored to each database searched, but includes some minor syntax errors (for example, "pharmaco?economic*" – the "?" character cannot be used to find hyphens or spaces in Ovid). The ERG considers that the use of a validated filter e.g. the Scottish Intercollegiate Guidelines Network (SIGN) economic evaluation filter, would have minimised the risk of missing potentially relevant economic studies. In addition, the ERG notes that the process of study selection and review described in the CS is not entirely clear. The PRISMA diagram presented in Figure 5-1 of the CS[13] (page 165) includes only those studies identified through the electronic searches; this should have also included studies identified through searching of conferences and HTA websites. There is also some ambiguity regarding the study selection process which is described as a three stage process but only appears to include two stages (sifting by title and abstract followed by full text review).

The results of the review are partially summarised in Table 5-2 of the CS.[13] Data extraction tables and quality assessment tables are presented in CS Appendix 9. The reasons for including only the 14 studies which adopted a Markov structure and a lifetime horizon (see CS[13] , Table 5-2), rather than the broader set of 28 included UK studies, are unclear from the CS. Perhaps more importantly, neither the main submission document nor the accompanying appendix offers any interpretation of results of the review of cost-effectiveness evidence, and these contain only very abbreviated information regarding the structures and data sources adopted in previous models. Neither the CS nor the accompanying appendix includes any discussion of key structural issues arising from previous models, for example, methods for modelling compound health states which incorporate prior events, approaches to modelling CV event risk using surrogate measures, or alternative methods for quantifying baseline event risk. Consequently, the extent to which the company's review has been used to inform the company's *de novo* model is unclear; this issue is discussed in more detail in Section 5.3.

Despite the limitations of the review, the ERG is satisfied that the company's searches are unlikely to have missed any relevant economic evaluation studies of evolocumab. The ERG notes that in September 2015, the US Institute for Clinical and Economic Review published a draft report assessing the cost-effectiveness of PCSK9 inhibitors for the treatment of hypercholesterolaemia.[49] Given the publication date, this study was not identified by the company's searches. The analysis was based on the previously published CVD Policy Model;[50,51] this is a Markov model of CHD and stroke incidence, prevalence, mortality, and costs in the US population over the age of 35 years. Within the analysis, the authors evaluate the comparative clinical effectiveness and cost-effectiveness of two PCSK9 inhibitors, evolocumab and alirocumab as a class, for people with elevated LDL-C. The health economic analysis was undertaken from a healthcare perspective over a time horizon of 20 years. The results of the analyses indicate that within the HeFH population, the ICER for PCSK9 inhibitors plus statins versus ezetimibe plus statins is approximately $681,000 per QALY gained. For people with non-familial primary hypercholesterolaemia with a prior history of CVD who are able to take statins, the ICER for the PCSK9 inhibitors plus statins versus ezetimibe plus statins was reported to be approximately $557,000 per QALY gained. For people with non-familial primary hypercholesterolaemia with a prior history of CVD who are unable to take statins, the ICER for PCSK9 inhibitors versus ezetimibe was reported to be about $506,000 per QALY gained.

5.2 Description of the company's model

5.2.1 Health economic evaluation scope

As part of their submission, the company submitted a fully executable health economic model programmed in Microsoft Excel. The company's model assesses the cost-effectiveness of evolocumab versus ezetimibe, each in combination with atorvastatin in patients who are able to take statins, or as monotherapy (without concomitant atorvastatin) in patients for whom statins are contraindicated or not tolerated. The company's model assesses the cost-effectiveness of evolocumab over a lifetime horizon from the perspective of the UK NHS; costs borne by Personal Social Services (PSS) were not included in the company's analysis. All costs and health outcomes were discounted at a rate of 3.5% per annum.

Table 26: Scope of the company's health economic analysis

Population	(i) People with non-familial primary hypercholesterolaemia and LDL-C >2.5mmol/L without a history of CVD, based on the subset of patients enrolled within the LAPLACE-2 trial[23] who had these characteristics. (ii) People with non-familial primary hypercholesterolaemia LDL-C >2.5mmol/L with a history of CVD, based on the subset of patients enrolled within the LAPLACE-2 trial[23] who had these characteristics. (iii) People with or without a history of CVD and a diagnosis of HeFH, based on the modified ITT population of the RUTHERFORD-2 trial.[21] These populations are further subdivided in terms of those patients who are able to take statins (denoted ST) and those for whom statins are contraindicated or not tolerated (denoted SI). Subgroup analyses are also presented for patients with additional risk factors in people with a history of CVD.
Interventions and comparators	For patients who are able to take statins, the base case analysis compares: • Evolocumab plus statins versus ezetimibe plus statins. For patients for whom statins are contraindicated or not tolerated, the base case analysis compares: • Evolocumab monotherapy versus ezetimibe monotherapy Additional scenario analyses are presented for evolocumab in combination with ezetimibe (with or without concomitant statins).
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS
Time horizon	Lifetime
Discount rate	3.5% per year

LDL-C – low density lipoprotein cholesterol; CVD – cardiovascular disease, ST – statin-tolerant; SI – statin intolerant; QALY – quality-adjusted life year; HeFH - Heterozygous familial hypercholesterolaemia

Population

The company's model assesses the cost-effectiveness of evolocumab in three main populations, based on the baseline characteristics of people enrolled in the LAPLACE-2 trial[23] and the RUTHERFORD-2 trial.[21]

(i) People with non-familial primary hypercholesterolaemia and LDL-C>2.5mmol/L without a history of CVD, based on the subset of patients enrolled into the LAPLACE-2 trial[23] who had these characteristics. Throughout the remainder of this chapter, this population is referred to as the non-familial primary prevention population. It should be noted that results for this population were deemed "invalid" by the company following the identification of problems in the model (the presence of negative probabilities) by the ERG during the clarification stage.

(ii) People with non-familial primary hypercholesterolaemia and LDL-C>2.5mmol/L with a history of CVD, based on the subset of patients enrolled into the LAPLACE-2 trial[23] who had these characteristics. Throughout the remainder of this chapter, this population is referred to as the non-familial secondary prevention population. The mathematical inconsistency described above is also applicable to this population however the company did not comment on the validity of results for this population.

(iii) People with a diagnosis of HeFH with or without a history of CVD, based on the modified ITT population of the RUTHERFORD-2 trial.[21] Throughout the remainder of this chapter, this population is referred to as the HeFH primary/secondary prevention population. The mathematical inconsistencies described above also apply to this population, however the company did not consider the analyses in the population to be invalid, but instead introduced adjustments to some transition probabilities to avoid the occurrence of negative transition probabilities under the base case assumptions; these issues are described in Section 5.3.

For all three populations described above, separate analyses are presented for: (a) patients who are able to take statins (ST), and; (b) patients for whom statins are contraindicated or not tolerated (SI). These subgroups are hereafter therefore denoted "ST" and "SI", respectively.

In addition, the model includes subgroup analyses based on the LAPLACE-2 trial in which further individual or combinations of risk factors are included (increased baseline LDL-C, presence of diabetes, presence of AF and number of vascular beds) in patients with a history of CVD. It should be noted that these are not within-trial subgroup analyses *per se* as they are evaluated within the model by manipulating the baseline characteristics of patients in the LAPLACE-2 primary hypercholesterolaemia LDL-C>2.5mmol/L secondary prevention population to reflect the scenario under consideration. For example, in order to evaluate evolocumab versus ezetimibe in patients with diabetes, all patients are assumed to have diabetes whilst their other characteristics are left unchanged at their observed baseline values.

It should be noted that the GAUSS-2 trial[24] was not used by the company to inform baseline population characteristics despite including a population of patients for whom statin therapies are contraindicated or not tolerated. The CS[13] (page 174) justifies this exclusion on the basis that patients for whom statins are contraindicated or not tolerated are a subgroup of the primary hypercholesterolaemia and mixed dyslipidaemia and HeFH populations, there are no RCTs assessing evolocumab in a HeFH statin-intolerant population, and patients for whom statin therapies are contraindicated or not tolerated are anticipated to have comparatively higher cholesterol levels.

Interventions

The intervention under consideration is evolocumab 140mg pre-filled syringe in 1mL solution. The company's base case analysis focusses only on the 140mg 2-weekly (Q2W) dose; the 420mg monthly (QM) dose is considered only within the company's scenario analysis (see CS,[13] Section 5.12). Patients receiving evolocumab are assumed to require training to administer subcutaneous treatment. Patients are assumed to receive evolocumab indefinitely for the remainder of their lifetime.

Comparators

The main comparator included in the company's model is ezetimibe 10mg once daily (OD) (oral tablet). Patients receiving ezetimibe are assumed to receive treatment for the remainder of their lifetime.

Within the non-familial primary prevention ST population, background statin therapy is assumed to be atorvastatin 20mg OD. Within the non-familial secondary prevention ST population, the background statin therapy is assumed to be atorvastatin 80mg OD. Page 229 of the CS[13] justifies this with respect to current NICE recommendations.[15] It should be noted that the LAPLACE-2 trial[23] also included other background statin therapies. Within the HeFH primary/secondary prevention population, background statin therapy was assumed to be atorvastatin 80mg OD irrespective of patients' history of prior CVD events. Patients for whom statin therapies are contraindicated or not tolerated are assumed to receive no background lipid-lowering therapy.

It should be noted that whilst the comparator specified in the final NICE scope[4] is ezetimibe (in combination with a statin or as monotherapy), the company's model also includes statins alone as a comparator in its own right. This is beyond the remit of the appraisal and is therefore not considered in detail in this ERG report.

5.2.2 Description of the company's health economic model structure and logic

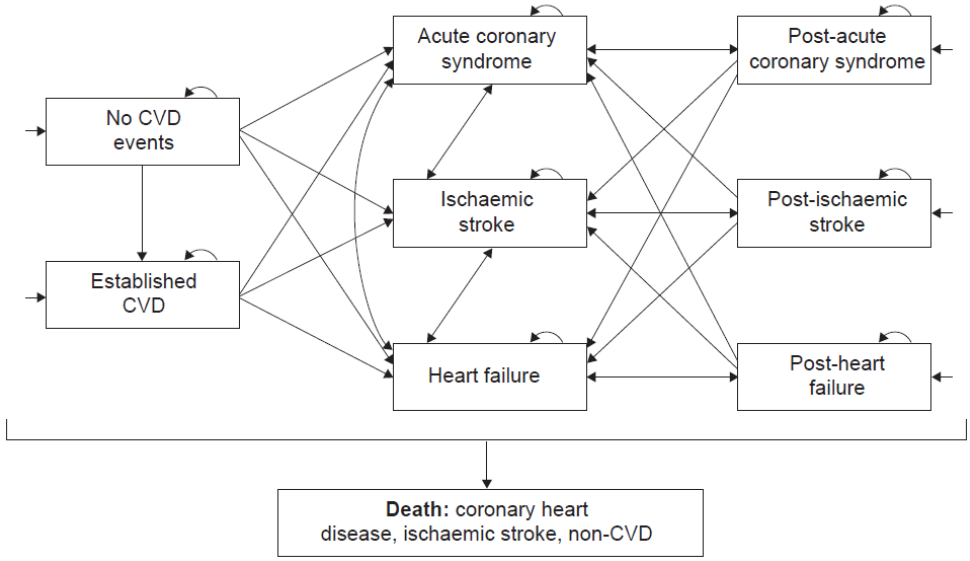
The description of the model's logic and input parameters contained within the CS is on some occasions brief and on others inaccurate.[13] The description of the economic model submitted by the

company presented here is largely based on information contained within the CS,[13] although in the instance of discrepancies between the CS and the model, the model is used as the basis of the description. It should also be noted from the outset that following the detection by the ERG of a serious programming error (the presence of negative transition probabilities) in the company's original model, the company submitted an amended model and an addendum outlining the revised results produced using this model.[52] The principal amendments made by the company relate to: (i) the removal of the functionality to conduct threshold analyses according to baseline LDL-C levels in the non-familial primary prevention population (base case analyses A and B), and; (ii) arbitrary adjustments to some transition probabilities for the analyses undertaken in the HeFH primary/secondary prevention population (base case analyses G and H). The analyses of the non-familial secondary prevention population (base case analyses C and D) are unaffected by the company's model amendments.

A simplified representation of the company's model structure is presented in Figure 3. The model adopts a Markov approach and simulates the experience of an average cohort of people with or without a history of CVD. Patients who are able to take statins are assumed to continue to do so indefinitely for the remainder of their lives; these patients are assumed to experience no change in LDL-C or CVD events above their current risk levels. Within the statin-tolerant populations, patients in the evolocumab and ezetimibe groups are assumed to receive these treatments in addition to statin therapy. In the analyses of patients for whom statins are contraindicated or not tolerated, patients are assumed to receive evolocumab and ezetimibe as monotherapy. Within the model, patients receiving these therapies benefit from reduced LDL-C, which is in turn, translated into benefits in terms of reduced CV events. The CS[13] (page 174) states that a Markov approach was adopted: (a) because it adequately reflects the scope of the disease and clinical practice and; (b) because it is commonly used in economic evaluations of drugs for reducing LDL-C in patients with hypercholesterolaemia.

The model is comprised of 24 mutually exclusive health states (see Table 27) and is evaluated using an annual cycle length. The model health states include three individual "acute" event states (where patients remain for a maximum duration of one year unless they experience the same event during the next cycle), five individual "chronic" event states (including three "post-event" health states - post-Acute Coronary Syndrome (ACS), post-ischaemic stroke (IS) and post-heart failure (HF), as well as no CVD and established CVD [ECVD]), and thirteen composite CVD health states (including "acute" and "post-event" health states, which contain either two or three individual health states), and three death states (CHD death, stroke death and death due to other causes).

Figure 3: Simplified representation of the company's model structure (reproduced from CS,[13] Figure 5-2, page 175)



CVD, cardiovascular disease

Table 27: Health states used in the company's model

Health state types	Health states included in model
Individual "acute" health states	• acute coronary syndrome (ACS) including myocardial infarction (MI) and unstable angina (UA) • ischemic stroke (IS) • heart failure (HF)
Individual "chronic" health states	• no CVD • established CVD (ECVD) including stable angina, transient ischemic attack (TIA), carotid stenosis, revascularisation without history of myocardial infarction (MI), abdominal aortic aneurism, peripheral vascular disease. • post-ACS • post-IS • post-HF
Composite health states (combination of "acute" and "chronic" health states	• combined 2-level health states (IS+post-ACS, post-IS+ACS, post-IS+post-ACS, HF+post-ACS, post-HF+ACS, post-HF+post-ACS, HF+post-IS, post-HF+post-IS) • combined 3-level health states (HF+post-IS+post-ACS, post-HF+post-IS+ACS, post-HF+post-ACS+IS, post-HF+post-IS+post-ACS)
Death states	• CVD death – coronary heart disease (CHD) death • CVD death - stroke death • non-CVD death.

The rationale for selecting ECVD, IS, ACS and HF to reflect the range of CVD events in the model described in the CS is rather limited.[13] The CS (page 176) states that ECVD events were separated from other CVD events (IS, ACS and HF) as they are less severe and are associated with lower

baseline risks of experiencing further CVD events, as well as lower management costs and higher utility values. The CS further states that ACS, IS and HF are separated into "acute" and "chronic" health states to account for the differences in risks, costs and HRQoL between the first and subsequent years.

For analyses undertaken within the non-familial primary prevention population, all patients enter the model in the "no CVD" health state. For analyses undertaken within the non-familial secondary prevention population, patients enter the model in one of the three post-CVD event health states ("post-ACS", "post-IS" or "post-HF") or the "ECVD" health state. Subgroup analyses are presented according to the type of previous CVD event experienced. For analyses undertaken within the HeFH primary/secondary prevention population, patients enter the model in the one of the three post-CVD event health states ("post-ACS", "post-IS" or "post-HF"), the "ECVD" health state or the "No CVD events" health state.

During a given cycle, patients in the "No CVD events" health state remain in this state until they experience:

- an acute non-fatal CVD event (ECVD, ACS, IS or HF);
- a fatal CVD event (CHD or stroke death), or;
- death due to causes other than CVD.

During any cycle following the first acute CVD event, patients are assumed to experience:

- no further CVD events (hence patients transit to the corresponding "post-event" health state);
- the same acute event (hence patients remain in the same acute event health state);
- a different acute event (hence patients transit to a composite health state incorporating the post-event state for previous events and the new acute event);
- a fatal CVD event, or;
- death due to causes other than CVD.

During any cycle following transition to a "post-event" health state, patients are assumed to experience:

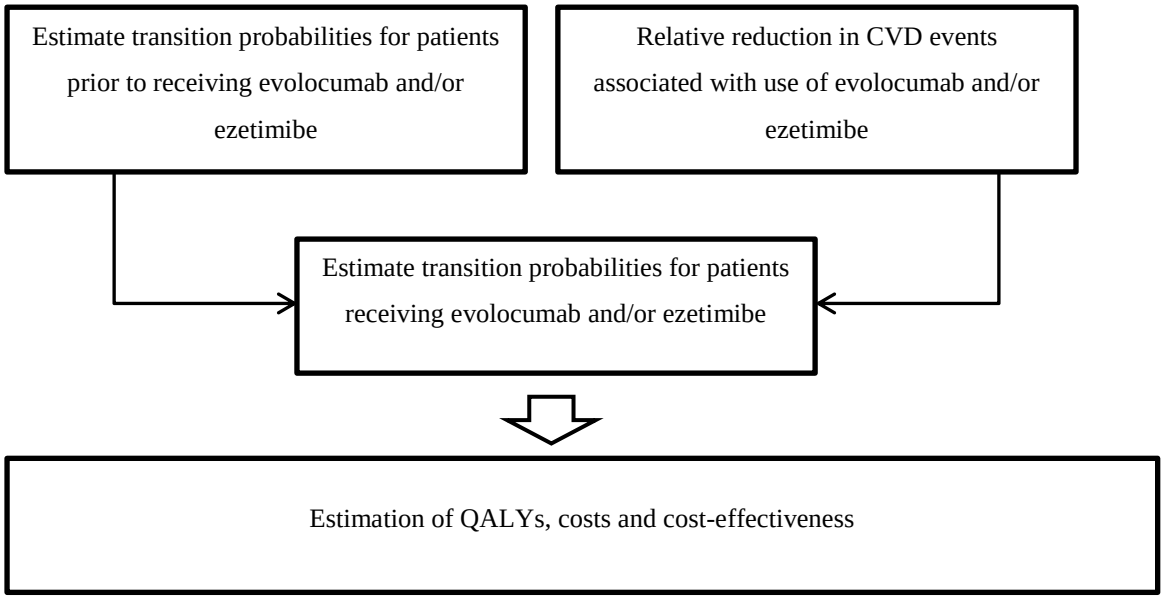
- the same acute event (hence patients transit to the corresponding acute health state or the relevant composite state if the individual has a history of other CVD events);
- a different acute event (hence patients transit to a composite health state incorporating the post-event state for the previous event and the new acute event);
- a fatal CVD event, or;
- death due to causes other than CVD.

The company's model also employs the following key structural assumptions:

- Upon experiencing a CVD event, patients cannot transit back to a less severe health state (e.g. patients cannot transit to ECVD once they have experienced a CVD event);
- For patients in a composite health state, the model assumes the highest probability, highest management cost and lowest utility for the relevant individual health states.
- Revascularisation procedures are not included as health states. Instead, only the costs of revascularisation procedures are included, based on a proportion of patients requiring revascularisation procedures in the "ACS" and "post-ACS" health states.

The logic adopted by the company's model is summarised in Figure 4. The company's model uses absolute reduction in LDL-C associated with the use of evolocumab and/or ezetimibe as a surrogate to predict a corresponding reduction in CVD events. The need to model this surrogate to final endpoint relationship is justified by the company based on the absence of data on the impact of evolocumab on CVD events from an RCT (see CS,[13] page 192, and as mentioned in Section 4.6 of this report). As noted in the CS, a double-blind, randomised, placebo-controlled, multicentre trial (the FOURIER study[32], clinicaltrials.gov identifier NCT01764633), which is assessing the impact of evolocumab when used in combination with a statin therapy in people with clinically evident CVD, is currently ongoing and is due to report in 2018.

Figure 4: Summary of the company's model logic



CVD – cardiovascular disease; QALYs – quality-adjusted life year

The logic employed within the company's model can be described in terms of four sequential components:

(i) Estimation of transition probabilities for people prior to receiving evolocumab and/or ezetimibe.

(ii) Estimation of the relative reduction in CVD events associated with the use of evolocumab and/or ezetimibe based on reductions in LDL-C observed in RCTs.[23,24]

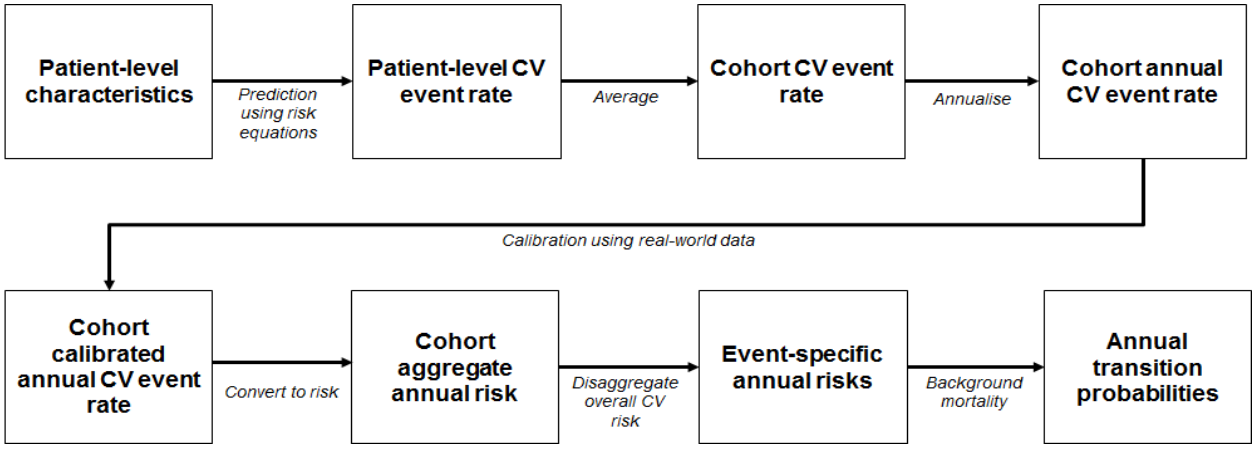
(iii) Estimation of transition probabilities in patients receiving evolocumab, ezetimibe or evolocumab plus ezetimibe.

(iv) Estimation of QALYs, costs and cost-effectiveness.

(i) Estimation of transition probabilities for people prior to receiving evolocumab and/or ezetimibe

The steps used by the company to estimate transition probabilities in the absence of evolocumab and/or ezetimibe (referred to as "population CV event rates" in the CS) are described in Figure 5.

Figure 5: Step-wise sequence of estimating event-specific transition probabilities from patient-level characteristics (reproduced from CS,[13] Figure 5-4 page 182)



CV - cardiovascular

Published risk equations[53,54] are applied to individual patient data (IPD) from the subgroup of patients enrolled in the LAPLACE-2 trial[23] who had a baseline LDL-C>2.5mmol/L and from the modified ITT population of the RUTHERFORD-2 trial[21] to estimate the average aggregate risk of the next CVD event for males and females separately. The Framingham equations for males and females[53] are used to estimate the risk of a first CVD event in people who do not have a history of CVD. The REduction of Atherothrombosis for Continued Health (REACH) Registry equations[54] are used to predict the risk of experiencing a fatal or any CVD event (assumed incorrectly to be non-fatal by the company) in people who have a history of CVD. The company assumes (incorrectly) that the risk predicted for "cardiovascular death" and "next cardiovascular event" from the REACH equations are independent of each other and can be added (effectively producing a total CVD risk). It should also be noted that the predicted risks from both the Framingham and REACH equations are actually probabilities which are bounded between 0 to 1, but are not treated as such within the company's model; these are instead

assumed to be "event rates" (see Figure 5, box 2 "patient-level CV event rate"). This error in logic is discussed in more detail in Section 5.3.

The calculated average aggregate risks of CVD events (10-year risk from Framingham[53] and 20-month risk from REACH[54]) are then transformed into annualised rates; these are calculated separately for males and females (using a sex-specific equation from Framingham and a covariate for sex within the REACH equation). Limited details are provided within the CS[13] regarding this step in the process. From the company's model, the age coefficients (for males and females separately) from the risk equations are used to obtain annual age- and sex-specific rates under the assumption that the event rate follows an exponential distribution such that the sum of the CVD event risks is equal to the average aggregate 10-year risk of CVD using the following formula:

$$risk(t) = \partial \times exp(\varphi)^{ln(\frac{age(t)}{\rho}} \quad [i]$$

Where:

$risk(t)$ = *annual risk at a given age*

∂ = *risk prediction by risk equation*

φ = *age coefficient in the risk equation*

$age(t)$ = *current age*

ρ = *mean age*

The annual age-specific risks obtained for males and females are then averaged to obtain an average annual age-specific risk; these are capped at a maximum age of 86 years (i.e. the risk is assumed to remain constant after age 85 years) and are subsequently multiplied by either: (a) state-specific calibration factors to reflect the performance of the risk equations in the UK for the non-familial primary hypercholesterolaemia populations (based on the LAPLACE-2 trial[23]), or (b) an overall calibration factor to reflect the differences in the risk of CVD events between HeFH and non-HeFH patients (HeFH analyses only). Following this process, the company transform the resulting risks onto the probability scale using the following formula:

$$probability = 1 - exp(-rate) \quad [ii]$$

The average aggregate annual age-specific probabilities of CVD events are then apportioned according to specific CVD events based on multinomial logistic regression models (see Section 5.2.2). The average aggregate risks for first CVD events derived from the Framingham equations[53] after calibration are apportioned into ECVD, ACS, IS, HF, CHD death and stroke death events. The risks for subsequent CVD events derived from the REACH Registry equations[54] after calibration are

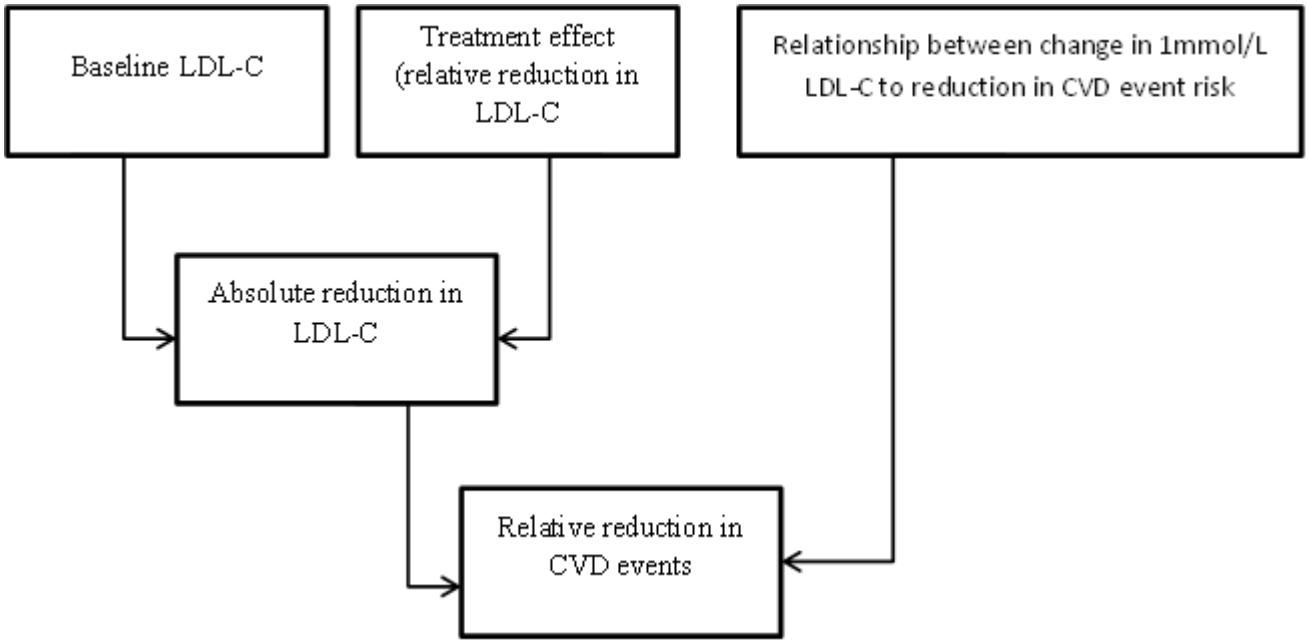
separated into ACS, HF and IS. The risks for cardiovascular death derived from the REACH Registry equation[54] after calibration are apportioned to either stroke death or CHD death.

(ii) Estimation of the relative reduction in CVD events associated with the use of evolocumab and/or ezetimibe based on reductions in LDL-C observed in RCTs

Separate to the derivation of the transition probabilities for patients receiving background statin therapies (for patients who are able to take statins) or no treatment (for patients for whom statins are contraindicated or not tolerated), the company's model calculates the relative reduction in CVD events associated with adding evolocumab and/or ezetimibe to statin therapy in people who are able to take statins, or with using evolocumab and/or ezetimibe as monotherapy for patients for whom statins are contraindicated or not tolerated.

The process by which the company derives the relative reduction in CVD events associated with the use of evolocumab and ezetimibe is described in Figure 6. This involves three stages: (a) defining baseline LDL-C; (b) applying a treatment effect (as a percentage reduction in LDL-C) associated with the use of evolocumab and/or ezetimibe to calculate the absolute reduction in LDL-C associated with additional lipid-lowering therapy, and; (c) applying a relationship which translates the reduction in 1mmol/L in LDL-C into a relative reduction in specific CVD events (non-fatal MI, any coronary revascularisation, IS, CHD death and IS death).

Figure 6: Company's approach to modelling the effects of LDL-C reduction on reductions in CV events



It should be noted that the company's model assumes that the minimum LDL-C is 40mg/dL (equivalent to 1.03mmol/L), thus it is assumed that evolocumab and ezetimibe cannot reduce LDL-C to a level lower than this threshold. To illustrate, assuming a baseline LDL-C of 2mmol/L and assuming that evolocumab reduces LDL-C by 1.5mmol/L, the model assumes that the absolute reduction with evolocumab would be 0.97mmol/L rather than 1.5mmol/L. This is likely to be conservative for evolocumab (as this therapy is associated with the largest reduction in LDL-C).

For the scenario evaluating evolocumab plus statins versus ezetimibe plus statins (referred to as Scenario 1 in the CS,[13] page 181 - base case analyses A, C and G), the reduction in CV events compared with background therapy is determined by: (a) the baseline LDL-C at entry of the trial; (b) the relative difference in LDL-C between evolocumab/ezetimibe and background statins (treatment difference) at the mean of week 10/12, and; (c) the relationship between absolute reductions in LDL-C and reductions in first CV events.

This is different in the scenario evaluating evolocumab monotherapy versus ezetimibe monotherapy in patients for whom statins are contraindicated or not tolerated (referred as Scenario 2 in the CS,[13] page 181 - base case analyses B, D and H) whereby the reduction in CV events is determined by: (a) the baseline LDL-C at entry of the trial (rather than LDL-C at 12 weeks); (b) the relative difference in LDL-C between evolocumab (or ezetimibe) and baseline LDL-C at entry of the trial (difference from baseline) rather the treatment difference at the mean of week 10/12, and; (c) the relationship between absolute reductions in LDL-C and reductions in CV events.

For Scenarios 3 and 4 (see CS[13] page 181 - scenario analyses E,F, I and J) whereby evolocumab is used in combination with ezetimibe, the company's model assumes that the treatment effect of evolocumab is sequential to the treatment effect of ezetimibe, i.e. the treatment effect for evolocumab is applied after adjusting for the effect of ezetimibe (representing the new baseline LDL-C level). As an illustrative example, assuming that the population has a baseline LDL-C of 2.5mmol/L and ezetimibe reduces LDL-C to 2.0mmol/L, the treatment effect of evolocumab is applied to the post-ezetimibe LDL-C (2.0mmol/L) rather than the pre-ezetimibe LDL-C (2.5mmol/L).

(iii) Estimation of transition probabilities in people receiving evolocumab, ezetimibe or evolocumab plus ezetimibe

The transition probabilities for patients receiving statins (for patients who are able to take statins) or no treatment (for patients for whom statins are contraindicated or not tolerated) estimated in Step (i) are adjusted using the relative reduction in CVD events estimated in Step (ii) using the following formula:

$$Probability\ after\ treatment = 1 - exp((CTTC\ rate\ ratio^{absolute\ LDL\text{-}C\ reduction}) \times log(1 - probability\ baseline)) \quad [iii]$$

The transition probabilities estimated in Step (i) that are adjusted by the treatment effects estimated in Step (ii) are summarised in Figure 7.

It should be noted that the CS states that *"patients in HF health states (either single or combined) experience no further treatment effect due to LDL-C lowering for risk of recurrent HF since findings suggest lack of benefit for lipid-lowering therapies once patients experience HF on events such as CHD death"* (CS,[13] page 197). This appears to be inconsistent with what is done in the company's model whereby a reduction in LDL-C in people with HF (either acute, post-health state or combined health state) is associated with a reduction in CHD death.

Figure 7: Health state transitions and applied treatment effects (reproduced from CS,[13] Figure 5-6, page 200)

FROM \ TO	NoCVD	ECVD	ACS	IS	HF	PostACS	PostIS	PostHF	CHDdeath	ISdeath	NonCVDdeath	IS +PostACS	PostIS +ACS	PostIS +PostACS	HF +PostACS	PostHF +ACS	PostHF +PostACS	HF +PostIS	PostHF +IS	PostHF +PostIS	HF +PostIS +PostACS	PostHF +PostIS +ACS	PostHF +PostACS +IS	PostHF +PostIS +PostACS
NoCVD	#	TE	TE	TE	TE				TE	T	T													
ECVD		#	TE	TE	TE				TE	T	T													
ACS			TE			#			TE	T	T	TE			TE									
IS				TE			#		TE	T	T		TE					TE						
HF					T			#	TE	T	T					TE			TE					
PostACS			TE			#			TE	T	T	TE			TE									
PostIS				TE			#		TE	T	T		TE					TE						
PostHF					T			#	TE	T	T					TE			TE					
IS+PostACS									TE	T	T	TE	TE	#							TE			
PostIS+ACS									TE	T	T	TE	TE	#							TE			
PostIS+PostACS									TE	T	T	TE	TE	#							TE			
HF+PostACS									TE	T	T				T	TE	#						TE	
PostHF+ACS									TE	T	T				T	TE	#						TE	
PostHF+PostACS									TE	T	T				T	TE	#						TE	
HF+PostIS									TE	T	T							T	TE	#		TE		
PostHF+IS									TE	T	T							T	TE	#		TE		
PostHF+PostIS									TE	T	T							T	TE	#		TE		
HF+PostIS+PostACS									TE	T	T										T	TE	TE	#
PostHF+PostIS+ACS									TE	T	T										T	TE	TE	#
PostHF+PostACS+IS									TE	T	T										T	TE	TE	#
PostHF+PostIS+PostACS									TE	T	T										T	TE	TE	#

Complementary	#
Transition	T
Transition with treatment effect	TE

ACS - acute coronary syndrome; CHD - coronary heart disease; CVD - cardiovascular disease; ECVD - established CVD; HF - heart failure; IS - ischaemic stroke.
Complementary defined as one minus all other transition probabilities in the row

(iv) Calculation of QALYs, costs and cost-effectiveness

Transition probabilities for each treatment group are generated according to Steps (i) to (iii) described above. For the composite health states, the highest transition probability is selected. For example, for an individual in the post-HF+stroke state, the probability of experiencing CHD death during the next cycle is calculated as the maximum of the probability of transiting from the post-HF state to the CHD death state and the probability of transiting from the stroke state to the CHD death state.

From the point at which transition probabilities are calculated, the model structure is straightforward. Simple matrix multiplication is used to calculate health state occupancy for each Markov cycle. The Markov trace is then half-cycle corrected.

Separate utilities are assigned to each of the model's health states. For composite health states, the lowest utility multiplier for individual states is selected. For example, the utilities for the individual post-HF and ischaemic stroke states are 0.683 and 0.628, respectively; thus for people in the post-HF+stroke state, a utility of 0.628 is applied. The impact of AEs on HRQoL is not included in the company's model.

Cost components within the model include the cost of lipid-lowering therapy, administration training costs (evolocumab only), monitoring costs, costs of revascularisation procedures, health state costs and the costs of CV-related death. Costs associated with managing AEs are not included in the company's model. In a similar manner to the approach used to apply health utilities, health state costs for composite health states are based on the highest cost of individual states. For example, the annual health state costs for the individual post-HF and ischaemic stroke states are £1,078.26 and £4,063.60, respectively; for patients in the post-HF+stroke state, a health state cost of £4,063.60 is applied.

The application of different treatment effects on LDL-C (and subsequently CV events) leads to different trajectories through the model's health states for each option. Total lifetime QALYs are calculated by simply applying the state-specific utilities to the probabilities of residing in each state over the model time horizon. Total costs are calculated by multiplying the state-specific costs by the probabilities of residing in each health state and combining these with the costs of drug acquisition, training and monitoring, incident revascularisation procedures and CV death. Incremental cost-effectiveness is calculated in a piecewise fashion as the difference in costs divided by the difference in QALYs for competing options.

5.2.4 Evidence used to inform the company's model parameters

5.2.4.1 Summary of evidence sources used to inform the company's model parameters

Table 28 summarises the sources used to inform the model's parameter values. These are described in further detail in the subsequent sections.

Table 28: Summary of evidence sources used to inform the company's model parameters

Parameter/group	Evidence source
Baseline characteristics	
Initial health state distribution (non-familial primary and secondary prevention populations)	LAPLACE-2[23] (subgroup with LDL-C>2.5mmol/L)
Initial health state distribution (HeFH population)	RUTHERFORD-2[21] modified ITT population
Baseline characteristics (non-familial primary and secondary prevention populations)	LAPLACE-2[23] (subgroup with LDL-C>2.5mmol/L)
Baseline characteristics (HeFH population)	RUTHERFORD-2[21] modified ITT population
CV event risks	
Risk of first CVD event (people without history of CVD)	D'Agostino *et al*[53] (Framingham Heart Study)
Risk of next CVD event (people with existing CVD)	Wilson *et al*[54] (REACH Registry)
Risk of fatal CVD event (people with existing CVD)	Wilson *et al*[54] (REACH Registry)
Calibration of risk predictions	
Calibration factors (non-familial primary and secondary prevention populations)	Company's CPRD/HES analysis[13]
Calibration factor (HeFH population)	Benn *et al*[55]
Risk of specific CV events	
Probability of specific CV events	Company's multinomial model derived from CPRD/HES analysis[13]
Treatment effects (LDL-C reduction and relationship to CV event risks)	
Relative reduction in LDL-C – evolocumab or ezetimibe plus statins versus statins at the mean of week 10/12	LAPLACE-2[23]
Relative reduction in LDL-C – evolocumab or ezetimibe versus baseline	GAUSS-2[24]
Relationship between LDL-C reduction and CV event reduction	Baigent *et al*[28]
Health-related quality of life	
State-specific health utilities	NICE CG181[15] (original sources – Dolan *et al*[56] Tsevat *et al*[57] Goodacre *et al*[58] Tengs *et al*[59] and Lacey *et al*[60]
Resource costs	
Drug acquisition costs	BNF[61] and CS[13]
s.c. injection training costs	NHS Reference Costs 2013/14[62]
Monitoring costs	PSSRU[63] and NHS Reference Costs 2013/14[62]
Health state costs	Company's CPRD/HES longitudinal study[13]
Costs of revascularisation	
Costs of CVD death	

5.2.4.2 Baseline characteristics

The company's model uses baseline individual characteristics in two ways: firstly to estimate the risk of CVD events and secondly to estimate the absolute reduction in LDL-C; these are in turn used to estimate the relative reduction in CVD events.

For the analyses of evolocumab in the non-familial primary prevention and secondary prevention populations, the company's model uses the subgroup of people enrolled within the LAPLACE-2 trial[23] who had a baseline LDL-C>2.5mmol/L. Baseline characteristics are based directly on the IPD for all variables (sex, age, SBP, HDL-C, diabetes, smoking, hypertension, total-cholesterol, LDL-C, triglycerides, BMI, previous events etc.), with the exception of the vascular beds and AF variables which were instead assumed to reflect the average values within the REACH Registry study[54] (see CS[13] Table 5-5 footnotes, page 183). This has an impact on the predicted risk of CV events in people with a history of CVD only insofar as they are covariates in the REACH Registry risk equation but not the Framingham risk equation. The ERG notes that by using the baseline characteristics for most variables from the same source, the company's model maintains the correlation between variables.

For the analyses of evolocumab in the HeFH primary/secondary prevention population, the company's model uses baseline characteristics from the modified ITT population of the RUTHERFORD-2 trial.[21] Similar to the analyses of the non-familial populations described above, baseline characteristics are based directly on the IPD for all variables (sex, age, SBP, HDL cholesterol, diabetes, smoking etc.), with the exception of the vascular beds and AF variables which were also instead assumed to reflect the average values within the REACH Registry study.[54] Again, this impact upon the predicted risk of CV events in the subset of patients with a history of CVD as they are included as covariates in the REACH Registry risk equations.

For the company's subgroup analyses in patients with existing CVD and additional risk factors (presence of diabetes, AF, number of vascular beds etc.), these variables are manually changed to reflect the characteristics of the subgroup whilst other characteristics are held at their observed values (rather than selecting out the subgroups of people within the trial who actually had these characteristics). This approach impacts upon the predicted risk of CVD events.

Whilst the analyses were removed by the company following the ERG's identification of the serious programming error (see Section 5.2.2), the company's analyses of the cost-effectiveness of evolocumab according to baseline LDL-C (3.5mmol/L and 6.0mmol/L) do not involve manipulating the IPD directly; instead, the average baseline LDL-C value is amended.

Within the analyses in the non-familial primary prevention population, all patients are assumed to enter the model in the "no CVD events" health state. The initial health state distribution within the non-familial secondary prevention population was based on the subset of patients enrolled within the LAPLACE-2 trial[23] who had a baseline LDL-C>2.5mmol/L. The initial health state distribution within the HeFH primary/secondary prevention population was based on the initial distribution of patients within the modified ITT analysis of the RUTHERFORD-2 trial.[21]

5.2.4.3 Prediction of CV event risk

Aggregate 10-year risk of CVD for people without a history of CVD

Irrespective of the analyses (non-familial primary hypercholesterolaemia/HeFH, statin tolerant/intolerant), the company's model uses results from published sex-specific multivariable-adjusted Cox proportional-hazards regression models derived from the US Framingham Heart Study[53] to predict the aggregate 10-year risk of CVD events (fatal and non-fatal coronary, cerebrovascular, and peripheral arterial disease and heart failure) in patients without a history of CVD. This study was undertaken in the US in a cohort of 8,491 individuals. The CS[13] states that this risk equation was selected based on a targeted literature review and that it was preferred to the QRISK2 risk equation (which is recommended in the UK) specifically because: (a) it includes a broader definition of CVD events and death (coronary death, MI, coronary insufficiency, and angina, cerebrovascular events including IS, haemorrhagic stroke, and TIA, peripheral arterial disease and HF); (b) it includes fewer variables to estimate baseline CVD risk (QRISK2 includes 14 variables whilst Framingham includes seven variables).

The general formula for the Framingham risk equation is presented below:

$$\hat{p} = 1 - S_0(t)^{\exp(\Sigma_{i=1}^{p} \beta_i X_i - \Sigma_{i=1}^{p} \beta_i \bar{X}_i)}, \qquad [iv]$$

The coefficients of the risk equations for males and females are summarised in Table 29. The ERG notes that whilst not used in the economic model, the D'Agostino[53] paper reports a series of calibration factors that can be used to estimate the risk associated with individual CVD events (CHD, stroke, CHF and intermittent claudication [IC]).

As mentioned in Section 5.2.2, the Framingham risk predictions are adjusted subsequently to: (a) reflect the performance of the risk equation in the UK, and; (b) reflect the increased risk in HeFH compared with people without HeFH.

Table 29: Framingham risk equations used in company's model (patients without a history of CVD)

Variable	Coefficients by sex	
	Male	**Female**
β*mean(x)	23.9802	26.1931
Constant	0.88936	0.95012
Log of age	3.06117	2.32888
Log of SBP if not treated	1.93303	2.76157
Log of SBP if treated	1.99881	2.82263
Log of total cholesterol	1.1237	1.20904
Log of HDL cholesterol	-0.93263	-0.70833
Diabetes	0.57367	0.69154
Smoking	0.65451	0.52873

HDL-C - high-density lipoprotein cholesterol; SBP - systolic blood pressure
Positive coefficients denote increased risk

It is important to note that baseline characteristics used in the company's model are assumed to be independent of whether an individual can or cannot take statins; in other words, the predicted aggregate 10-year risk of experiencing a CVD event is assumed to be the same irrespective of whether an individual is receiving statin therapy.

The ERG also notes that for the HeFH primary/secondary prevention population, which is comprised of a mix of patients who have a history of CVD and patients who have no history of CVD, the Framingham equation is used irrespective of whether patients in the trial (used in the economic model) have a history of CVD or not.

Aggregate 20-month risk of CVD events in people who have a history of CVD

For patients who have a history of CVD, the REACH Registry risk equations[54] are used to estimate the risk of subsequent CVD events. The REACH equations are international risk models estimated in 33,419 randomly selected individuals included in the REACH registry and validated in 16,270 individuals of the same registry. The models can be used to predict: (a) the 20-month risk of any secondary cardiovascular events (referred as "next cardiovascular event" by the authors), and; (b) the 20-month risk of cardiovascular death in outpatients with established atherothrombotic disease.

The 20-month risk for cardiovascular death is calculated as:

$$r = 1 - 0.97749^{exp(\sum \beta X - 4.03317)} \qquad [v]$$

The risk for next cardiovascular event is given as:

$$r = 1 - 0.93681^{\exp(\sum \beta X - 2.68845)} \qquad [vi]$$

where β is the regression coefficient and X is the level for each risk factor.

The coefficients of the REACH Registry risk equations are summarised in Table 30.

Table 30: REACH Registry risk equations used in company's model (patients with a history of CVD)

Variable	Coefficients by type of CV event	
	Cardiovascular death	Next cardiovascular event
β*mean(x)	4.03317	2.68845
Baseline risk	0.97749	0.93681
Male	0.24519	0.10246
Age	0.04966	0.03089
Diabetes mellitus	0.46141	0.37824
Event in previous year	0.26681	0.38168
Heart failure in previous year	0.89976	0.51873
Atrial fibrillation	0.42705	0.26652
Vascular beds	0.24928	0.30277
BMI < 20 kg/m^2	0.55132	0.31428
Smoking	0.30925	0.24121
Statins	-0.22296	-0.28332
Acetylsalicylic acid	-0.17968	-0.10151
Eastern Europe or Middle East	0.25934	0.27574
Japan or Australia	-0.65524	-0.31604

BMI - body mass index; CVD - cardiovascular disease; HDL-C - high-density lipoprotein cholesterol; REACH - REduction of Atherothrombosis for Continued Health. Positive coefficients denote increased risk

As discussed in Section 5.2.2, the company's model incorrectly assumes that the two risk equations (next cardiovascular event and cardiovascular death) are independent of each other. The risk equation for "next cardiovascular event" is assumed to represent the risk of the next non-fatal event and the risk equation for "cardiovascular death" is assumed to represent the risk of a fatal event. As with the Framingham equation, the CS[13] states that the REACH equations were identified through a targeted literature review. The REACH Registry equations were selected for use in the company's model as they predict aggregated CVD risk of recurrent non-fatal and fatal CV events rather than individual events.

The REACH Registry risk equations are used for both the analyses undertaken in the non-familial populations and the HeFH primary/secondary prevention population. The REACH equations are also used in the company's subgroup analyses in people with existing CVD, raised LDL-C and additional risk factors (such as presence of diabetes, AF or 2/3 vascular beds).

5.2.4.4 Calibration of risk predictions

Adjustment/calibration factors to reflect the performance of the risk equations to the UK (non-familial primary hypercholesterolaemia populations)

Whilst the company's model uses the risks predicted using the Framingham and REACH Registry risk equations to predict the probabilities of CVD events, the CS argues that these are not appropriate for the UK context and therefore require adjustment using a process referred to as "calibration." Appendix 10 of the CS[13] presents details of a critical appraisal of sources used in NICE CG181 and considers these to be inappropriate for two key reasons: (i) because the sources are dated and (ii) because the sources do not relate to people considered to be at high-risk. The ERG notes however that it is unclear whether the company's definition of "high-risk" relates to a higher risk of CVD or whether this is defined solely according to raised LDL-C or presence of risk factors.

The company undertook a separate study linking data from the Clinical Practice Research Datalink (CPRD - primary care), Hospital Episode Statistics (HES - secondary care) and the Office for National Statistics (ONS – cause of death) to estimate "calibration factors" to be used in the health economic model to adjust the risks predicted using the Framingham and REACH equations to match CV event rates observed in the UK. CVD events were chosen to reflect the health states in the company's health economic model. In brief, this involved four steps:

(i) Linking the data from the CPRD, HES and ONS. The discussion section of CS Appendix 11 mentions that only about half of the CPRD cohort could be linked to the HES and ONS data, thereby reducing the sample size.

(ii) Estimating the "observed" crude CV event rates in the CPRD and HES datasets in 5 populations: (a) people with diabetes free of CVD at baseline; (b) people with existing ECVD; (c) people with existing ACS; (d) people with existing IS, and; (e) people with existing HF. Crude CV event rates were calculated by dividing event counts by person-years of follow-up. CV event rates are stratified by the time period of follow-up (acute - one year; versus long-term - after year 1).

(iii) Estimating the predicted risk of CVD events using the Framingham and REACH equations in the CPRD and HES datasets.

(iv) Comparing the "observed" and predicted risks and calculating calibration factors to adjust the risk of CVD events calculated using the Framingham and REACH equations in the health economic model. As the Framingham and REACH Registry equations predict the 10-year and 20-month probabilities respectively, the company states that two adjustments were made: (a) adjusting the probability into yearly rates, and; (b) removing the effect of age. However, the CS contains very limited details regarding this process.

The calibration factors used in the company's model (referred to as mean rate ratios in the CS[13]) are presented in Table 31. It should be noted that in order to reflect the model structure and logic, these calibration factors were estimated separately for acute and chronic events and are separated in terms of fatal and non-fatal events in patients with a history of prior CVD events. Further details on the company's calibration approach are reported in CS Appendix 11.[13]

[redacted]

The CS[13] (page 191) acknowledges some of the limitations of the approach used, notably the potential mismatch between CVD events included in the risk equations and those included in the CPRD/HES dataset.

Adjustment/calibration factors to reflect the increased risk of patients with HeFH (HeFH population)

For the HeFH primary/secondary prevention analysis, a different approach is employed by the company whereby the baseline risks predicted using the Framingham and REACH equations are adjusted using a relative risk between patients with HeFH and without HeFH. The company (see CS[13] page 191 and Appendix 12) undertook a targeted review to identify studies that report CVD risk in patients with HeFH. The CS states that 14 studies met the inclusion criteria for the review and were formally assessed for bias. Of these, the study reported by Benn *et al*[55] was judged by the company as being at the lowest risk of bias as it included a direct comparison of FH and non-FH populations in the same study and because it reported on both fatal and non-fatal CV events. Benn *et al* reports adjusted

odds ratios (ORs) for coronary artery disease (CAD) as a function of the Dutch Lipid Clinic Network (DLCN) criteria for a diagnosis of FH in individuals on and off lipid-lowering medication from the general population, based on an unselected community-based population of 69,016 participants in Copenhagen. Within this study, amongst individuals who were not treated with cholesterol-lowering therapies, the adjusted OR for coronary artery disease was 13.2 (95%: 10.0 – 17.4) for those with definite/probable FH and 4.8 (4.3-5.3) for those with possible FH, compared with individuals with unlikely FH not treated with cholesterol-lowering therapies. Amongst individuals receiving cholesterol-lowering therapies, the authors report ORs of 10.3 (7.8 –13.8) and 14.8 (12.9 –17.1) respectively, compared with unlikely FH not treated with cholesterol-lowering therapies.

By pooling these data, the company adjusted the baseline CV risk predicted using the Framingham and REACH equations by a relative risk of 7.1 (95% CI 5.7, 8.7) to reflect the increased risk in the HeFH population. In the original CS, the company stated that this relative risk was calculated by pooling the statin and no statin groups and states that this was done *"to represent real-world treatment practice, accounting for the mix of primary and secondary prevention patients as well as different treatment paradigms"* (see CS[13] page 191). Following clarification, the company provided details on these calculations and showed that a simple pooling of data was conducted. The CS further states that *"the rate ratio was validated through estimation of a 10-year risk of CV events for the RUTHERFORD-2 patient population."* It is however unclear how the rate was validated.

5.2.4.5 Risk of specific CV events

Given that the Framingham and REACH Registry risk equations predict the aggregate risk of CVD events, the company's model uses data from the CPRD/HES dataset to apportion the aggregate CVD risks to specific CVD events by age. Multinomial logistic regression models were calculated from the CPRD/HES datasets to estimate the proportion of events that were non-fatal ACS, HF, IS and CV death (IS death and CHD death) in the secondary prevention cohorts, and the proportion of events that were ECVD, non-fatal ACS, HF, IS and CV death in the diabetes primary prevention cohort. The regression models and details are available in CS Appendix 11.[13] An example of the event distribution by age for patients with prior ACS is shown in Figure 8.

[redacted]

It should be noted that the multinomial models include both fatal and non-fatal events. As the company's model separates fatal and non-fatal secondary CVD events, a normalisation adjustment is made within the economic model to estimate the split of fatal and non-fatal CVD events separately as these are assumed to be independent.

5.2.4.6 Treatment effects – relative reduction in LDL-C for evolocumab and/or ezetimibe

The treatment effect estimates used in the economic model are presented in Table 32.

Table 32: Mean percent change in calculated LDL-C from baseline at mean of weeks 10/12 for evolocumab and ezetimibe when used in combination with statins or as monotherapy (adapted from CS,[13] Table 5-10, page 193)

Outcome	Evolocumab 140mg Q2W	Evolocumab 420mg QM	Ezetimibe 10mg od[b]
Combination with a statin (based on LAPLACE-2)			
Mean percent change from baseline[a] (95% CI) [SE]	-71.77 (-74.69, -68.85) [1.49]	-69.12 (-73.49, -64.76) [2.23]	-26.56 (-30.70, -22.42) [2.11]
Monotherapy (based on GAUSS-2)			
Mean percent change from baseline[a] (95% CI) [SE]	-57.10 (-60.84, -53.36) [1.90]	-55.82 (-58.88,-52.76) [1.55]	-17.83 (-21.01, -14.65) [1.62]

CI - confidence interval; LDL-C - low-density lipoprotein cholesterol; od - once daily; Q2W - every 2 weeks; QM - monthly; SE - standard error

[a]Least squares mean from the repeated measures model which includes treatment group, stratification factors (from IVRS), scheduled visit, dose frequency and the interaction of treatment with scheduled visit as covariates.

[b]Based on post hoc pooled analysis of all ezetimibe arms and all placebo arms in LAPLACE-2 and GAUSS-2, respectively.

For people who are able to take statins, the company uses the treatment effect from the LAPLACE-2 trial,[23] calculated as the percent change from the LDL-C at the mean of week 10/12 in patients on

evolocumab and ezetimibe (in addition to a statin) compared with the LDL-C at the mean of week 10/12 in patients receiving statin therapy only (note that CS Table 5-10 incorrectly states that this reflects the change from baseline). The CS[13] (page 193) further states that the treatment effect from the LAPLACE-2 trial was assumed to be generalisable to the HeFH population given the absence of a head-to-head trial of evolocumab versus ezetimibe (with or without a statin) in patients with HeFH and due to the consistency in the treatment effect of evolocumab regardless of individual population and individual characteristics, dosing regimen and presence and type of background lipid-lowering therapy. The CS also mentions that "*this approach is supported by the economic evaluation of ezetimibe that was utilised in NICE TA132, in which an assumption was made that the treatment effect of ezetimibe in non-HeFH patients was generalisable to patients with HeFH, in the absence of HeFH-specific effectiveness data"* (see CS[13] page 193).

For patients for whom statins are contraindicated or not tolerated, the company's model uses the treatment effect from the GAUSS-2 trial,[24] calculated as the percentage change in LDL-C at the mean of weeks 10/12 for evolocumab and ezetimibe compared with the LDL-C at baseline (entry into the trial). The treatment effect from GAUSS-2 was also assumed to be generalisable to the HeFH population.

The CS[13] (page 193) states that the treatment effects were taken from the calculated percent change at the mean of 10/12 weeks as this provides a time-averaged efficacy estimate over week 10 and week 12 and because the calculated approach to LDL-C assessment (rather than the reflexive approach) reflects best clinical practice and is in line with the marketing authorisation for evolocumab.[26] The treatment effect is assumed to apply indefinitely whilst on treatment. The company states (see CS[13] page 193) that this assumption is supported by findings from the ongoing OSLER 1/2 long-term extension studies which show that LDL-C reductions are maintained for more than two years.

5.2.4.7 Relationship between the absolute LDL-C reduction and CVD event reduction

The link between absolute reduction in LDL-C and reduction in CVD events was based on a published meta-analysis of 26 trials conducted by the CTT collaboration.[28] This meta-analysis reported a proportional reduction in specific CV events per mmol/L reduction in LDL-C. The meta-analysis used by the company reports the rate reduction in CV events calculated across 26 statin trials whereby statins were compared with other lipid-lowering agents or placebo, including five trials (referred to as "more vs less") in which more intensive regimens were compared with less intensive regimens.

The model uses results from the subgroup analysis of the five "more vs less" trials where possible, with the exception of death events. The CS[13] (page 197) justifies this choice as the populations and interventions in the studies within this meta-analysis were deemed to be more representative of the

high-risk CV individuals eligible for treatment with evolocumab. It should be noted that the relationship estimated from these five trials corresponds to the reduction in first CVD event only in patients with a history of CVD. The rate ratios used in the company's health economic model are summarised in Table 33.

Table 33: Proportion of change in CVD event risk per mmol/L LDL-C change (reproduced from CS[13] Table 5-12 page 197)

CV event	Rate ratio (95% CI)	Source	Reference
ACS	0.71 (0.58, 0.87)	Figure 2. More vs. less statins (non-fatal MI)	Baigent *et al* 2010[28]
Revascularisation	0.66 (0.60, 0.73)	Figure 2. More vs. less statins (any coronary revascularisation)	
IS	0.69 (0.50, 0.95)	Figure 2. More vs. less statins	
HF	0.71 (0.58, 0.87)	Assumption: equal to ACS in the model	N/A
CHD death	0.80 (0.74, 0.87)	Figure 5. (CHD)	Baigent *et al* 2010[28]
Stroke death[a]	1.04 (0.77, 1.44)	Figure 5. (IS)	

a Rate ratio assumed to be 1.00.
ACS - acute coronary syndrome; CHD - coronary heart disease; CI - confidence interval; CV - cardiovascular; CVD - cardiovascular disease; HF - heart failure; IS - ischaemic stroke; LDL-C - low-density lipoprotein cholesterol; MI - myocardial infarction; N/A - not applicable

The company's model makes the following assumptions regarding the relationship between reductions in LDL-C and reductions in CV events:

- The benefits manifest immediately (year 1 onwards).
- The relationship between reductions in LDL-C and CVD events (which relate to the effect on the first CVD event) observed in the CTTC meta-analysis is also representative of the effect that would be observed for the reductions in subsequent CV events.
- The relative reduction in CVD event rate per mmol/L reduction in LDL-C is independent of baseline levels, familial or non-familial hypercholesterolaemia, prognostic factors such as age, gender, co-morbidities (e.g. diabetes), and CV history or burden.
- LDL-C cannot reduce to a level below 40mg/L (equivalent to 1.03mmol/L)
- The CS further states that "*the rate ratio for new onset HF is equal to that for MI. Patients in the HF health states (either individual states or composite states) experience no further treatment effect due to LDL-C lowering for risk of recurrent HF since findings suggest lack of benefit for lipid-lowering therapies once patients experience HF on events such as CHD death*."
- The treatment effect for ACS is applied for patients transitioning from the "No CVD" state to the "ECVD" state.
- A treatment effect for revascularisation procedures has been applied to the 'post-ACS' health state alone. This impacts only on costs since revascularisation procedures are not included as separate health states.

- The rate ratio for stroke death is equal to one. This has been assumed because a non-significant effect was observed for LDL-C reduction for this CV event (RR = 1.041; 95% CI 0.77-1.41).

It should be noted that the company assesses the validity of their approach by providing a comparison with data from a pre-specified exploratory analysis of adjudicated CV events in OSLER and OSLER-2 which showed statistically significant reductions in CV events of over 50% after approximately 1 year of treatment with evolocumab plus standard of care versus standard of care alone, together with data from the IMPROVE-IT trial which demonstrated that ezetimibe added to simvastatin further lowered LDL-C and significantly reduced the occurrence of a composite endpoint of CV death, MI, unstable angina requiring hospitalisation, coronary revascularisation, or stroke compared with statin alone (p=0.016). However, on page 144 of the CS,[13] the company recognises that the OSLER extension studies were not powered for CVD outcomes, that the numbers are very small, that the populations are mixed, and that the results are therefore highly uncertain.

5.2.4.8 Health related quality of life

The CS includes details of a systematic review of studies estimates of HRQoL of various CV states (see CS,[13] Section 5.4). This was an update of a previous review (conducted in 2012) which was re-run in January 2015. Searches for HRQoL studies were conducted in MEDLINE and EMBASE by applying a quality of life filter to a list of CV events of interest. According to the text of the CS[13] (page 206), a total of 171 studies were included in the review (although the ERG notes that the PRISMA diagram presented on page 207 indicates that 173 studies were included). The CS also provides details of a *de novo* time trade-off (TTO) study undertaken by the company.

Neither the company's systematic review nor the Amgen TTO study is used to inform the utilities used in the company's base case analyses. Instead, utility values were based on those used in the model developed to inform NICE CG181.[15] The company justifies this choice on the basis that these utility values were deemed *"to be robust and suitable for a UK assessment of lipid-lowering therapy"* (see CS[13] page 219). The TTO study is used in the company's scenario analyses (see Section 5.2.6). The company states that HRQoL estimates based on NICE CG181 were mostly patient-reported using the EQ-5D questionnaire, and collected in the UK.

The precise sources used to inform the health utilities in the company's model are not clear from the CS; Table 5-17 of the CS simply lists the source of these values as NICE CG181.[15] The original sources of the utility values used in the company's model are summarised in Table 34, together with brief details of the study type, population, instrument used and approach used to derive each estimate.

The model assumes that utility is dependent on age, based on an analysis of the UK EQ-5D valuation study[56] reported by Ward *et al*.[64] Ward *et al* modelled a linear relationship between age and utility whereby utility decreases with increasing age with intercept=1.060 and gradient=-0.004.

The utility multiplier for the "No CVD" state is assumed to be 1.00, hence the utility score applied in the model is simply the age-adjusted utility for the general population.

The utility score for the ECVD state was based on a study of TTO valuations for 67 individuals who had recently experienced an MI; a utility multiplier of 0.88, based on the average TTO value for all 67 respondents, is used in the company's model.

For the acute ACS state, a utility multiplier of 0.77 is applied based on an RCT of an observational chest unit versus routine care for people with acute undifferentiated chest pain.[58] Within the trial reported by Goodacre *et al*,[58] health utility was assessed using the EQ-5D questionnaire at two days, one month and six months following the initial visit. The values used in the model appear to represent the average of the 6-month EQ-5D scores across both trial arms. The utility for the post-ACS state was assumed to be the same as that for the ECVD state, based on Tsevat *et al*.[57]

For the IS state, utilities were based on a meta-analysis of HRQoL estimates for stroke.[59] Based on a hierarchical linear model (HLM) meta-regression of studies reporting elicited TTO estimates from community members, Tengs *et al*[59] report TTO utilities of 0.52 for major stroke, 0.68 for moderate stroke, and 0.87 for minor stroke. An overall utility for stroke was calculated by weighting utilities of stroke according to severity by their respective frequencies as reported in a cost of illness model reported by Youman *et al*.[65] The same utility multiplier (relative to age-adjusted background utility) is used for both the acute stroke and post-stroke states.

The utility multiplier for the acute HF state was taken from a longitudinal study relating to a consecutive sample of 229 people discharged from hospital after acute MI[60] (rather than people with HF). This study reports EQ-5D utilities at 6-weeks and at 1-year. The utility score at 6-weeks (utility = 0.683) was used in the company's model. The same utility multiplier (relative to age-adjusted background utility) is used for both the acute HF state and post-HF states.

Table 34: Health utilities used in the company's model

Health state	Utility value (95% CI)	Original source	Study type	Population	Instrument	Derivation
Background utility						
No CVD	Age-adjusted	Dolan *et al*,[56] Ward *et al*[64]	Health valuation study	General population	EQ-5D	Linear association between age and utility
Utility multiplier (relative to age-adjusted background utility)						
No CVD	1.00	Assumption	n/a	n/a	n/a	n/a
ECVD	0.88 (0.84, 0.92)	Tsevat *et al*[57]	Health valuation study	People who had recently had an MI	TTO	Mean of all valuations equal to 0.88
ACS	0.77 (0.73, 0.81)	Goodacre *et al*[58]	RCT	People with acute, undifferentiated chest pain	EQ-5D	Mean EQ-5D in both groups at 6 months
IS	0.63 (0.55, 0.71)	Tengs *et al*[59]	Meta-analysis (meta-regression)	Studies reporting on severity of stroke	TTO	Utility by severity weighted by frequencies reported by Youman *et al*[65]
HF	0.68 (0.64, 0.72)	Lacey *et al*[60]	Longitudinal study	People recovering from an acute MI	EQ-5D	Post-MI 6-week mean
Post-ACS	0.88 (0.84, 0.92)	Tsevat *et al*[57]	Health valuation study	People who had recently had an MI	TTO	Mean of all valuations equal to 0.88
Post-IS	0.63 (0.55, 0.71)	Tengs *et al*[59]	Meta-analysis (meta-regression)	Studies reporting on severity of stroke	TTO	Utility by severity weighted by frequencies reported by Youman *et al*[65]
Post-HF	0.68 (0.64, 0.72)	Lacey *et al*[60]	Longitudinal study	People recovering from an acute MI	EQ-5D	Post-MI 6-week mean

CVD – cardiovascular disease; ECVD – established cardiovascular disease; IS – ischaemic stroke; HF - heart failure; MI - myocardial infarction; EQ-5D – Euroqol 5-Dimensions; TTO – time trade off

The company's model assumes that neither ezetimibe nor evolocumab is associated with a decrement in HRQoL. This is justified by the company as ezetimibe is an oral agent which is administered daily whilst evolocumab is a subcutaneously injectable drug (individuals use a prefilled pen that auto-injects the drug when pressed).

5.2.4.9 Resource costs

The CS[13] presents the methods and results of a systematic review of studies reporting direct cost estimates for the treatment of specific CV events. Searches were undertaken in MEDLINE, EMBASE, EconLit and NHS EED for studies indexed during the period 1 January 2000 to 31 March 2015. In addition, conference abstracts from the ISPOR, AHA, ACC, ESC, and EAS conferences during the period 2013 to 2014 were also searched. The review included 48 studies. A summary of those studies which used a Markov approach and which adopted a lifetime time horizon are summarised in Table 5-20 of the CS (see CS,[13] page 227). However, the findings of this review are not directly used to inform the company's *de novo* health economic analysis.

Drug acquisition costs

Table 35 summarises the drug acquisition costs for evolocumab, ezetimibe and statins included in the company's model. The costs of atorvastatin 20mg, atorvastatin 80mg and ezetimibe 10mg were based on the list prices sourced from the NHS Drug Tariff.[61] The annual per patient costs of 20mg atorvastatin and 80mg atorvastatin were estimated to be £18.38 and £35.33, respectively. The annual per patient cost of 10mg ezetimibe was estimated to be £342.97. At the time of writing, the cost of evolocumab had not been listed on the BNF;[61] this cost was instead sourced from the company.[13] The annual per patient cost for 140mg evolocumab Q2W was assumed to be [redacted] whilst the annual per patient cost for 420mg evolocumab QM was assumed to be [redacted]

Table 35: Description of interventions/comparators assessed in the company's model (adapted from CS,[13] Table 5-21, page 229)

Drug	Formulation	Dosing description	Cost per pack	Units per pack	Doses per year	Annual cost	Source
Evolocumab	140mg PFP	140mg q2w	[redacted]	2	26	[redacted]	CS[13]
	140mg PFP	420mg qm	[redacted]	2	36	[redacted]	NHS Drugs Tariff[61]
Ezetimibe	10mg tablet	10mg od	£26.31	28	365	£342.97	
Atorvastatin	20mg tablet	20mg od	£1.41	28	365	£18.38	
	80mg tablet	80mg od	£2.71	28	365	£35.33	

PFP - prefilled pen; q2w - every 2 weeks; qm - monthly; SC - subcutaneous

Other costs used in the company's model

Table 36 summarises the other cost components used in the company's model.

Table 36: Other costs included in the company's model

Cost parameter	Cost	Source
Training and monitoring costs		
Cost s.c. injection training	£84.00*	Curtis 2014[63]
Cost monitoring year 1	£238.72	Based on NHS Reference Costs 2013/14[62] and Curtis 2014[63]
Cost monitoring subsequent years	£101.08	
Health state costs		
No CVD (annual)	£0.00	Company's CPRD/HES longitudinal study[13]
ECVD (annual)	£522.34	
ACS (annual)	£3,263.63	
Stroke (annual)	£4,063.60	
HF (annual)	£3,178.32	
Post-ACS (annual)	£522.34	
Post-stroke (annual)	£887.33	
Post-HF (annual)	£1,078.26	
Other		
CHD death (once only cost)	£717.96	
Stroke death (once only cost)	£1,847.92	
Revascularisation	£5,648.60	

s.c. – subcutaneous; CVD – cardiovascular disease; ECVD – established cardiovascular disease; ACS – acute coronary syndromes; HF – heart failure; CHD – coronary heart disease; CPRD - Clinical Practice Research Datalink; HES – Hospital Episode Statistics

** Applied only to the evolocumab group*

Training

Patients receiving evolocumab are assumed to receive training for self-administration by a nurse upon initiation of treatment. A one-off cost is assumed at entry into the model. The company assumes that patients receive 1 hour of nurse training at a cost of £84.00 based on the cost per hour for a nurse (day ward, including staff nurse) derived from the PSSRU.[63]

Monitoring

The company's model assumes that no additional monitoring is required for people receiving evolocumab over and above those which are part of routine clinical practice and assumed the annual monitoring costs to be £238.72 for the first year and £101.08 for subsequent years. Patients are assumed to require an initial appointment at initiation and a subsequent follow-up in the lipid clinic to assess treatment efficacy and tolerability (two appointments in first year). Subsequently, patients are assumed to be treated in primary care and incur one appointment every year. The company states that monitoring costs associated with tests and appointments following discharge are based on assumptions made by the Guideline Development Group for CG181[15] and cost are taken from the UK tariff.[62,63]

Health state costs

Health state costs were based on a retrospective longitudinal observational cohort study undertaken using data from the CPRD and HES.[13,66] These data were used to estimate acute and long-term health

care resource use and costs associated with first and subsequent CV events. The analysis used data for individuals from between January 2006 and March 2012 to construct a cohort of 24,093 individuals who were aged ≥18 years, who were hospitalised for their first CV event, had received at least two prescriptions for lipid-lowering therapy (statins, ezetimibe, fibrates, nicotinic acid, or bile acid sequestrants) in the 180 days prior to the event and for whom at least 12 months of data prior to the index date and 30 days afterwards were available from both the CPRD and HES. Individuals were classed as "low-risk" or "high-risk" on the basis of prior conditions. The "high-risk" individuals (n=17,685) had a prior diagnosis of diabetes, peripheral arterial disease, ischaemic heart disease [excluding MI or unstable angina], or angina pectoris, whilst the "low-risk" individuals (n=6,408) did not have any of these conditions. A third group was formed from both the high-risk and low-risk groups, comprising of those individuals who experienced a second CV event (n=5,274).

Individuals were followed from the date of the first CV event to either the next CV event or until the final follow-up date (March 2012). The costs associated with specific CV events were estimated based on resource use for each individual during the three intervals: (i) the baseline period (12-months prior to an event); (ii) the acute period (6-months after an event), and; the long-term period (the subsequent 30 months). Resource use in the study included healthcare visits to general practitioners, referrals to specialists (as reported in CPRD), CV and non-CV hospitalisations (intensive care unit, cardiovascular ward/clinic, general ward, surgical procedures, and emergency room visits, all as reported by HES), and prescriptions for medications (including lipid-lowering therapy, antihypertensive therapy, antithrombotic therapy, and anti-diabetic therapy). Unit costs were based on the PSSRU,[63] NHS Reference Costs 2013/14[62] and the NHS Drugs Tariff.[61] In order to produce annual acute costs for use in the model, the acute and long-term costs were combined (assuming that the total annual event cost is comprised of 6 months in the acute state and 6-months in the annual state).

Revascularisation costs

The company assumed a revascularisation cost of £5,648.60 based on the CPRD/HES study.[13] The company assumed that all people in the ACS health state undergo a revascularisation procedure and 10% of people in the post-ACS health state undergo a revascularisation procedure annually. The CS[13] (page 223) states that these assumptions are in line with NICE CG181[15] and that no revascularisation cost was included for stable angina in the company's model, hence this is likely to be conservative.

Costs of CV-related death

The costs associated with death due to fatal ischaemic stroke and death due to CHD were estimated from the CPRD study.[13] These were assumed to be £717.96 and £1,847.92, respectively. These costs are applied in the model only to patients transiting to these states.

5.2.5 Summary of analyses presented within the CS

The range of the economic analyses presented in the CS are summarised in Table 37.

(i) **Base case analyses** (see CS,[13] Sections 5.7 to 5.10, analyses A, D G and H). For the non-familial primary prevention population, the company's base case analyses are presented as threshold analyses of 10-year CVD risk. Analyses are presented for comparisons of evolocumab plus statins versus ezetimibe plus statins in patients who are able to tolerate statins (ST population) and evolocumab versus ezetimibe in patients for whom statins are contraindicated or not tolerated (SI population). For the non-familial secondary prevention population and the HeFH primary/secondary population, cohort-based cost-effectiveness analyses are presented for comparisons of evolocumab plus statins versus ezetimibe plus statins for the ST population and evolocumab versus ezetimibe for the SI population. Results are presented as ICERs based on point estimates of parameters.

(ii) **Scenario analyses for evolocumab plus ezetimibe combination therapy** (see CS,[13] Section 5.12, Analyses E, F, I and J). Scenario analyses are presented for comparisons of evolocumab plus ezetimibe plus statins versus ezetimibe plus statins for the ST population and evolocumab plus ezetimibe versus ezetimibe for the SI population. Results for these scenarios are presented as ICERs based on point estimates of parameters.

(iii) **Probabilistic sensitivity analyses** (see CS,[13] Section 5.11). Probabilistic sensitivity analysis (PSA) results are presented for all comparisons presented in the base case analysis (analyses A, D, G and H). For the non-familial primary prevention population, PSA results are presented in terms of the probability that evolocumab (with statins or as monotherapy) produces the greatest net benefit at willingness-to-pay (WTP) thresholds of £20,000 per QALY gained and £30,000 per QALY gained at the 10-year CVD risk levels required to achieve those thresholds within the deterministic analysis. Probabilistic ICERs are not reported for these threshold analyses. For the non-familial secondary prevention population and the HeFH primary/secondary prevention population, results are presented in terms of probabilistic ICERs, cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

(iv) **Deterministic sensitivity analyses** (see CS,[13] Section 5.11). Deterministic sensitivity analyses were conducted only for those base case comparisons of evolocumab plus statins versus statins in the non-familial primary prevention ST population (based on a cohort analysis rather than according to LDL-C threshold), the non-familial secondary prevention ST population (analysis C) and the HeFH primary/secondary prevention ST population (analysis G). DSA results are presented as tornado diagrams.

(v) **Additional scenario analyses** (see CS,[13] Section 5.12). Additional scenario analyses are presented to assess the cost-effectiveness of evolocumab plus statins versus ezetimibe plus statins according to the severity of hypercholesterolaemia based on LDL-C at baseline; these

analyses are presented only for the non-familial secondary prevention ST population (analysis C) and the HeFH primary/secondary prevention ST population (analysis G). Further scenario analyses were also conducted to assess the impact of monthly evolocumab dosing, treatment durations of 5-, 10- and 20-years, alternative discount rates, risk capping at age 75, the use of costs derived from NICE CG181,[15] the use of TTO utility estimates derived from the Amgen-sponsored utility study and the use of alternative assumptions regarding nurse training. These additional analyses are presented only for the base case comparisons of evolocumab plus statins versus statins in the non-familial primary prevention ST population (based on the cohort rather than LDL-C threshold), the non-familial secondary prevention ST population (analysis C) and the HeFH primary/secondary prevention ST population (analysis G).

(vi) **Subgroup analyses** (see CS,[13] Section 5.13). The CS presents three sets of subgroup analyses; these are reported only for the comparison of evolocumab plus statins versus ezetimibe plus statins in the non-familial secondary prevention ST population (analysis C).

a. *Individual risk factors*. The following risk factors were explored: LDL-C 3.0mmol/L to 6.0mmol/L in increments of 0.5mmol/L, gender, presence of diabetes, number of vascular beds (2 or 3), presence of atrial fibrillation, CV events in the previous year (characterised as the starting state for the model).

b. *Combinations of individual risk factors with baseline LDL-C, age and sex*. Analyses were presented for people with individual risk factors (diabetes, AF, 2/3 vascular beds and history of CVD events) combined with baseline LDL-C 3.5-4.5mmol/L, sex and age.

c. *Combinations of two risk factors with baseline LDL-C, age and sex.* Analyses were presented for people with two risk factors (including diabetes, AF, 2/3 vascular beds and history of ACS) combined with baseline LDL-C 3.0-4.0mmol/L, sex and age.

Table 37: Summary of results presented within the CS[13]

Analysis	Population	Analysis type	Base case /scenario analysis	Intervention	Comparator	Types of analyses undertaken for comparison			
						Deterministic/ probabilistic	DSA	Scenario analyses	Subgroup analyses
A	Non-familial PP, ST	Threshold	Base case	Evolocumab+statins	Ezetimibe+statins	Both	No*	No*	No
B	Non-familial PP, SI	Threshold	Base case	Evolocumab	Ezetimibe	Both	No*	No*	No
C	Non-familial SP, ST	Cohort	Base case	Evolocumab+statins	Ezetimibe+statins	Both	Yes	Yes	Yes
D	Non-familial SP, SI	Cohort	Base case	Evolocumab	Ezetimibe	Both	No	No	No
E	Non-familial SP, SI	Cohort	Scenario	Evolocumab+ezetimibe	Ezetimibe	Deterministic	No	No	No
F	Non-familial SP, ST	Cohort	Scenario	Evolocumab+ezetimibe+statins	Ezetimibe+statins	Deterministic	No	No	No
G	HeFH PP/SP, ST	Cohort	Base case	Evolocumab+statins	Ezetimibe+statins	Both	Yes	Yes	No
H	HeFH, PP/SP, SI	Cohort	Base case	Evolocumab	Ezetimibe	Both	No	No	No
I	HeFH PP/SP, SI	Cohort	Scenario	Evolocumab+ezetimibe	Ezetimibe	Deterministic	No	No	No
J	HeFH PP/SP, ST	Cohort	Scenario	Evolocumab+ezetimibe+statins	Ezetimibe+statins	Deterministic	No	No	No

PP – primary prevention; SP – secondary prevention; ST – statin tolerant; SI – statin intolerant; HeFH - Heterozygous familial hypercholesterolemia; DSA – deterministic sensitivity analysis
** Deterministic sensitivity analyses and scenario analyses undertaken for overall primary prevention cohort rather than for those with 10-year CV risk threshold (see CS[13] Figure 5-20 and Table 5-64)*

5.2.6 Cost-effectiveness results presented within the CS

5.2.6.1 Base case cost-effectiveness results (deterministic)

Table 38 summarises the deterministic cost-effectiveness results presented within the CS.[13] For the sake of brevity, and in line with the final NICE scope,[4] results are presented only for the comparison of evolocumab (with or without statins) versus ezetimibe (with or without statins).

Non-familial primary prevention population (analyses A and B)

Within the non-familial primary prevention ST population (analysis A), the company's threshold analyses indicate that in people with a baseline LDL-C of 3.5mmol/L, the ICER for evolocumab plus statins versus ezetimibe plus statins would be below £30,000 per QALY gained in people with a 10-year CVD risk of 79% (or higher). The corresponding 10-year risk thresholds for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 73% and 70%, respectively. Within the non-familial primary prevention SI population (analysis B) with a baseline LDL-C of 3.5mmol/L, the ICER for evolocumab versus ezetimibe would be below £30,000 per QALY gained in people with a 10-year CVD risk of 81% (or higher). The corresponding 10-year risk thresholds for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 75% and 71%, respectively.

The company's analyses suggest that it is not possible under any combination of baseline LDL-C and 10-year CVD risk for evolocumab to achieve an ICER below £20,000 per QALY gained.

Non-familial secondary prevention population (analyses C and D)

Within the non-familial secondary prevention ST population (analysis C), the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.44 QALYs at an additional cost of £51,407 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £116,713 per QALY gained. Within the non-familial secondary prevention SI population (analysis D), the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.42 QALYs at an additional cost of £50,542 as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £119,971 per QALY gained.

HeFH primary/secondary prevention population (analyses G and H)

Within the HeFH primary/secondary prevention ST population (analysis G), the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.20 QALYs at an additional cost of £53,565 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £44,741 per QALY gained. Within the HeFH primary/secondary prevention SI population (analysis H), evolocumab monotherapy is expected to produce an additional 1.10 QALYs at an additional cost of £51,749 as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £47,193 per QALY gained.

Table 38: Summary of company's cost-effectiveness results (deterministic)

Analysis	Population characteristics and comparison	Evolocumab		Ezetimibe		Incremental		
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER
Non-familial primary prevention population - threshold analysis (λ=£30,000/QALY)								
Analysis Ai	LDL-C=2.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Aii	LDL-C=3.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Aiii	LDL-C=3.5, ST (evo+statins vs eze+statins), 10yr risk=79%	8.15	£56,110	6.74	£13,952	1.41	£42,158	**£29,896**
Analysis Aiv	LDL-C=4.0, ST (evo+statins vs eze+statins), 10yr risk=73%	8.95	£59,792	7.40	£13,577	1.55	£46,215	**£29,864**
Analysis Av	LDL-C=4.5, ST (evo+statins vs eze+statins), 10yr risk=70%	9.46	£62,016	7.83	£13,232	1.63	£48,784	**£29,962**
Analysis Bi	LDL-C=2.5, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bii	LDL-C=3.0, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Biii	LDL-C=3.5, SI (evo vs eze), 10-year risk=81%	7.58	£53,626	6.27	£14,344	1.31	£39,282	**£29,980**
Analysis Biv	LDL-C=4.0, SI (evo vs eze), 10-year risk=75%	8.34	£57,135	6.90	£14,075	1.44	£43,059	**£29,954**
Analysis Bv	LDL-C=4.5, SI (evo vs eze), 10-year risk=71%	8.92	£59,743	7.38	£13,775	1.54	£45,968	**£29,939**
Non-familial primary prevention population - threshold analysis (λ=£20,000/QALY)								
Analysis Avi	LDL-C=2.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Avii	LDL-C=3.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Aviii	LDL-C=3.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Aix	LDL-C=4.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Ax	LDL-C=4.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bvi	LDL-C=2.5, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bvii	LDL-C=3.0, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bviii	LDL-C=3.5, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bix	LDL-C=4.0, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Analysis Bx	LDL-C=4.5, SI (evo vs eze), not achievable	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Non-familial secondary prevention population - cohort analysis								
Analysis C	ST (evo+statins vs eze+statins)	8.06	£71,709	7.62	£20,302	0.44	£51,407	**£116,713**
Analysis D	SI (evo vs eze)	7.94	£70,912	7.52	£20,371	0.42	£50,542	**£119,971**
HeFH primary/secondary prevention population - cohort analysis								
Analysis G	ST (evo+statins vs eze+statins)	10.05	£72,262	8.86	£18,697	1.20	£53,565	**£44,741**
Analysis H	SI (evo vs eze)	9.69	£70,754	8.6	£19,005	1.10	£51,749	**£47,193**

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe; LDL-C - low-density lipoprotein cholesterol

5.2.6.2 Probabilistic sensitivity analysis results

Table 39 summarises the probabilities that evolocumab (with or without statins) produces more net benefit than ezetimibe (with or without statins) at WTP thresholds of £20,000 per QALY gained and £30,000 per QALY gained, respectively.

Non-familial primary prevention population (analyses A and B)

Within the non-familial primary prevention ST population who have a baseline LDL-C of 3.5mmol/L and a 10-year CVD risk of 79%, the probability that evolocumab plus statins produces more net benefit than ezetimibe plus statins at a WTP threshold of £30,000 per QALY gained is estimated to be 0.38. The corresponding probabilities for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 0.41 and 0.37, respectively. Within the non-familial primary prevention SI population who have a baseline LDL-C of 3.5mmol/L, the probability that evolocumab produces more net benefit than ezetimibe at a WTP threshold of £30,000 per QALY gained is estimated to be 0.42. The corresponding probabilities for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 0.43 and 0.42, respectively.

Non-familial secondary prevention population (analyses C and D)

Within the non-familial secondary prevention ST population, the probabilistic ICER for evolocumab plus statins versus ezetimibe plus statins is reported to be £119,012 per QALY gained. This is slightly higher than the deterministic estimate of £116,713 per QALY gained. The probability that evolocumab plus statins produces more net benefit than ezetimibe plus statins in this population is expected to be approximately zero. Within the SI population, the probabilistic ICER for evolocumab versus ezetimibe is reported to be £123,780 per QALY gained. This is again slightly higher than the deterministic estimate of £119,971 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe in this population is expected to be approximately zero.

HeFH primary/secondary prevention population (analyses G and H)

Within the HeFH primary/secondary prevention ST population, the probabilistic ICER for evolocumab plus statins versus ezetimibe plus statins is reported to be £46,412 per QALY gained. This is slightly higher than the deterministic estimate of £44,741 per QALY gained. The probability that evolocumab plus statins produces more net benefit than ezetimibe plus statins in this population is expected to be approximately zero. Within the HeFH primary/secondary prevention SI population, the probabilistic ICER for evolocumab versus ezetimibe is reported to be £48,362 per QALY gained. This is also slightly higher than the deterministic estimate of £47,193 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe in this population is expected to be approximately zero.

Table 39: Summary of probabilistic sensitivity analysis results

Analysis	Population characteristics and comparison	Probabilistic ICER	Probability evolocumab optimal at WTP threshold	
			λ=£20,000/QALY gained	λ=£30,000/QALY gained
Non-familial primary prevention population - threshold analysis (λ=£30,000/QALY)				
Analysis Ai	LDL-C=2.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Ai	LDL-C=3.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Aiii	LDL-C=3.5, ST (evo+statins vs eze+statins), 10yr risk=79%	NR	n/a	0.38
Analysis Aiv	LDL-C=4.0, ST (evo+statins vs eze+statins), 10yr risk=73%	NR	n/a	0.41
Analysis Av	LDL-C=4.5, ST (evo+statins vs eze+statins), 10yr risk=70%	NR	n/a	0.37
Analysis Bi	LDL-C=2.5, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Bi	LDL-C=3.0, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Biii	LDL-C=3.5, SI (evo vs eze), 10-year risk=81%	NR	n/a	0.42†
Analysis Biv	LDL-C=4.0, SI (evo vs eze), 10-year risk=75%	NR	n/a	0.43†
Analysis Bv	LDL-C=4.5, SI (evo vs eze), 10-year risk=71%	NR	n/a	0.42†
Non-familial primary prevention population - threshold analysis (λ=£20,000/QALY)				
Analysis Avi	LDL-C=2.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Avii	LDL-C=3.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Aviii	LDL-C=3.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Aix	LDL-C=4.0, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Ax	LDL-C=4.5, ST (evo+statins vs eze+statins), not achievable	n/a	n/a	n/a
Analysis Bvi	LDL-C=2.5, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Bvii	LDL-C=3.0, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Bviii	LDL-C=3.5, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Bix	LDL-C=4.0, SI (evo vs eze), not achievable	n/a	n/a	n/a
Analysis Bx	LDL-C=4.5, SI (evo vs eze), not achievable	n/a	n/a	n/a
Non-familial secondary prevention population - cohort analysis				
Analysis C	ST (evo+statins vs eze+statins)	**£119,012**	0.00	0.00
Analysis D	SI (evo vs eze)	**£123,780**	0.00	0.00
HeFH primary/secondary prevention population - cohort analysis				
Analysis G	ST (evo+statins vs eze+statins)	**£46,412**	0.00	0.00
Analysis H	SI (evo vs eze)	**£48,362**	0.00	0.00

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe; LDL-C - low-density lipoprotein cholesterol; WTP – willingness-to-pay

† The £20,000/QALY threshold referred to in Table 5-54 is mislabelled and should refer to the probability of being optimal at £30,000 per QALY gained

5.2.6.3 Scenario analysis results – evolocumab in combination with ezetimibe

Table 40 summarises the results of the company's scenario analyses in which evolocumab is given in combination with ezetimibe (with/without concomitant statins).

Non-familial secondary prevention population (analyses E and F)

Within the non-familial secondary prevention SI population (analysis E), the company's scenario analysis suggests that evolocumab plus ezetimibe is expected to produce an additional 0.49 QALYs at an additional cost of £55,158 compared with ezetimibe; the resulting ICER is estimated to be £112,561 per QALY gained. Within the ST population (analysis F), evolocumab plus ezetimibe plus statins is expected to produce an additional 0.44 QALYs at an additional cost of £55,872 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £126,849 per QALY gained.

HeFH primary/secondary prevention population (analyses I and J)

For the HeFH primary/secondary prevention SI population (analysis I), the company's scenario analysis suggests that evolocumab plus ezetimibe is expected to produce an additional 1.29 QALYs at an additional cost of £56,950 as compared against ezetimibe monotherapy; the resulting ICER is expected to be £44,224 per QALY gained. Within the ST population (analysis J), evolocumab plus ezetimibe plus statins is expected to produce an additional 1.26 QALYs at an additional cost of £58,503 as compared against ezetimibe plus statins; the resulting ICER is expected to be £46,592 per QALY gained.

Table 40: Summary of company's scenario analysis results (evolocumab plus ezetimibe - deterministic)

Analysis	Population characteristics and comparison	Evolocumab plus ezetimibe		Ezetimibe		Incremental		
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER
Non-familial secondary prevention population – cohort analysis								
Analysis E	SI (evo+eze vs eze)	8.01	£75,528	7.52	£20,371	0.49	£55,158	**£112,561**
Analysis F	ST (evo+eze+statins vs eze+statins)	8.06	£76,174	7.62	£20,302	0.44	£55,872	**£126,849**
HeFH primary/secondary prevention - cohort analysis								
Analysis I	SI (evo+eze vs eze)	9.88	£75,955	8.6	£19,005	1.29	£56,950	**£44,224**
Analysis J	ST (evo+eze+statins vs eze+statins)	10.11	£77,200	8.86	£18,697	1.26	£58,503	**£46,592**

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe; LDL-C - low-density lipoprotein cholesterol

5.2.6.4 Deterministic sensitivity analysis results (evolocumab plus statins versus ezetimibe plus statins)

The company's DSA results are summarised in Figures 9 to 11. Within the non-familial primary and secondary prevention populations, the five most influential parameters were the treatment duration, the relationship between LDL-C reduction and CHD death, the impact of ezetimibe on LDL-C, the CPRD calibration rate ratios and the relationship between LDL-C reduction and ischaemic stroke death. Within the HeFH primary/secondary prevention population, the five most influential parameters were the treatment duration, the relationship between LDL-C reduction and CHD death, the impact of ezetimibe on LDL-C, the HeFH calibration rate ratio and the relationship between LDL-C reduction and ischaemic stroke. It is noteworthy that the ICERs for evolocumab in all three populations remain consistently greater than £30,000 per QALY gained for all sensitivity analyses.

Figure 9: Tornado diagram for evolocumab plus statins versus ezetimibe plus statins in the primary hypercholesterolaemia LDL-C>2.5mmol/L primary prevention population (reproduced from CS,[13] Figure 5-20, page 267)

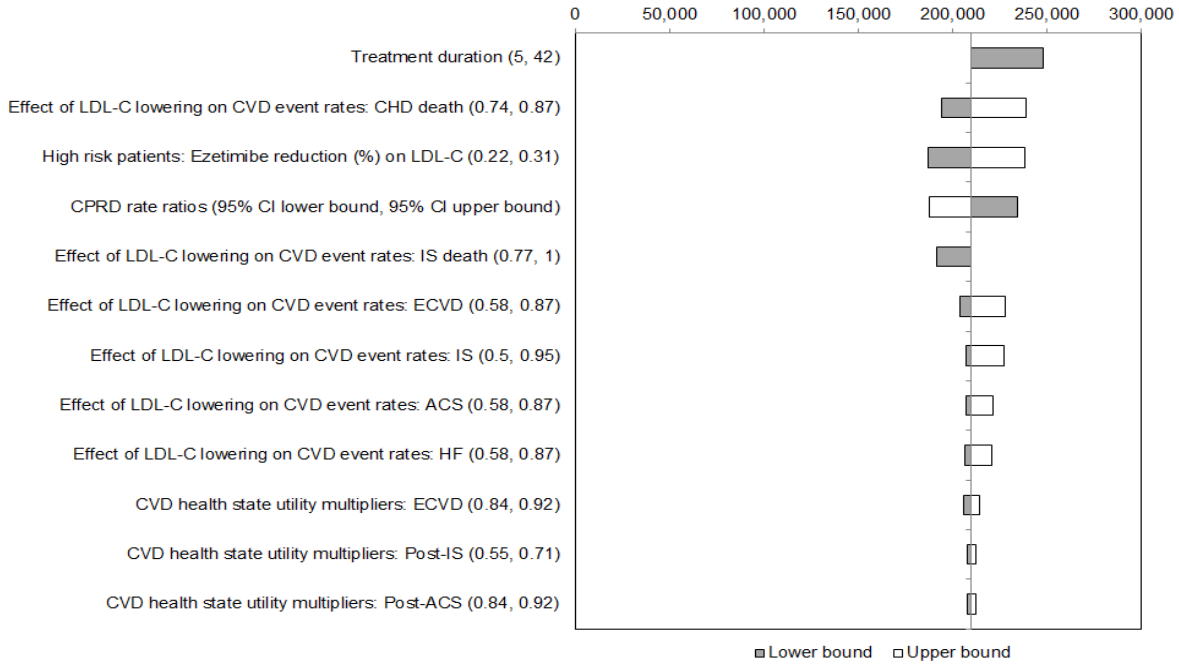


Figure 10: Tornado diagram for evolocumab plus statins versus ezetimibe plus statins in primary hypercholesterolaemia LDL-C>2.5mmol/L secondary prevention population (reproduced from CS,[13] Figure 5-21, page 267)

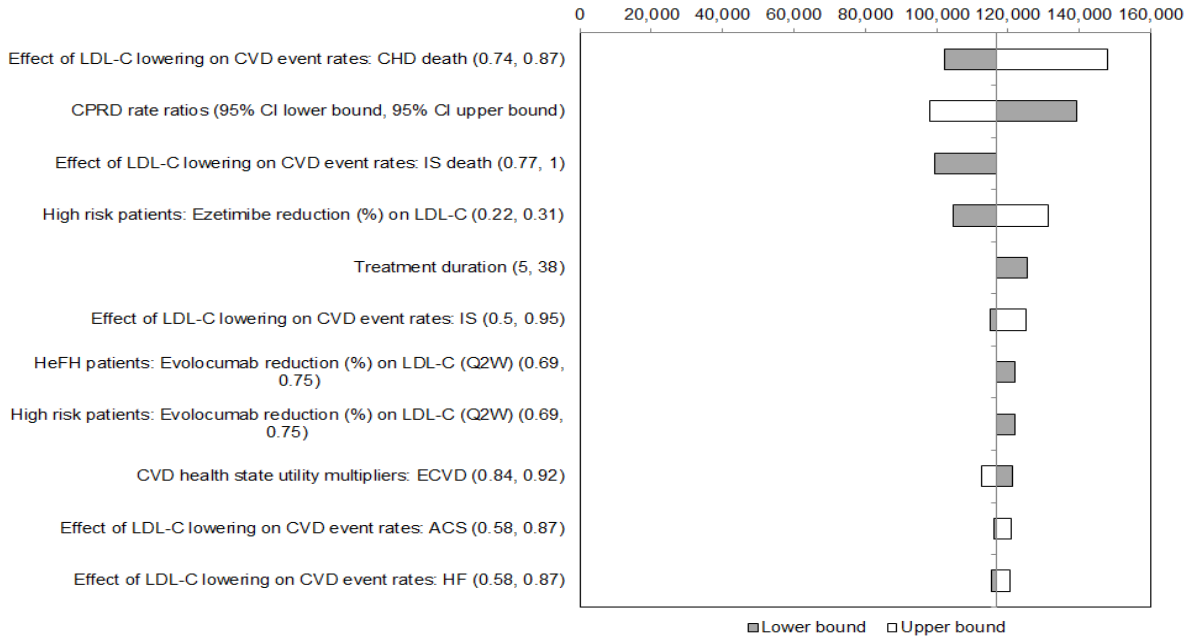
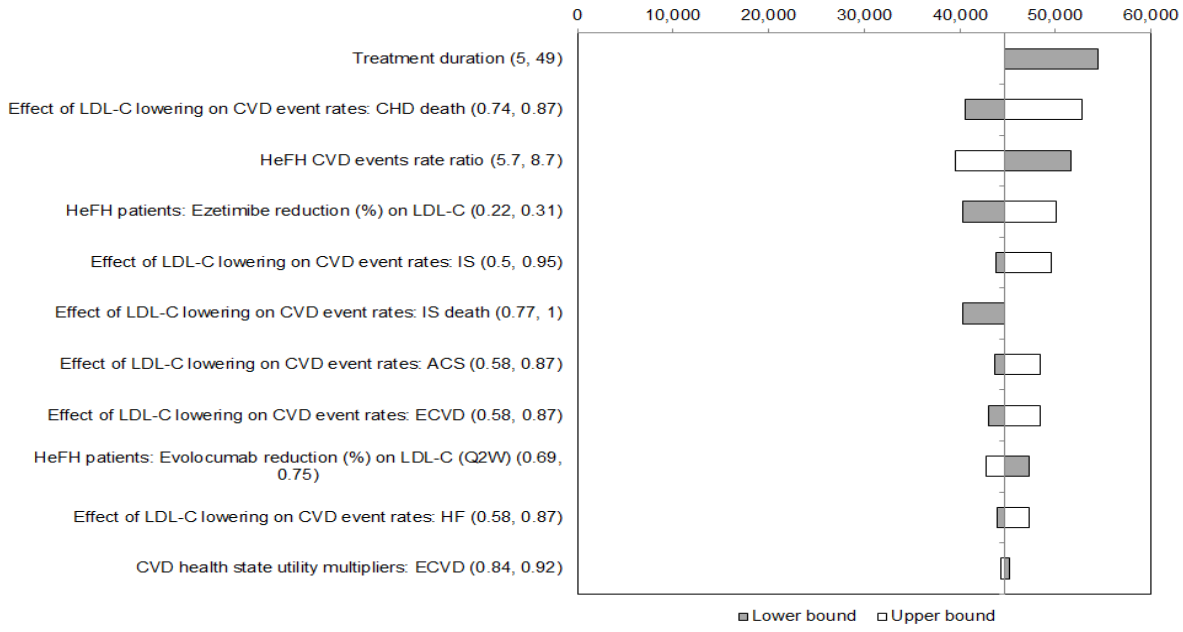


Figure 11: Tornado diagram for evolocumab plus statins versus ezetimibe plus statins in HeFH primary and secondary prevention population (reproduced from CS,[13] Figure 5-22, page 268)



5.2.6.6 Additional scenario analyses

Severity of hypercholesterolaemia according to baseline LDL-C (analyses C and G only)

Within the non-familial secondary prevention ST population (analysis C), the ICERs for evolocumab plus statins versus ezetimibe plus statins in patients with LDL-C values of 3.0mmol/L and 6.0mmol/L, the ICERs are estimated to be £146,532 per QALY gained and £91,341 per QALY gained, respectively.

Within the HeFH primary/secondary prevention ST population (analysis G), the ICER for evolocumab plus statins versus ezetimibe plus statins in people with LDL-C values of 3.0mmol/L and 6.0mmol/L are £62,432 per QALY gained and £36,212 per QALY gained, respectively.

Other scenario analyses (analyses A, C and G only)

Within the non-familial primary prevention ST population, the base case ICER for evolocumab plus statins versus ezetimibe plus statins for the overall cohort is reported to be £210,093 per QALY gained. It should be noted that this ICER does not appear anywhere else in the CS.[13] Within this population (see CS[13] Table 5-64), the lowest reported ICER for evolocumab plus statins versus statins relates to the scenario in which the evolocumab QM dose is used; the ICER is reported to be £76,325 per QALY gained. However, the ERG notes that this is an error since the scenario assumes that the monthly evolocumab dose is both less effective and more expensive than the Q2W dose used in the company's base case analysis. A re-run of this analysis undertaken by the ERG indicates that the ICER for evolocumab plus statins versus ezetimibe plus statins within this scenario is considerably higher at £299,916 per QALY gained. Within the non-familial primary prevention population scenario analyses, the highest ICER was reported for the scenario in which costs were undiscounted and health outcomes were discounted at a rate of 6% per annum; in this scenario, the ICER for evolocumab plus statins versus ezetimibe plus statins was £559,793 per QALY gained.

Within the non-familial secondary prevention ST population, the lowest ICER reported relates to the scenario in which health utilities were taken from the Amgen TTO utility study; in this scenario the ICER for evolocumab plus statins versus ezetimibe plus statins was reported to be £88,572 per QALY gained. The highest ICER was reported for the scenario in which costs were undiscounted and health outcomes were discounted at a rate of 6% per annum; in this scenario, the ICER for evolocumab plus statins versus ezetimibe plus statins was £258,684 per QALY gained.

In the HeFH primary/secondary prevention ST population, the lowest ICER was reported for the scenario in which costs and health outcomes were undiscounted; in this scenario, the ICER evolocumab plus statins versus ezetimibe plus statins was £34,407 per QALY gained. The highest ICER was reported for the scenario in which costs were undiscounted and health outcomes were

discounted at a rate of 6% per annum; in this scenario, the ICER evolocumab plus statins versus ezetimibe plus statins was £105,987 per QALY gained.

5.2.6.7 Subgroup analyses

Individual risk factors (analysis C only)

In the company's analysis of individual risk factors in the non-familial secondary prevention ST population, the reported ICERs for evolocumab plus statins versus ezetimibe plus statins range from £76,451 per QALY gained (people with 3 vascular beds) to £224,001 per QALY gained (all patients assumed to enter the model in the acute IS health state).

Combination of one additional risk factor and baseline LDL-C, age and sex (analysis C only)

In the company's analysis of individual risk factors combined with baseline LDL-C, age and sex in the non-familial secondary prevention ST population, the reported ICERs for evolocumab plus statins versus ezetimibe plus statins range from £61,380 per QALY gained (LDL-C=4.5mmol/l, male, age+10years, 3 vascular beds) to £250,530 per QALY gained (LDL-C=3.5mmol/L, female, cohort age, history of acute IS).

Combination of two additional risk factors and baseline LDL-C, age and sex (analysis C only)

In the company's analysis of two additional risk factors combined with baseline LDL-C, age and sex undertaken in the non-familial secondary prevention ST population, the reported ICERs for evolocumab plus statins versus ezetimibe plus statins range from £49,528 per QALY gained (LDL-C=4.0mmol/L, male, age+10years, diabetes and ACS) to £98,100 per QALY gained (LDL-C=3mmol/L, female, age=cohort, AF and 2 vascular beds).

5.2.6.8 Amended model results

As discussed in Section 5.2.2, during the clarification stage of the appraisal, the ERG identified a serious programming error within the company's model whereby it was possible for many of the transition probabilities, and hence the health state populations in the Markov trace, to be negative. This is clearly mathematically inconsistent. Consequently, NICE submitted a request to the company to rectify the error. In response, the company submitted an amended model and an addendum detailing revised results produced using this amended model. The addendum[52]stated:

"As noted by the ERG, non-fatal and fatal CV events are estimated independently. As such, in certain extreme scenarios of CV risk, negative transition probabilities may occur. This issue has precipitated in the manufacturer submission (NHS list price) in the threshold analyses for patients 'without existing CVD', whereby such extreme scenarios have been modelled on the basis of CVD risk to demonstrate cost-effectiveness according to willingness-to-pay thresholds. Therefore, we

acknowledge that the analyses for this population (at NHS list price) are invalid due to this finding and have been revised.

Additionally, it has been identified that for the heterozygous familial hypercholesterolaemia (HeFH) population with previous history of heart failure, some transition probabilities are negative for patients above 90 years of age. On examination of the Benn, et al (2010) publication that has been used as the basis for the HeFH CV event rate calibration, we note that the prevalence of heart failure is not reported. In the absence of this information and additional data, we have removed the heart failure history risk adjustment for HeFH patients. This prevents the occurrence of negative transitions in patients above 90 years of age; and may result in conservative estimates for other younger populations.

Therefore, the cost effectiveness analyses have been updated for these populations:

Patients without existing CVD

- *Threshold analysis according to CVD risk and willingness-to-pay thresholds*
- *Probabilistic sensitivity analyses*

Patients with HeFH

- *Base case results*
- *Sensitivity analyses (deterministic and probabilistic)*
- *Scenario analyses"*

On the basis of the addendum document text, reproduced above, the company's analyses within the non-familial primary prevention population are considered to be "invalid" and therefore the ERG would advise that these are disregarded. With respect to the non-familial secondary prevention population, the company's amendment does not affect this population hence the analyses remain unchanged and the company's preferred estimates of the cost-effectiveness of evolocumab in this population are as reported above. With respect to the HeFH primary/secondary prevention population, the model has been amended; the impact of this amendment on the base case and scenario analyses is summarised in Tables 41 and 42. The ERG's concerns regarding the original submitted model and the amended model are discussed in detail in Section 5.3.

(i) Base case cost-effectiveness results (amended model)

The base case and scenario analysis ICERs for evolocumab in the HeFH primary/secondary prevention population presented in the company's addendum[52] are higher than those reported in the

original CS.[13] For the HeFH primary/secondary prevention ST population (analysis G), the company's amended base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.15 QALYs at an additional cost of £73,620 as compared with ezetimibe plus statins; the resulting ICER is estimated to be £47,195 per QALY gained. The probabilistic ICER is slightly higher at £48,664 per QALY gained. The probability that evolocumab plus statins produces more net benefit than ezetimibe plus statins is approximately zero at a WTP threshold of £30,000 per QALY gained. In the HeFH primary/secondary prevention SI population (analysis H), evolocumab monotherapy is expected to produce an additional 1.05 QALYs at an additional cost of £52,486 as compared against ezetimibe monotherapy; the resulting ICER is expected to be £49,900 per QALY gained. The probabilistic ICER is higher at £51,061 per QALY gained. The probability that evolocumab produces more net benefit than ezetimibe is approximately zero at a WTP threshold of £30,000 per QALY gained.

The company's scenario analysis in the HeFH primary/secondary SI prevention population (analysis I) suggests that, evolocumab plus ezetimibe is expected to produce an additional 1.24 QALYs at an additional cost of £57,664 as compared against ezetimibe monotherapy; the resulting ICER is expected to be £46,685 per QALY gained. In the ST population (analysis J), evolocumab plus ezetimibe plus statins is expected to produce an additional 1.20 QALYs at an additional cost of £59,174 as compared against ezetimibe plus statins; the resulting ICER is expected to be £49,138 per QALY gained.

Other results presented in the company's addendum

Deterministic sensitivity analyses (analysis G only)

The company's amended DSA results are similar to those presented within the CS.[13] Within the amended analysis, the five most influential variables remain the same as those within the CS (treatment duration, relationship between LDL-C reduction and CHD death, the impact of ezetimibe on LDL-C, the HeFH calibration rate ratio and the relationship between LDL-C reduction and ischaemic stroke).

Severity of hypercholesterolaemia according to baseline LDL-C (analysis G only)

For the HeFH primary prevention/secondary prevention ST population (analysis G), the ICERs for evolocumab plus statins versus ezetimibe plus statins in patients with LDL-C values of 3.0mmol/L and 6mmol/L, the ICERs are £66,196 per QALY gained and £37,995 per QALY gained, respectively. These values are slightly higher than those presented within the CS.[13]

Other scenario analyses (analysis G only)

In the HeFH primary/secondary prevention ST population, the lowest ICER was reported for the scenario in which costs and health outcomes were undiscounted; for this scenario, the ICER evolocumab plus statins versus ezetimibe plus statins was £36,339 per QALY gained. The highest ICER was reported for the scenario in which costs were undiscounted and health outcomes were discounted at a rate of 6% per annum. For this scenario, the ICER evolocumab plus statins versus ezetimibe plus statins was £112,741 per QALY gained. These values are also higher than those presented in the CS.[13]

Table 41: Amended base case and scenario analysis results for HeFH primary and secondary prevention analyses

Analysis	Population characteristics and comparison	Evolocumab		Ezetimibe		Incremental		
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER
HeFH primary and secondary prevention - cohort analysis - base case analyses								
Analysis G	ST (evo+statins vs eze+statins)	10.17	£73,620	9.02	£19,431	1.15	£54,189	**£47,195**
Analysis H	SI (evo vs eze)	9.82	£72,303	8.77	£19,817	1.05	£52,486	**£49,900**
HeFH primary and secondary prevention - cohort analysis - scenario analyses								
Analysis I	SI (evo+eze vs eze)	10.01	£77,481	8.77	£19,817	1.24	£57,664	**£46,685**
Analysis J	ST (evo+eze+statins vs eze+statins)	10.23	£78,604	9.02	£19,431	1.20	£59,172	**£49,138**

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe

Table 42: Amended summary of probabilistic sensitivity analysis results

Analysis	Population characteristics and comparison	Probabilistic ICER evolocumab+/-statins vs. ezetimibe+/-statins	Probability evolocumab+/-statins optimal at willingness-to-pay threshold	
			λ=£20,000/QALY gained	λ=£30,000/QALY gained
HeFH primary and secondary prevention - cohort analysis				
Analysis G	ST (evo+statins vs eze+statins)	£48,664	0.00	0.00
Analysis H	SI (evo vs eze)	£51,061	0.00	0.00

QALY – quality-adjusted life year; n/a – not applicable; ICER – incremental cost-effectiveness ratio; ST – statin tolerant; SI – statin intolerant; evo – evolocumab; eze – ezetimibe

5.3 Critical appraisal of the company's health economic analysis

5.3.1 Methods for reviewing the company's economic evaluation and model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which the analysis is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists[48,67] to critically appraise the company's model and analysis.
- Scrutiny of the company's model by health economic modellers and discussion of identified issues amongst all members of the ERG.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and assumptions underlying the company's model.
- A partial re-build of the deterministic version of the company's model to assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any errors in the implementation of the model. It should be noted that this double-programming exercise was undertaken using the transition probabilities calculated within the company's model and did not include the replication of these by the ERG.
- Examination of concordance between the description of the model reported within the CS[13] and the company's executable model.
- Replication of the base case results, PSA, 1-way sensitivity analysis and scenario analysis presented within the CS.[13]
- Checking of parameter values used in the company's model against the original data sources.

The ERG notes that the methods and results of the economic analysis presented in the CS are reported over more than 110 pages, and are accompanied by several detailed appendices covering specific elements of the model, including the methods for estimating calibration factors and reviews of "real-world" studies, resource valuation studies and risk equations. Consequently, the critical appraisal presented in this section refers to the most important issues identified by the ERG. It is possible that given the wealth of information submitted by the company, the ERG critique may not be exhaustive and some less substantial sources of bias may not have been identified.

5.3.2 Summary of main issues identified within the critical appraisal

Box 2 summarises the main issues identified within the ERG's critical appraisal of the company's submitted health economic analysis. These issues are discussed in further detail in the subsequent sections.

Box 2: Summary of main issues identified within the critical appraisal of the company's model

1. Deviations from the NICE Reference Case[68]
2. Concerns regarding the conceptualisation and implementation of the company's model structure and logic
3. Concerns regarding the populations and baseline characteristics included in the company's analyses
4. Issues regarding the use of CVD risk equations and the need for subsequent calibration
5. Concerns regarding the derivation of calibration factors to adjust the baseline risk of CVD for the raised LDL-C analysis
6. Issues surrounding the derivation of the calibration factor to adjust the baseline risk of CVD for people with HeFH
7. Concerns regarding the appropriateness of treatment effects
8. Comments regarding the relationship between LDL-C reduction and CVD events
9. Limited relevance of health utility estimates
10. Discrepancies in the cost parameters used in the company's model
11. Errors in the interpretation/reporting of health economic results

(1) Deviations from the NICE Reference Case

Table 43 summarises the extent to which the company's submitted health economic analysis adheres to the NICE Reference Case.[68]

Table 43: Adherence of the company's economic analysis to the NICE Reference Case

Attribute	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The scope of the company's health economic analysis is partly in line with the NICE scope. Within the non-familial primary hypercholesterolaemia population, the company focuses on a subgroup (those with LDL-C>2.5mmol/L for non-familial) of patients with primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia for whom lipid-modifying therapies, would be considered. It is unclear whether this modelled population fully reflects the population of people unable to reach LDL-C goals with the maximum tolerated dose of a statin. The ERG also notes that the analysis of the HeFH population is presented for a combined population of those patients who have a history of CVD and those who do not have a history of CVD. The ERG would suggest that for clinical and economic reasons, these populations should be considered separately.
Comparator(s)	As listed in the scope developed by NICE	The comparators used are in line with the final NICE scope.[4] Ezetimibe (alone or in combination with statins) is considered in all analyses. Comparisons against statins alone are also presented within the CS,[13] although the ERG notes that these are not included within the final NICE scope.[4]
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health benefits relate to those enjoyed by NHS patients.
Perspective on costs	NHS and PSS	An NHS perspective is considered. Costs borne by PSS are excluded from the company's economic analysis.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The model estimates the incremental cost per QALY gained for evolocumab (with/without ezetimibe and or/statin therapy) versus ezetimibe (with/without statin therapy).
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A lifetime horizon is used in the company's base case analysis. Shorter time horizons are considered within the company's scenario analyses.
Synthesis of evidence on health effects	Based on systematic review	The risk of CVD events is derived from two published algorithms: the Framingham equations[53] for first CVD events, and the REACH Registry equations[54] for subsequent CVD events. These risks are then adjusted using a process of calibration. The main efficacy parameters (relative reductions in LDL-C) are taken from the LAPLACE-2 trial for patients who are able to take statins and from GAUSS-2 for patients for whom statin therapies are contraindicated or not tolerated. These are individual studies included within the company's systematic review. The relationship between a reduction in LDL-C and CVD events is taken from a meta-analysis published by the CTTC.

Attribute	Reference case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health outcomes are valued using QALYs. Utility values are taken from a range of sources; these are however dated and are not all are measured using the EQ-5D questionnaire but are instead based on TTO valuations. Some utility values used do not correspond to the health state intended to be reflected in the company's model.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The company's model uses cost estimates taken from the NHS Drugs Tariff,[61] NHS Reference Costs,[62] the PSSRU[63] and an analysis of CPRD/HES data.[13] The cost of evolocumab was sourced from the company.[13]
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits are discounted at 3.5%

The company's health economic model partly meets the requirements of the NICE Reference Case.[68] Within the analyses of the non-familial populations, the company's model includes only patients with a baseline LDL-C>2.5mmol/L. Clinical advice received by the ERG suggests that the inclusion of a population only with an LDL-C>2.5mmol/L is likely to exclude most UK individuals. Clinical experts suggested that most UK individuals with CVD currently attain a target of LDL-C of 2mmol/L on statins. Hence, clinical experts felt that the population included in the economic model is likely to be a small residual population of people in the UK. It is also unclear whether this specifically reflects the population of people unable to reach LDL-C goals with the maximum tolerated dose of a statin, as indicated within the wording of the marketing authorisation for evolocumab.[26] It is further noteworthy that within the HeFH population, the model evaluates a mixed population of patients who have a history of CVD events and people who have no history of CVD. Clinical advice received by the ERG suggests that it may be more appropriate to evaluate these two populations separately. The ERG notes that the ICERs for both separate populations are however similar, based on the submitted company's model. The interventions and comparators included in the company's model are appropriate and reflect the marketing authorisation for evolocumab. The time horizon, perspective and discount rate

are appropriate. No additional equity weighting is applied to estimated QALY gained. Issues surrounding the prediction of baseline risk, relative treatment effects, the measurement and valuation of HRQoL and costs are detailed in the subsequent sections.

(2) Concerns regarding the conceptualisation and implementation of the company's model structure and logic

The ERG has a number of concerns regarding the company's implemented model: some of these represent major mathematical errors whilst others indicate the improper use of the available evidence. Consequently, the ERG has serious doubts regarding the validity of the results presented within the CS and would advise considerable caution in their interpretation and use in informing decision-making. The main concerns identified by the ERG can be separated into four sets of issues: (a) the company's general modelling approach; (b) the conceptual representation of the condition; (c) the model process and logic; and; (d) model implementation and misspecification of evidence inputs. These conceptual and structural problems are complex and intertwined, and the resolution of individual issues in isolation would not result in an appropriate or credible model. Rather, the ERG considers that the joint resolution of these problems would require a 'full' rethinking of the model's logic. As such, their impact on the expected cost-effectiveness of evolocumab is not clear. It should also be noted that based on the company's existing model structure and the information provided within the CS,[13] the ERG is unable to amend the company's model to produce an analysis which aligns a logically consistent model structure with conceptually appropriate model inputs.

(a) General modelling approach

The company's model adopts a cohort Markov approach. Whilst previous economic evaluations of cholesterol lowering therapies have also followed this general methodology, this imposes significant constraints and a number of assumptions are required in order to relax the "memoryless" property of the Markov approach. This is particularly relevant in instances whereby the model is required to account for patients' histories of multiple CVD events and whereby the risk of such events is ongoing over time. Whilst the derivation of the Markov trace and subsequent costs and health effects in the company's model is straightforward (see Section 5.2.2), the preceding derivation of calibrated baseline event risks is convoluted and difficult to follow, both in terms of logic and implementation using mathematical formulae. Although this issue is minor compared with the other structural issues described below, implementing the model as a patient-level simulation may have increased the transparency and flexibility of the model, required fewer assumptions to account for previous CV events and may have obviated problems relating to the handling of competing risks of first and subsequent fatal and non-fatal CVD events.

(b) Conceptual representation of the condition

Health states within the company's model are defined by CVD events; this is appropriate for modelling cholesterol lowering therapies. However, the choice of which health states (CVD events) should be included in the model is a matter of debate. The company conducted an impressive review of 108 previous economic models; one of these included studies related to the model developed to inform NICE CG181.[15] However, as noted in Section 5.1, the CS provides only a very brief summary of the included studies and the extent to which this review has been used to inform the company's model structure is unclear. In particular, the ERG notes that the health states used in the company's model are different to those used in the NICE CG181 model.[15] The CS does not include a description of how the health states were selected nor does it explain why these should be considered more relevant than those states included in the NICE CG181 model (or indeed within any of the other 107 published economic evaluations identified within the company's review).

In particular, the company's model has the following features: (a) the inclusion of HF as a health state; (b) the inclusion of only IS as opposed to any stroke (e.g. haemorrhagic), and; (c) the use of composite health states which include a combination of up to three individual health states (e.g. ACS plus post-IS plus post-HF). The ERG has concerns regarding the inclusion of the HF state given the paucity of data on the impact of cholesterol lowering therapies on this type of event or the impact of CHD death following HF. This issue is recognised within the CS[13] (page 197), hence its inclusion in the model is unclear. Notably, the CS states that *"patients in HF health states (either single or combined) experience no further treatment effect due to LDL-C lowering for risk of recurrent HF since findings suggest lack of benefit for lipid-lowering therapies once patients experience HF on events such as CHD death"* (CS[13] page 197). This appears to be inconsistent with what is done in the company's model whereby a reduction in LDL-C in patients with HF (in either an acute, post-event state or combined health state) is associated with a reduction in CHD death. Furthermore, the company does not provide any justification regarding the inclusion of only IS. However, the ERG notes that based on the CTTC meta-analysis,[28] the effect of LDL-C reduction, which is used as a surrogate for CVD event reduction, is greater for IS compared with any stroke (RR = 0.69 for IS versus 0.74 for any stroke). Further, whilst it is plausible that people may experience multiple different types of CV events over their lifetime, there are no data available to inform these transitions and therefore the company's model makes a number of arbitrary assumptions regarding maximum event risk to in order populate these cells in the transition matrix. This may be considered to increase uncertainty rather than accuracy in the model's results.

As described in Section 5.2, the company's model uses absolute LDL-C reduction as a surrogate for relative reduction in CVD events. The ERG notes that LDL-C reduction has been accepted as a surrogate in previous appraisals.[14] Little justification is provided regarding why other potential

surrogates such as HDL-C or total cholesterol were not considered. Clarification was requested from the company regarding the use of this surrogate in the economic model (see clarification response,[35] question B10). In their response, the company stated:

"LDL-C was the only surrogate considered for CVD risk in the economic evaluation given that the body of evidence supporting LDL-C as a therapeutic target and surrogate for CV outcomes is overwhelming. This evidence comes from a range of studies including epidemiological studies, genetic variants (both gain-of-function and loss-of-function), and interventional studies with LDL-C-lowering therapies. In contrast, the relationship between other lipid markers and CV event rates, and whether changing these markers through therapeutic intervention has an effect on CVD risk, is less well-established and understood. Therefore, other markers were not considered. Although evolocumab also has a significant positive effect on other lipid markers (e.g. non-HDL-C and Lp[a]), the primary effects of evolocumab are on LDL-C. We anticipate that improvements in these other markers may contribute to reduction in CV risk, but in the absence of data supporting the impact of altering these markers on CV risk, they were not used in the model as a surrogate." (Clarification response,[35] question B10).

Whilst the ERG acknowledges the lack of data on the impact of evolocumab on CVD events, it is important to reiterate that the reliance on the use of a surrogate endpoint contributes to the overall uncertainty in the model. Given the current clinical evidence base, it remains unclear whether evolocumab is associated with a benefit in terms of reduced CVD events and specifically whether the effect of evolocumab would be commensurate with benefits observed for other lipid-lowering therapies (e.g. statins and ezetimibe).

(c) Model process and logic

For the analysis of patients with non-familial primary hypercholesterolaemia (based on a subset of the LAPLACE-2 trial[23]), the company's model uses a three-step approach to estimate the risk of CVD events. This involves: (i) using of the Framingham[53] and REACH Registry[54] equations to predict the baseline risk of CVD events depending on individual characteristics in a subset of the LAPLACE-2 trial; (ii) estimating calibration factors to adjust predictions from the Framingham and REACH equation to "real world data" (estimated from the company's analysis of CPRD/HES data), and; (iii) adjusting the baseline risks estimated using the Framingham and REACH Registry equations by these estimated calibration factors.

The ERG has concerns regarding this overall modelling approach. Specifically, the ERG believes the approach used by the company to be circular, overly-complicated and counter-intuitive, as it requires a number of assumptions and adjustments when estimating and applying the calibration factors (see

Section 5.2.2). The ERG notes that based on information provided within the CS[13] and during the clarification process,[35] the baseline risk of experiencing CV events could have been estimated directly from the company's CPRD and HES analysis, and that the use of the Framingham and REACH equations is not necessary as it does not appear to provide additional information compared with using the CPRD and HES data. In effect, the company's approach involves estimating CV risk using equations then adjusting these to reflect real-world CPRD/HES data rather than using the CPRD/HES data directly. The ERG sought clarification from the company regarding this matter (see clarification response,[35] question B33). The company's response stated that:

"…*the economic model could indeed have directly used the CPRD study event rates to model an overall high-risk population as per the study cohort definitions. However, this approach would not have permitted us to assess specific high-risk populations such as those with existing CVD with 1 or 2 additional risk factors who remain at the highest residual risk*."

The ERG considers the company's response to be unsatisfactory because: (a) the analyses in individuals with additional risk factors (AF and 2/3 vascular beds) are presented only within the company's subgroup analyses and do not reflect the main population specified in the NICE scope,[4] and; (b) the company's analysis in patients with existing CVD with one or two additional risk factors employs arbitrary manipulations of the IPD which will ultimately produce biased risk estimates. The ERG considers that it would have been more appropriate to estimate baseline CVD risk from the CPRD/HES data and to subsequently adjust these using relative risks from the published literature to reflect these additional risk factors. It is also noteworthy that the company's process for estimating CVD risk in all populations requires several other assumptions (e.g. removing the effect of age and sex), the validity of which are unclear.

(d) Model implementation and misspecification of evidence inputs

Upon scrutinising the company's model, the ERG identified a number of inconsistencies and errors in the model's implementation and logic, which appear to be due to a misinterpretation or misuse of evidence. These are described in below.

Firstly, the company's model treats the predictions from the Framingham[53] and REACH Registry[54] risk equations as event rates (see CS,[13] Figure 5-4, page 182). However, in response to a request for clarification from the ERG, the company recognised that the risk predicted by these equations are actually probabilities which are bounded between 0 to 1 (see clarification response,[35] question B17).

In addition, the company's model misinterprets what the REACH Registry risk equations[54] are predicting. As detailed in Section 5.2, the REACH Registry risk equations predict: (i) the risk of any

"next cardiovascular event", which includes any fatal and non-fatal CVD events, and; (ii) the risk of "cardiovascular death" which includes only fatal events. However, the company treats predictions from the REACH Registry risk equations for "next cardiovascular event" and "cardiovascular death" as being independent of one another and assumes that the risk for "next cardiovascular event" predicted by the REACH Registry equation includes only non-fatal events. This is incorrect and was confirmed through correspondence between the ERG and the author of the REACH Registry paper.[54] This has important implications in that it invalidates the calibration factors estimated using the CPRD/HES dataset and also inflates the number of non-fatal CVD events predicted by the model. Since the model artificially inflates total CVD risk, the ICERs for evolocumab are likely to be underestimated.

Further, since the model estimates the risk of fatal and non-fatal CVD events separately and without constraint, this leads to mathematical inconsistencies when the risk of fatal and non-fatal CVD events is high. Consequently, when the sum of predicted probabilities for fatal and non-fatal CVD events exceeds 1, this leads to a situation whereby some of the transition probabilities and health state populations become negative. This error is accentuated by the use of calibration factors which have been estimated independently for fatal and non-fatal events. As discussed in Section 5.2, this unequivocal error was raised by the ERG at the clarification stage in order to provide the company with an opportunity to re-submit an amended version of the model which was mathematically sound. In response, the company recognised that results for the non-familial population were "invalid" due to the presence of negative probabilities, yet the amended model did not include a correction of the underlying mathematical inconsistency. Instead, the company introduced arbitrary adjustments to some transition probabilities to prevent the model from generating negative probabilities for the HeFH population; this amendment results in slightly lower CV risks for the HeFH population. The ERG notes that whilst this is a structural problem, the company's amendment treats this as a parametric issue. The ERG highlights that it should not be possible under any combination of model parameter inputs for transition probabilities or health state populations to be negative, even at the highest levels of predicted CV risk. Despite the company's amendment to the model, negative probabilities are still possible when different input parameters are used, for example, when the cap for age is increased from 85 to 90 years, or when the adjustment factors for the HeFH population are increased to the upper CI reported within the CS.[13] As such, the company's amended model does not resolve the problem, it simply makes it less visible.

There also appears to be some confusion and inconsistency in terms of the general logic of the company's model. The company estimates the risk of CVD using baseline characteristics at entry into the LAPLACE-2/RUTHERFORD-2 trials and uses the LDL-C at baseline to represent the risk of CVD for people treated with statins. However, the model then applies the treatment effect (a relative

reduction in LDL-C) for ezetimibe and evolocumab calculated from the treatment difference (statins versus ezetimibe or evolocumab) at the mean of weeks 10/12, rather than based on the change from baseline. The ERG believes there is a mismatch as the treatment effect used in the model does not match the baseline LDL-C level from which it is estimated. This leads to a larger treatment effect being used in the model (treatment difference of -71.8% at week 10/12 against statins vs. -64.33% from baseline in the LAPLACE-2 trial). The impact on the ICER is unclear as this over-estimates the absolute reduction in LDL-C and hence also the relative reduction in CVD events. However, the ERG notes that this inconsistency affects both the ezetimibe and evolocumab groups and is somewhat mitigated by the constraint included in the company's model whereby LDL-C after treatment cannot decrease below 40mg/L (equivalent to 1.03mmol/L).

With respect to the HeFH population, the CS[13] (page 191) acknowledges the lack of a specific CV risk equation for these patients. Hence, the company's model estimates the risk of CVD events using the Framingham[53] and REACH Registry[54] risk equations in the RUTHERFORD-2 trial and then adjusts this using a relative risk for the HeFH population based on Benn *et al*.[55] The ERG considers this to be inappropriate since the baseline risk in the non-HeFH population used in the company's model already reflects people who are at a higher risk due to higher baseline cholesterol. A more appropriate approach would have involved applying the HeFH adjustment factor to the baseline risk of CVD for the general population; this would have been consistent with the nature of the relative risk estimated within the Benn study.

As a consequence of these problems, the ERG urges caution in the interpretation and use of all of the results presented in the CS[13] and the subsequent addendum.[52]

(3) Concerns regarding the populations and baseline characteristics included in the company's analyses

Baseline characteristics for the non-familial primary hypercholesterolaemia population are taken from a subset of the LAPLACE-2 trial; for the HeFH population, these are based on the modified ITT population of the RUTHERFORD-2 trial. These are used to estimate baseline CVD risk then to calculate the absolute LDL-C reduction for evolocumab and ezetimibe. The ERG notes that there is uncertainty with respect to whether the populations included in the LAPLACE-2 and RUTHERFORD-2 trials are representative of primary hypercholesterolaemia people in England (see Chapter 4). Whilst the company's analysis of the non-familial population includes only those patients in LAPLACE-2 who had a baseline LDL-C>2.5mmol/L, it is unclear whether this truly reflects a high-risk population who may benefit from treatment using evolocumab. The ERG also notes that the model assumes the same baseline characteristics in terms of age, gender, LDL-C and other covariates (and hence the same baseline risk of CVD events) for patients who are able to take statins and those

for whom statins are contraindicated or not tolerated. It is likely that CVD risk is related to whether a patient's LDL-C can be controlled using statins; as such the use of baseline characteristics from the GAUSS-2 trial may be more appropriate for the evaluation of patients who are unable to take statins. The CS[13] (page 174) makes the following statement regarding why data from the LAPLACE-2 and RUTHERFORD-2 trials were assumed for both statin tolerant and intolerant populations:

"LAPLACE-2 and RUTHERFORD-2 were used instead of GAUSS-2, since patients that are intolerant or contraindicated to statins are anticipated to have a greater severity of hypercholesterolaemia as they cannot achieve adequate LDL-C control with lipid-lowering therapies (e.g. low dose statin or alternative lipid-lowering therapy). Baseline LDL-C levels were 2.7 mmol/L to 2.9 mmol/L, 3.9 mmol/L to 4.2 mmol/L, and 5.0 mmol/L to 5.1 mmol/L in LAPLACE-2, RUTHERFORD-2 and GAUSS-2, respectively. Therefore, the LAPLACE-2 and RUTHERFORD-2 patient populations were used with additional cost-effectiveness analyses based on severity of hypercholesterolaemia (baseline LDL-C) to represent populations that are intolerant or contraindicated to statins." (CS,[13] page 174)

This argument appears somewhat contradictory in that the CS argues that the average LDL-C level is higher in statin intolerant patients, yet the company's model uses the LDL-C from LAPLACE-2 (which includes primarily statin tolerant patients) and is lower than what was observed in the GAUSS-2 trial. The ERG believes that the GAUSS-2 population would be more representative of patients for whom statin therapy is contraindicated or not tolerated. The ERG acknowledges that assumptions would be required for the evaluation of the HeFH population.

The CS[13] (page 174) further states that: *"the patient populations from LAPLACE-2 and RUTHERFORD-2 were used since statin intolerance or contraindication is considered a subgroup of the primary hypercholesterolaemia and mixed dyslipidaemia, and HeFH populations."* Whilst the ERG believes the statement from the company to be correct, it should be noted that as the LAPLACE-2 and RUTHERFORD-2 trials include a mix of people who are able to take statins and who are contraindicated or intolerant to statin therapies, the analyses presented by the company for patients who are able to take statins (which are based on the treatment effect calculated across of the overall LAPLACE-2 and RUTHERFORD trials) actually reflect the results for the overall population which includes a mixture of statin tolerant and intolerant populations.

The ERG also questions the baseline characteristics used within the company's subgroup analyses. The company conducted a number of analyses in people with diabetes, AF or 2/3 vascular beds. In these analyses, the company's model assumes that all patients have the specific subgroup characteristic, whilst all other baseline characteristics are held at their observed baseline values.

However, people with diabetes, for instance, are likely to have different characteristics to those patients included in the LAPLACE-2 trial, specifically in terms of cholesterol level, history of CVD and other risk factors.[45] The ERG sought clarification on why the company adopted this approach, rather than selecting out the smaller subset of patients who actually had these particular characteristics (see clarification response,[35] question B15). In response, the company did not provide a rationale but instead provided a comparison of predicted CVD risk for patients with diabetes in the LAPLACE-2 trial (n=61) versus the company's subgroup approach. Whilst the predicted risks using the alternative approaches were broadly in agreement, the ERG believes that the approach used by the company is arbitrary and notes that people with type 1, newly diagnosed or poorly diagnosed type 2 diabetes were excluded from the trial, thereby limiting the relevance of the comparison provided in the company's response.

(4) Issues regarding the use of CVD risk equations and the need for subsequent calibration

As discussed above, the ERG has concerns regarding the need to use risk equations in the model (with subsequent calibration) rather than using direct data on observed CVD event rates, and the misinterpretation and use of the REACH Registry[54] risk equations. In addition, the ERG has concerns regarding the choice of risk equations and how these are used in the company's model. Whilst alternative risk equations are available (e.g. the QRISK2,[22] upon which the model developed to inform NICE CG181[15] was based), the company's model uses the US Framingham risk equation[53] to estimate the 10-year risk of CVD in people without a history of CVD. The CS[13] justifies this choice based on three points:

(i) The US Framingham risk equations[53] include a broader definition of events compared with the UK QRISK2 equations.[22] Whilst this is true, the ERG considers this argument to be mitigated by the fact that the company then calibrates the Framingham risk estimates using data from CPRD/HES.

(ii) Fewer variables are required to estimate the 10-year risk of CVD using the Framingham equations compared with the QRISK2 equations.[22] The ERG sought clarification regarding which additional variables would be required and whether these would be available in the evolocumab trials (see clarification response,[35] question B12). In response, the company provided a table summarising the variables in QRISK2 that fully align, partially align or do not align with data collected within the evolocumab trials. The ERG agrees that using QRISK2 would have been more difficult and would have required further assumptions, compared with the US Framingham risk equation.

(iii) The CS[13] asserts that CVD event rates would need to be calibrated irrespective of the choice of risk equation. The ERG requested clarification from the company regarding the basis of this assertion (see clarification response,[35] question B14). The company responded that calibration is necessary for two reasons: (a) the narrower definition of CVD events based on

the QRISK2 equations, and; (b) the representation of a higher risk population within the company's economic model. Whilst the arguments suggested by the company are reasonable, the ERG notes that whilst not stated explicitly, the US Framingham equation suffers from the same biases as the QRISK2 equations as this was not developed in a high-risk population.

Overall, whilst the ERG considers that the QRISK2 equation would require additional assumptions compared with the Framingham risk equations and that other risk equations are available, the arguments provided by the company appear insufficient in that they suggest that neither Framingham nor QRISK2 are appropriate and that the use of either would require calibration and/or adjustment.

In the secondary prevention setting, the REACH equations include a variable for whether the individual is receiving statin treatment or not. This variable is set to "yes" both in the analyses for patients who are able to take statins and for patients who are unable to take statins. The ERG believes that the variables should be set to "no" for the analyses relating to patients for whom statin therapy is contraindicated or not tolerated. This is likely to increase the risk of CVD in statin intolerant populations and likely to result in an improvement in the ICER for evolocumab.

Within the non-familial secondary prevention subgroup analyses which include diabetes as an additional risk factor, the company's model estimates CV risk using the REACH equations together with arbitrary assumptions regarding the presence/absence of particular baseline characteristics. The ERG considers that whilst the REACH Registry equations include a variable for diabetes, the UK Prospective Diabetes Study (UKPDS) could have been used. The ERG sought clarification from the company regarding why the UKPDS risk engine was not used to assess CV risk in the diabetic population and to discuss the limitations of using the Framingham equations in the diabetic population in the CPRD dataset (see clarification response,[35] question B13). In response, the company stated that *"The UK Prospective Diabetes Study (UKPDS) risk equation is indeed relevant for estimating risk of a first CV event in a diabetic population without existing CVD. As a diabetic population was not specifically modelled, we did not feel it was necessary to use this risk equation to estimate baseline CV risk*" (Clarification response,[35] question B13). Whilst no analysis is presented for primary prevention in people with diabetes, the ERG disagrees with the response provided by the company as the UKPDS risk equations can also be used to estimate the risk of subsequent CV events and therefore could have been used for the secondary prevention analyses in patients with diabetes. It should be noted that for primary prevention, the QRISK2 risk assessment tool is recommended to assess CVD risk in people with type 2 diabetes.

As noted above, the analyses undertaken in the HeFH population reflects a mixture of those people who have a history of CVD and those who do not. Advice received by the ERG suggests that from a

clinical perspective, it would make more sense to consider the two populations separately. Further, from an economic standpoint, the same is true as combining the two separate populations groups may lead to erroneous recommendations on the use of health technologies which are efficient in one population but not in another. Within the HeFH primary/secondary prevention analysis, the Framingham and REACH equations are applied to the entire cohort of people recruited into the trial, irrespective of their history of CVD. This is not appropriate, as the Framingham equations are appropriate only in people without a history of CVD and the REACH equations are appropriate only in people with a history of CVD. The ERG sought clarification from the company regarding why the 10-year risk was calculated for the overall population in the RUTHERFORD-2 trial in the HeFH population (see clarification response,[35] question B31). In response, the company stated that: *"the Framingham equation was only applied for transitions for HeFH patients without existing CVD (i.e. primary prevention). The primary and secondary prevention populations in HeFH were not evaluated separately to reflect the decision problem. The economic model cannot assess primary and secondary prevention cohorts simultaneously, therefore average cohort patient characteristics from the primary and secondary prevention population from RUTHERFORD-2 are used for the cost-effectiveness analysis."*

The ERG considers the response from the company to be unsatisfactory and somewhat contradictory. For clarity, in the company's implemented model, the 10-year risk of CVD estimated using the Framingham equation is estimated from the entire RUTHERFORD-2 trial population; this risk is only applied for the transition between the no CVD to CVD states. The company appears to suggest that the primary and secondary prevention analyses cannot be estimated simultaneously. The ERG disagrees with this statement as this is what is currently done in the model, i.e. a proportion of the cohort enters the model in the no CVD state and the remaining patients enter the model in the ECVD and post-event states. The model does however have the functionality to consider the primary prevention and secondary prevention HeFH populations separately. The ERG notes that the NICE scope does not specify whether the population should be evaluated separately or as a combined group.

(5) Derivation of calibration factors to adjust the baseline risk of CVD for the raised LDL-C analysis

The CS contains only limited information regarding the process of calibration of risk factors. However, the company also submitted an accompanying appendix which provides further details on the methodology adopted. Owing to time constraints, the ERG was unable to provide a full assessment of this but note several concerns regarding the derivation and validation of the company's calibration factors:

(a) Given the lack of reliability of the Framingham equations in people with diabetes, it is uncertain if the resulting calibration factors would be appropriate for the population included

in the economic model which does not reflect a diabetic population. The extent of this potential bias is uncertain.

(b) The company appears to have made a complicated age adjustment in order to be able to compare the predictions from the risk equations with the event rates in the CPRD/HES data. The comparability of the two is unclear.

(c) The calibration factors estimated for secondary prevention of non-fatal events are incorrect due to the misuse of the REACH equations, as described above.

(d) A number of assumptions are also made when the baseline characteristics are not available in the CPRD/HES data (e.g. presence of AF and number of vascular beds). These variables are used to predict the risk of secondary events, and therefore may bias the REACH predictions and associated calibration factors.

(e) Linking data from the CPRD, HES and ONS meant that only half of the people could be linked and included in the analysis. This reduces the sample size and is likely to introduce selection biases. The extent of this bias is uncertain.

In brief, the ERG has concerns regarding the calibration factors and re-iterate that estimating the event rate from the CPRD/HES data may have produced less bias than predicting CV risk using risk equations which were considered by the company *a priori* to produce inaccurate predictions of CV event risk.

(6) Issues surrounding the derivation of the calibration factor to adjust the baseline risk of CVD for people with HeFH

The company assumes a relative risk of 7.1 for CVD events for People with HeFH (relative to people without HeFH), based on study reported by Benn *et al*.[55] The ERG sought clarification from the company regarding the derivation of their estimated relative risk. Following clarification, the ERG is satisfied with the mathematical approach used by the company to calculate this parameter value. However, the ERG questions the value used for the following reason. The Benn *et al*[55] study provided a comparison of the risk of CVD events between the general population and patients with HeFH. However, in the company's model, this relative risk is applied to an already high-risk population (people with an LDL-C>2.5mmol/L). As such, this is likely to over-estimate the risk of CVD events in the company's analyses within the HeFH population. The magnitude of this bias is uncertain. Furthermore, a UK study by Neil *et al*[69] reported a lower standardised mortality ratio (SMR) for CHD in people treated with statins; the SMR was 1.03 for primary prevention and 3.88 for secondary prevention in people aged between 20 to 79 years old. A broadly similar SMR was reported in a recent Norwegian study based on registry data from 4,688 male and female individuals from the Unit for Cardiac and Cardiovascular Genetics (UCCG) Registry with verified molecular genetic diagnosis of familial hypercholesterolemia linked to the Norwegian Cause of Death Registry. The study

reported that compared with the Norwegian population, CVD mortality was significantly higher in the UCCG Registry in all age groups younger than 70 years (SMR 2.29, 95% CI 1.65 to 3.19 in men and women combined; SMR 2.00, 95% CI 1.32 to 3.04 in men; SMR 3.03, 95% CI 1.76 to 5.21 in women). The SMR across all ages (including people over the age of 70 years old) was 1.56 (1.41 in males and 1.75 in females).

The ERG recognises that there are methodological and country differences between the studies that may explain estimated differences in risk. The ERG believes that data from the Neil *et al*[69] study may be more appropriate as this is a UK source. Furthermore, estimates from this study are in line with recent data reported in Norway. However, several assumptions would be required as this study only reported on differences in the risk of fatal events. It is also worth noting that a UK study showed that people with treated HeFH are not at increased risk of fatal stroke compared with general population.[70] The ERG notes that assuming a lower HeFH adjustment factor (which is more plausible) would lead to (potentially substantial) increases in the ICER for evolocumab in the HeFH population.

(7) Concerns regarding the appropriateness of treatment effects

For the analyses in people who are able to take statins, the company applied the treatment effect (reduction in LDL-C) calculated from the treatment difference at the mean of week 10/12 between evolocumab and ezetimibe compared with statins. As mentioned above, the ERG believes that the treatment effect calculated from change from baseline is more appropriate. The ERG is generally satisfied with the company's approach for using the mean of week 10/12. The company also uses the pooled treatment effect calculated from a random effects model. Given the absence of heterogeneity, the ERG considers this to be unnecessary.

For the non-familial population analyses in patients who are able to take statins, the company uses the treatment effect calculated from the overall LAPLACE-2 trial population despite including only a subset of this population in the health economic model. Clarifications were requested from the company to provide additional analyses of treatment effect for the subgroup of people included in the model (i.e. patients in the LAPLACE-2 trial with an LDL-C>2.5mmol/L) for primary prevention and secondary prevention separately (see clarification response, question B4). The treatment effects were provided by the company (available in the clarification response document); however, given the structural issues in the model, these were not considered further by the ERG.

For the HeFH analysis in patients who are able to take statins, the company uses the treatment effect from the LAPLACE-2 trial rather than the RUTHERFORD-2 trial, despite the latter specifically relating to the population under consideration. The company provides three reasons for this: (i) the absence of head-to-head data in HeFH for evolocumab plus statins versus ezetimibe plus statins; (ii)

the treatment effects from LAPLACE-2 and GAUSS-2 are deemed to be generalisable to the HeFH population since the treatment effect of evolocumab was consistent regardless of the population and individual characteristics, evolocumab dosing regimen (140 mg Q2W or 420 mg QM), and presence and type of background lipid-lowering therapy, and; (iii) this approach was used in NICE TA132 whereby the treatment effect of ezetimibe in people without HeFH was assumed to be generalisable to people with HeFH.

The ERG believes that the treatment effect for evolocumab from the RUTHERFORD-2 trial should be used for the HeFH population who are able to take statins. Whilst the ERG recognises the lack of effectiveness data for ezetimibe, the ERG notes that the treatment difference (calculated using the random effects model) between statin and evolocumab Q2W at the mean of week 10/12 appears to be statistically greater in the LAPLACE-2 trial (non-familial) compared with the RUTHERFORD-2 trial (HeFH population) with no overlap between the confidence intervals: LAPLACE-2 trial (-71%; -74.7% to -68.9%) vs. RUTHERFORD-2 trial (-61.3%; -67.2% to – 55.4%). The ERG believes that a better approach would have been to use the treatment effect calculated from the RUTHERFORD-2 trial for evolocumab and possibly to make a conservative assumption for ezetimibe assuming the effect from the LAPLACE-2 trial or alternatively, to calculate the treatment effect between ezetimibe and evolocumab from the LAPLACE-2 trial and to apply this treatment effect to the evolocumab treatment effect from the RUTHERFORD-2 population.

In patients unable to take statins, the company uses the treatment effect from baseline from the GAUSS-2 trial for both the non-familial and HeFH populations. The ERG is generally satisfied with the approach used by the company in the absence of data for this population.

Within the model, the company assumes that the treatment effect is maintained indefinitely based on evidence from the OSLER studies which demonstrate a sustained reduction in LDL-C up to 2 years. It is however uncertain if the treatment effect would be maintained beyond this point.

The treatment effects from the LAPLACE-2 and RUTHERFORD-2 trials are used independent of baseline characteristics and presence of diabetes or risk factors. It is unclear whether the treatment effect would be the same between the overall population and people with diabetes or other risk factors.

Finally, for the analyses whereby evolocumab is used in combination with ezetimibe, the company assumed that the treatment effect of evolocumab would be sequential to the treatment effect following ezetimibe, i.e. that the treatment effect of evolocumab versus statins would apply to the LDL-C following ezetimibe. This is uncertain.

(8) Comments regarding the relationship between LDL-C reduction and CVD events

Findings from the CTTC meta-analysis are used to represent the relationship between LDL-C reduction and reduction in CVD events. Despite the source being appropriate, the ERG notes that it is unclear from the CS how this source was identified and whether a systematic review was conducted to identify if alternative sources would have been more appropriate.

Data from the five trials comparing "less versus more" intensive lipid lowering therapies were used, rather than the overall 26 trials included in the meta-analysis. The ERG was satisfied with the rationale provided by the company. The ERG notes that the five trials were conducted in secondary prevention (i.e. people with a history of CVD). It is unclear whether the relationship would be the same in the primary prevention setting. The company also acknowledges that the relationship was for the first (recurrent) CV event and that it is unclear whether the relationship would be maintained for subsequent events.

Assumptions are made by the company which may be considered to be matters of judgement. The company assumes that the relationship between LDL-C reduction and non-fatal MI would hold for HF (first event). The ERG questions this assumption as there is little evidence on the impact of LDL-C reduction on HF. The company further states in the CS (page 194) that *"the rate ratio for new onset HF is equal to MI. Patients in HF health states (either single or combined) experience no further treatment effect due to LDL-C lowering for risk of recurrent HF since findings suggest lack of benefit for lipid-lowering therapies once patients experience HF on events such as CHD death."* This appears to be inconsistent with what is done in the company's model where a reduction in LDL-C in people with HF (either acute, post-health state or combined health state) is associated with a reduction in CHD death.

Similarly, the company also uses the relationship observed for non-fatal MI (secondary prevention) for patients transitioning from "No CVD" to "ECVD." Whilst the ERG recognises the lack of data; this assumption is essentially arbitrary.

The company further assumes that the relative reduction in CV event rate per mmol/L reduction in LDL-C is independent of baseline levels, familial or non-familial hypercholesterolaemia, prognostic factors such as age, gender, co-morbidities (e.g. diabetes), and CV history or burden. The ERG is satisfied with this assumption as this is supported by subgroup analysis in the CTTC meta-analysis.

The company uses a relative risk of 1 (no effect associated with LDL-C reduction) for death due to stroke, rather than the value of 1.04 reported in the CTTC meta-analysis; this is due to the lack of

statistical significance in this outcome. The ERG considers that the reported relative risk of 1.04 should have been used, allowing for the impact of uncertainty in this parameter to be handled within the PSA. Similarly, the company use a relative risk of 0.80 (0.74, 0.87) for CHD death based on the broader set of 26 trials, rather than the five "more versus less" subgroup. The ERG believes that the value of 0.85 from the five "more vs less" trials should have been used for consistency.

The ERG notes also that the relative reduction in fatal CV event rate per mmol/L reduction in LDL-C from the CTTC meta-analysis is applied independently of previous events. This is unlikely to be correct as the reduction in fatal CV events is correlated with the reduction in non-fatal events. However, the ERG recognises the difficulties in including correlation within the model.

(9) Limited relevance of health utility estimates

The company's estimates of HRQoL were based on estimates used within the model developed to inform NICE CG181.[15] Whilst the company undertook a large systematic review of studies reporting on health utilities associated with individual or multiple CV events (see CS,[13] Section 5.4), this is not used in any way to inform the company's *de novo* model. Further, as mentioned in Section 5.2.4.8, the sources of these studies and the instruments used to generate health utilities are not clearly presented within the CS. Of the seven acute and post-event state utilities used in the model, only three of these (ACS, HF and post-HF) are based on EQ-5D valuations; all other health utilities have been taken from studies using the TTO method. This does not satisfy the requirements of the NICE Reference Case.[68] It is also worth noting that for the HF and post-HF EQ-5D valuations, the health state being valued in the study actually relates to people who have experienced an MI.[60] Similarly, the health utility for the ECVD state is taken from a study in which people had recently experienced an MI.[57] Had the company chosen utility studies from their literature review, it is unclear whether such interpolation between valuations for different events would have been necessary. Overall, the ERG considers that the selected health utilities in some instances deviate from the NICE Reference Case and the relevance of some of the valuations to the modelled health states is unclear.

It should also be noted that the linear relationship assumed between age and health utility based on the Dolan EQ-5D valuation study[56] is crude. A more recent equation based on data from the Health Survey for England (HSE) has been published.[71] The ERG considers that this would have provided a better indication of the relationship between age and background HRQoL.

(10) Discrepancies in the cost parameters used in the company's model

Overall, the ERG does not have major concerns regarding the costs used in the company's model, but note that there are some discrepancies.

Advice received from expert advisors to the ERG suggests that the patent for ezetimibe is due to expire in 2018. Whilst the company's model uses current NHS Drug Tariff prices for ezetimibe, it may have been prudent to explore the impact of lower acquisition costs for ezetimibe on the cost-effectiveness of evolocumab.

The ERG also notes that the current prices reported by the Commercial Medicines Unit (CMU)[72] for atorvastatin are slightly lower than those used in the company's model (atorvastatin 20mg [28 tabs] – eMit price=£1.02 vs NHS Drugs Tariff =£1.41; atorvastatin 80mg [28 tabs] – eMit price £1.90 vs NHS Drugs Tariff=£2.71). This discrepancy has only a very minor impact upon the cost-effectiveness of evolocumab in the statin tolerant population.

The ERG notes also that there are discrepancies in the assumptions regarding monitoring between the CS[13] and the company's model, and that neither reflects the assumptions used in the model developed to inform NICE CG181.[15] Resource use associated with monitoring assumed in NICE CG181,[15] the CS[13] and the company's model are summarised in Table 44.

As shown in Table 44, the discrepancy between the CS and the model is minor and is a result of different assumptions regarding LFTs tests and HbA1c test costs. The assumptions employed by the Guideline Development Group (GDG) lead to a lower monitoring cost for subsequent years as they include fewer GP visits. Since the costs of monitoring are low and are common to each treatment group, they do not have a material impact upon the ICER for evolocumab versus ezetimibe, irrespective of the assumptions used.

Health state costs

The ERG is generally satisfied with the health state costs used as these are broadly similar to those estimated within NICE CG181.[15] However, the ERG notes that there may be some double counting due to the separate inclusion of revascularisation costs which may already be accounted for in other health state costs.

Table 44: Resource use associated with monitoring reported in the CS,[13] NICE CG181[15] and company's model

Resource component	Year 1			Subsequent years			Unit cost reported in CS[13]	Source
	CS[13]	Company's model	NICE CG181[15]	CS[13]	Company's model	NICE CG181[15]		
Appointments								
Lipid clinic	2	2	n/a	0	0	n/a	£87.77	NHS Reference Costs 2013/14[62]
GP appointment	1	1	1.2	2	2	1	£45.00	Curtis *et al*[63]
HCA appointment	1	1	2	1	1	1	£6.46	
Blood tests								
Total cholesterol	3	3	2	2	1	1	£1.18	NHS Reference Costs 2013/14[62]
HDL cholesterol	3	3	2	1	1	1	£1.18	
LFT	2	2	2	1	0	1	£1.18	
$HbA1_c$	1	1	0	1	1	0	£1.18*	
Totals (assuming GDG assumptions for all items except lipid clinic appointments and based on CS-reported unit costs)								
Total monitoring cost	**£238.72**	**£238.72**	**£249.56**	**£102.38**	**£101.08**	**£56.19**		

**Unit cost of £2.25 applied in company's model*

(11) Errors in the interpretation/reporting of health economic results

There are several problems regarding the interpretation of the results presented within the CS. These concern: (a) errors in the interpretation of the results presented in the tables within the CS; (b) reporting of redundant ICERs in the CS, and; (c) misinterpretation of the primary prevention LDL-C threshold analyses.

(i) Errors in the interpretation of the results presented in the tables within the CS

With reference to the company's subgroup analyses of individual risk factors combined with baseline LDL-C, age, and gender (see CS[13] Table 5-69, and accompanying text on page 279), the CS states:

"Secondly, the impact of combining one of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 5 69). The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000. These results indicate that evolocumab can be considered a cost-effective treatment option in patients with a baseline LDL-C of 3.5 mmol/L and one the following risk factors, when age and gender are taken into consideration:

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

With reference to the company's subgroup analyses of two risk factors combined with baseline LDL-C, age, and gender (see CS[13] Table 5-70, and accompanying text on page 281), the CS states:

"Thirdly, the impact of combining two of the other risk factors with varying age (+5 and +10 years) and gender (male or female) was assessed (Table 5 70). The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000. These results indicate that evolocumab can be considered a cost-effective treatment option in patients with a baseline LDL-C of 3.0 mmol/L and two of the following risk factors, when age and gender are taken into consideration:

- *diabetes mellitus*
- *CV risk factors deemed at equivalent risk to diabetes mellitus:*
    - *moderate to severe CKD (eGFR < 60 mL/min/1.73 m2)*

    - *two or more documented acute ischaemic CV events or revascularisation procedures*
    - *Elevated plasma Lp(a) ≥ 77 mg/dL (≥ 90% centile)*
- *two or more vascular beds*
- *ACS in the past 12 months*
- *other CV conditions that significantly elevate risk of further CV events: heart failure (HF) and atrial fibrillation"*

The ERG notes however that none of the ICERs presented in Table 5-69 or Table 5-70 are below £30,000 per QALY gained. In response to a request for clarification from the ERG, the company stated:

"We can confirm that this text is not applicable to the cost-effectiveness results presented for patients with existing CVD and one or two additional risk factors since all the values in the tables are above £30,000 per QALY gained." (clarification response,[35] question B6).

The ERG suggests that these statements within the CS should be disregarded.

(ii) Reporting of redundant ICERs in the CS[13]

Page 160 of the CS[13] states that *"The incremental cost per QALY gained is approximately £15,119 to £18,200 for evolocumab versus ezetimibe in patients with HeFH when assessed across the four treatment scenarios."* As shown in Table 38, the deterministic ICERs for evolocumab versus ezetimibe based on the company's original model (pre-amendment) are in the range £44,741 to £47,193 per QALY gained. The ICERs reported on page 160 of the CS do not appear anywhere else within the submission. In response to a request for clarification on this matter, the company confirmed that the text quoted above was made in error, and stated:

"The cost-effectiveness results summarised in Section 5, page 160 of the evidence submission, should indeed reflect the incremental cost-effectiveness ratios (ICERs) presented in Tables 5-27, 5-42, 5-47, 5-62 and 5-63 of the evidence submission" (clarification response,[35] question B7).

The ERG again suggests that this statement within the CS is disregarded.

(iii) Misinterpretation of the primary prevention LDL-C threshold analyses.

Within the non-familial primary prevention population, the CS presents threshold analyses to identify the minimum 10-year risk required in order for evolocumab (with or without statins) to be considered cost-effective at thresholds of £20,000 per QALY gained or £30,000 per QALY gained when

compared against ezetimibe (with or without statins, see Table 38). Following the identification of the error resulting in negative transition probabilities, the company declared these analyses to be "invalid." In spite of this, the ERG also has concerns regarding what these threshold analyses were actually suggesting. According to the CS[13] (pages 23, 173 and 241), the threshold analyses were conducted *"to establish the minimum 10-year CVD risk (measured using a risk assessment tool such as QRISK2) at which treatment with evolocumab in accordance with its MA would be deemed a cost-effective use of NHS resources according to willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained."* There are two problems associated with the company's interpretation. First, the company's model uses Framingham to predict 10-year CV risk in people with no history of CVD. Whilst the Framingham risk equations are effectively bypassed within their threshold analyses by directly inputting the 10-year CV risk level (rather than using the risk equation to generate this), the casemix of people with a risk of *x* at 10-years calculated using Framingham would be different from that for people with a risk of *x* at 10-years as calculated using the QRISK2 equation. Secondly, the company's threshold analyses estimate the optimum threshold based on the risk of experiencing one or more events at 10-years; this is based on the proportion of people who have transited to one of the acute or post-event health states at 10-year in the model (i.e. the sum of the acute and post-event health state populations in the Markov trace at 10-years). Both the QRISK2 and the Framingham equations estimate the 10-year risk of experiencing a first CV event, rather than multiple CV events. Consequently, by considering both the first event and any subsequent events at 10-years the company's model over-predicts the risk threshold.

Model errors and other issues surrounding model implementation

The ERG partially rebuilt the company's model in order to assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any errors in the implementation of the model. Due to the complexity of the methods by which the company's model estimates transition probabilities using CVD event risks, age- and sex-adjustments, calibration and the distributions of fatal/non-fatal events, the ERG's double-programming exercise started from the point at which the baseline transition probabilities had been estimated (i.e. these baseline probabilities were taken directly from the company's model). The model rebuild was undertaken to estimate costs and health outcomes for evolocumab plus statins, ezetimibe plus statins and statins alone for three scenarios: (i) the LAPLACE-2 high-risk primary prevention cohort-based cost-effectiveness analysis (as presented in CS[13] Table 5-64); (ii) the LAPLACE-2 high-risk secondary prevention cohort-based cost-effectiveness (as presented in CS[13] analysis C); and (iii) the HeFH primary and secondary prevention cohort-based cost-effectiveness (as presented in CS[13] analysis G). Table 45 presents a comparison of total QALYs and costs for each option across each of these three analyses, as estimated by the company's model and the ERG's rebuilt model. As shown in Table 45, the results of the ERG's double-programming exercise are almost exactly the same results as the company's model, with only

a very slight discrepancy in estimates of total costs. As such, the ERG is satisfied that the Markov component of the company's model has been implemented correctly and without significant error. Ultimately, the more substantive issues relate to the conceptualisation and implementation of the model, specifically in terms of deriving the baseline risks and treatment effects, as described above.

Table 45: Comparison of company's model and ERG's rebuilt model

	Company's model		**ERG rebuilt model**		**Difference**	
Primary prevention (based on LAPLACE-2 LDL-C>2.5mmol/L)						
Option	QALYs	Costs	QALYs	Costs	QALYs	Costs
Statins	11.56	£5,412.39	11.563	5412.390	0.00	£0.00
Ezetimibe+statins	11.84	£9,867.56	11.84	£9,867.56	0.00	£0.00
Evolocumab+statins	12.15	£75,020.08	12.15	£75,020.31	0.00	-£0.23
Secondary prevention (based on LAPLACE-2 LDL-C>2.5mmol/L)						
Option	QALYs	Costs	QALYs	Costs	QALYs	Costs
Statins	7.28	£17,959.38	7.28	£17,959.38	0.00	£0.00
Ezetimibe+statins	7.62	£20,302.09	7.62	£20,302.09	0.00	£0.00
Evolocumab+statins	8.06	£71,709.45	8.06	£71,710.11	0.00	-£0.65
HeFH (based on RUTHERFORD-2)						
Option	QALYs	Costs	QALYs	Costs	QALYs	Costs
Statins	8.04	£17,244.06	8.04	£17,244.06	0.00	£0.00
Ezetimibe+statins	8.86	£18,696.88	8.86	£18,696.88	0.00	£0.00
Evolocumab+statins	10.05	£72,262.24	10.05	£72,262.77	0.00	-£0.53

5.4 Conclusions of the cost effectiveness section

The CS includes a systematic review of economic evaluations of lipid-lowering therapies together with a *de novo* model-based economic evaluation to assess the incremental cost-effectiveness of evolocumab versus ezetimibe (both with or without statins) for the treatment of patients with LDL hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia.

The company's systematic review included 108 previously published economic evaluations. One of the included studies is the model developed to inform NICE CG181.[15] None of these assessed the cost-effectiveness of evolocumab.

The company developed *a de novo* health economic model to assess evolocumab versus ezetimibe (both with and without statins) in three populations:

(i) People with non-familial primary hypercholesterolaemia who have no history of CVD (primary prevention);

(ii) People with non-familial primary hypercholesterolaemia who have existing CVD (secondary prevention), and;

(iii) People with HeFH, comprising a mix of people who have no history of CVD and people who have existing CVD (primary and secondary prevention).

For all three populations, separate analyses are presented for people who are able to take statins (denoted ST) and for people for whom statins are contraindicated or not tolerated (denoted SI). The company's base case assesses evolocumab with/without statins; additional scenario analyses are presented in which evolocumab is used in combination with ezetimibe.

The company's base case model adopts a Markov approach and evaluates costs and health outcomes from the perspective of the NHS over a lifetime horizon. The model includes 24 mutually exclusive health states which include three individual "acute" event states (where patients remain for a maximum duration of one year unless they experience the same event during the next cycle), five individual "chronic" event states (including three "post-event" health states - post-ACS, post-IS and post-HF, as well as no CVD and ECVD), and thirteen composite CVD health states (including "acute" and "post-event" health states, which contain either two or three individual health states), and three death states (CHD death, stroke death and death due to other causes). The model is evaluated using an annual cycle length and is half-cycle corrected. Baseline characteristics for the non-familial primary and secondary prevention populations were based on IPD for a subset of people from the LAPLACE-2 trial[23] (those with LDL-C>2.5mmol/L), whilst baseline characteristics for the HeFH population were based on IPD from the modified ITT population of the RUTHERFORD-2 trial.[21] The model uses risk equations from the Framingham Heart Study and REACH Registry to predict CV risk and then adjusts these using calibration factors derived from an analysis of the CPRD/HES[13] or using literature.[55] For patients who are able to take statins, LDL-C treatment effects were based on the LAPLACE-2 trial.[23] For patients for whom statins are contraindicated or not tolerated, treatment effects were based on the GAUSS-2 trial.[24] The impact of lowering lipid levels was modelled based on an assumed relationship between LDL-C reduction and CV event reduction.[28] Health utilities were based on EQ-5D or TTO studies used in the NICE CG181 model.[15] Costs were based on the NHS Drugs Tariff,[61] NHS Reference Costs[62] the PSSRU[63] and a CPRD/HES costing analysis.[13]

The company's original base case model indicates the following results. Within the non-familial primary prevention ST population, the company's threshold analyses indicate that in people with a baseline LDL-C of 3.5mmol/L, the ICER for evolocumab plus statins versus ezetimibe plus statins would be below £30,000 per QALY gained in people with a 10-year CVD risk of 79% (or higher). The corresponding 10-year risk thresholds for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 73% and 70%, respectively. Within the non-familial primary prevention SI population with a baseline LDL-C of 3.5mmol/L, the ICER for evolocumab versus ezetimibe would be below £30,000 per QALY gained in people with a 10-year CVD risk of 81% (or higher). The corresponding 10-year risk thresholds for people with a baseline LDL-C of 4.0mmol/L and 4.5mmol/L are estimated to be 75% and 71%, respectively. Within the non-familial secondary prevention ST population, the company's base case analysis suggests that evolocumab plus statins is

expected to produce an additional 0.44 QALYs at an additional cost of £51,407 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £116,713 per QALY gained (probabilistic ICER=£119,012 per QALY gained). Within the non-familial secondary prevention SI population, the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.42 QALYs at an additional cost of £50,542 as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £119,971 per QALY gained (probabilistic ICER=£123,780 per QALY gained). Within the HeFH primary/secondary prevention ST population, the company's base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.20 QALYs at an additional cost of £53,565 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £44,741 per QALY gained (probabilistic ICER=£46,412 per QALY gained). Within the HeFH primary/secondary prevention SI population, evolocumab monotherapy is expected to produce an additional 1.10 QALYs at an additional cost of £51,749 as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £47,193 per QALY gained (probabilistic ICER=£48,362 per QALY gained).

The ERG critically appraised the company's economic analysis and partially double-programmed the company's health economic model using transition probabilities derived from the company's model. Whilst the ERG's rebuild of the Markov component of the model did not did not identify any major problems, serious programming/logic errors were identified in the transition probabilities used in the company's model whereby under certain combinations of parameter inputs, some of the model's transition probabilities and hence health state populations became negative. The ERG requested that the company submit an amended model which rectifies this problem. In response, the company acknowledged the problem and suggested that their results for the non-familial primary prevention population should be considered to be "invalid." The company also submitted an amended model and accompanying addendum[52] which includes an additional assumption which affects the risk predictions in the HeFH primary/secondary prevention population. The results for the non-familial secondary prevention population were unaffected by the company's amendments to the model.

The amendment to the company's model indicates the following results. Within the HeFH primary/secondary prevention ST population, the company's amended base case analysis suggests that evolocumab plus statins is expected to produce an additional 1.15 QALYs at an additional cost of £73,620 as compared with ezetimibe plus statins; the resulting ICER is estimated to be £47,195 per QALY gained (probabilistic ICER=£48,664 per QALY gained). Within the HeFH primary/secondary prevention SI population, evolocumab monotherapy is expected to produce an additional 1.05 QALYs at an additional cost of £52,486 as compared against ezetimibe monotherapy; the resulting ICER is expected to be £49,900 per QALY gained (probabilistic ICER=£51,061 per QALY gained).

The ERG has a number of concerns regarding the company's implemented model; some of these represent major mathematical errors whilst others indicate the improper use of the available evidence. Consequently, the ERG has serious doubts regarding the validity of the results presented within the CS and would advise considerable caution in their interpretation and use in informing decision-making. The key issues identified by the ERG are briefly summarised in Table 46. Owing to the problems discussed in Section 5.3, the ERG did not consider it appropriate or valuable to undertake additional exploratory analyses using either the original or amended versions of the company's model.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Table 46 summarises the main concerns expressed by the ERG following the critical appraisal of the CS and submitted company's model.

Table 46: Summary of key concerns identified by the ERG

Deviations from the NICE reference case • Only the subgroup of patients with LDL-C>2.5mmol/L is included in the non-familial analyses • Difficulties in interpreting results from the mixed (primary and secondary prevention) HeFH population
Concerns regarding the conceptualisation and implementation of the company's model structure and logic • Use of a Markov approach which lacks flexibility. • Conceptual representation of the condition (choice of health states, use of LDL-C reduction as a surrogate for CVD events). Lack of clarity on selection and appropriateness of health states included in the company's model. • Model process and logic (circular approach). Direct data on CVD events from CPRD/HES could have been used directly to estimate CVD event probabilities. • Model implementation and misspecification of evidence inputs (including misinterpretation of the REACH predictions, absence of constraints leading to negative probabilities, inconsistent approach to estimating treatment effects and the baseline LDL-C, over-estimation of event risk in the HeFH population).
Concerns regarding the baseline characteristics/populations included in the company's analyses • Uncertainty with respect to whether the populations included in the LAPLACE-2 and RUTHERFORD-2 trials are representative of patients with primary hypercholesterolaemia in England. • Inclusion of only those patients in LAPLACE-2 who had a baseline LDL-C>2.5mmol/L. It is unclear whether this truly reflects a high-risk population who may benefit from treatment using evolocumab. • Same baseline characteristics assumed for patients who are able to take statins and those for whom statins are contraindicated or not tolerated. • Arbitrary manipulation of trial data for the subgroup analyses in patients with diabetes and/or additional risk factors
Issues regarding the use of CVD risk equations and the need for subsequent calibration • Use of risk equations rather than direct data on event rates • Misuse of the REACH equations • Use of the Framingham and REACH equations for the HeFH population

Concerns regarding the derivation of calibration factors to adjust the baseline risk of CVD for the raised LDL-C analysis

- Estimation of calibration factors for primary prevention in people with diabetes. It is uncertain if the resulting calibration factors would be appropriate for the population included in the economic model which does not have diabetes.
- Complicated age adjustment used to compare the predictions from the risk equations with the event rates in the CPRD/HES data.
- Calibration factors estimated for secondary prevention for non-fatal events incorrect due to the misuse of the REACH equations.
- Assumptions used whereby baseline characteristic variables are not available in the CPRD/HES dataset (AF and number of vascular beds).
- Potential selection biases. Linking data from the CPRD, HES and ONS meant that only half of the people could be linked and included in the analysis.

Issues surrounding the derivation of the calibration factor to adjust the baseline risk of CVD for people with HeFH

- Benn *et al*[55] compares CVD event risk between the HeFH population and the general population. Application of this relative risk to an already high-risk population (LDL-C≥2.5mmol/L is likely to over-estimate CVD event risk for patients with HeFH.
- Other sources suggest a lower risk of CVD in the HeFH population.

Concerns regarding the appropriateness of treatment effects

- Use of treatment difference at mean of week 10/12 between evolocumab and ezetimibe compared with statins rather than the difference from baseline
- Use of treatment effect from LAPLACE-2 for the HeFH population (rather than RUTHERFORD-2)
- Uncertainty regarding duration of LDL-C improvement.

Comments regarding the relationship between LDL-C reduction and CVD events

- Assumed relationship for HF equal to relationship observed for non-fatal MI (this is a matter of debate as there is no evidence that LDL-C lowering is associated with a reduction in HF).
- Use of a relative risk of 1.0 for IS death rather than 1.04
- Use of a relative risk of 0.8 for CHD death rather than 0.84
- Assumed relationship for ACS for people transitioning from 'No CVD' to 'ECVD'.
- Unclear whether LDL-C reduction is associated with a reduction in CHD death following HF
- Effect of LDL-C reduction is assumed to be independent between non-fatal and fatal CVD events

Limited relevance of health utility estimates

- Systematic review of HRQoL studies does not appear to be used.
- Of the seven acute and post-event state utilities used in the model, only three of these (ACS, HF and post-HF) are based on EQ-5D valuations.

Discrepancies in the cost parameters used in the company's model

- Patent expiry of ezetimibe
- Discrepancies in monitoring cost assumptions

Errors in the interpretation/reporting of health economic results

- Errors in the interpretation of the results presented in the tables within the CS
- Reporting of redundant ICERs in the CS
- Misinterpretation of the primary prevention LDL-C threshold analyses.

As a consequence of the issues outlined in Table 46, the ERG has serious doubts regarding the validity of the cost-effectiveness results presented within the CS and would advise considerable caution in their interpretation and use in informing decision-making.

7 END OF LIFE

End of life criteria were not relevant to this submission.

8 OVERALL CONCLUSIONS

The principal efficacy review represents a good quality systematic review of four relevant, good quality RCTs. The trials were generally consistent with the NICE scope. The primary efficacy outcome was mean percentage change in LDL-C from baseline, and mean treatment difference across trial arms, at follow-ups of 12 weeks (LAPLACE-2, GAUSS-2, DESCARTES and RUTHERFORD-2) and 52 weeks (DESCARTES).

In the LAPLACE-2 trial, at 12 weeks, patients with primary hypercholesterolaemia on background atorvastatin therapy (intensive and non-intensive doses) had a treatment difference in mean percentage change in LDL-C from baseline of -46.9 (95% CI, -53.0 to -40.7, $p<0.001$) and -42.5 (95% CI, -47.9 to -37.0, $p<0.001$) for the Q2W and QM doses of evolocumab respectively, compared with ezetimibe (fixed effects model).

In the GAUSS-2 trial, at 12 weeks, patients with primary hypercholesterolaemia who were statin intolerant had a treatment difference in mean percentage change in LDL-C from baseline of -39.3 (95% CI, -45.0 to -33.5, $p<0.001$) and -38.1 (95% CI, -42.9 to -33.4, $p<0.001$) for the Q2W and QM doses of evolocumab compared with ezetimibe.

In the placebo-controlled RUTHERFORD-2 trial, at 12 weeks, patients with HeFH on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -62.7 (95% CI, -66.3 to -59.1) and -56.6 (95% CI, -60.9 to -52.3) for the Q2W and QM doses of evolocumab, respectively. The treatment difference in mean percentage change compared with placebo was -60.6 (95% CI, -66.7 to -54.5, $p<0.001$) and -60.3 (95% CI, -67.8, -52.9, $p<0.001$) for the Q2W and QM doses of evolocumab, respectively. The ERG received clinical advice that the HeFH population of the RUTHERFORD trial with a confirmed genetic mutation was higher than might be found in usual clinical practice in the UK, but the implications of this are unclear. The ERG also noted, following clinical advice, that the proportion of patients with CHD was higher in the intervention arms of the RUTHERFORD-2 trial (i.e. 30-36%) compared with what would be expected in clinical practice in a HeFH population, and was higher than the prevalence reported for the other three trials (e.g. LAPLACE-2 trial arm populations ranged from 17% to 24% with CHD characteristics).

In the placebo-controlled DESCARTES trial, patients with primary hypercholesterolaemia on background statin therapy (intensive and non-intensive doses) had a mean percentage change in LDL-C from baseline of -50.6 (95% CI, -53.2 to -48.0) for the QM dose of evolocumab at 52 weeks. The

treatment difference in mean percentage change compared with placebo was -59.3 (95% CI, -63.8 to -54.9, $p<0.001$) at 52 weeks.

The results for other lipid parameters, such as non-HDL-cholesterol, HDL-cholesterol, triglycerides, apolipoprotein B and lipoprotein(a), were consistent with the results for LDL-C, and pre-specified subgroup analyses demonstrated that these results were not sensitive to the different doses of evolocumab, or other key variables, such as LDL-C baseline levels, severity of hypercholesterolaemia or CVD risk factors. The ERG noted that only 12-week evidence was available for the efficacy of the Q2W dose, while the QM dose had some data for 52 weeks. Additional clinical efficacy evidence was provided from a non-RCT study (TAUSSIG) and two open-label, extension trials (OSLER1 and 2). However, the extension studies included some trials with populations and/or comparators that were excluded from the principal review of four RCTs and it is unclear how these trials and the non-RCT study were identified for inclusion in the company's review. The inclusion of these studies was justified by the company on account of the longer-term evidence both from the extension studies and from TAUSSIG on the HeFH subgroup (36 weeks). An NMA was not performed, although this might have been possible using particular trial evidence from both the primary non-familial hypercholesterolaemia population and the HeFH subgroup.

The clinical effectiveness review found that evolocumab is efficacious at lowering LDL-C, but in itself this is not a clinically important outcome: its importance is derived from it being a surrogate for CVD. Although there is an established relationship between statin-generated LDL-C reduction and reduced CV events, the impact of evolocumab on CVD has not been demonstrated: there is little or no direct evidence on this relationship. The ongoing FOURIER trial (clinicaltrials.gov identifier NCT02207634) aims to evaluate the impact of evolocumab on CVD outcomes, but only in people who have already had a CV event. The ERG also noted that there was no evidence on the relative efficacy of evolocumab versus ezetimibe in the familial hypercholesterolaemia subgroup, or for evolocumab in combination with ezetimibe in any population, and there was little or no direct trial evidence for evolocumab in terms of health-related quality of life or apheresis.

The submission of safety evidence was a non-systematic review of good quality RCTs, providing evidence for up to two years. There were no obvious safety concerns, with most AEs being balanced across evolocumab and comparator trial arms, and very small numbers of SAEs. However, the ERG noted that relatively higher 12-week AE rates were reported in patients who had HeFH or who had primary non-familial hypercholesterolaemia and were statin-intolerant. Similarly, these rates were also relatively higher for trials with a longer follow-up duration. This suggests that some patient subgroups might experience more frequent events and that all patients are at risk of AEs over time, though the rates are generally similar to comparators. The ERG noted also that the longer-term

evidence presented was derived from some trials with populations who would not be eligible to receive evolocumab in clinical practice in the NHS (e.g. people who were not on maximum-tolerated doses of statins). More long-term data are therefore needed in relevant UK populations, although it is not clear whether ongoing trials will address this.

Based on the company model, the probabilistic ICERs for evolocumab against ezetimibe are above £119,000 per QALY gained within the non-familial population and are approximately £49,000 within the HeFH population. However, the ERG has a number of concerns regarding the company's implemented model; some of these represent major mathematical errors whilst others indicate the improper use of the available evidence. The key concerns identified by the ERG can be separated into four sets of issues: (a) the company's general modelling approach; (b) the conceptual representation of the condition; (c) the model process and logic; and; (d) model implementation and misspecification of evidence inputs. The ERG also expresses concerns regarding the conduct of the analysis for the HeFH population. These conceptual and structural problems are complex and intertwined, and the resolution of individual issues in isolation would not result in an appropriate or credible model. Rather, the ERG considers that the joint resolution of these problems would require a full "rethinking" of the model's logic. Consequently, the ERG has serious doubts regarding the validity of the results presented within the CS and would advise considerable caution in their interpretation and use in informing decision-making. As such, the expected cost-effectiveness of evolocumab in the non-familial and HeFH populations is unclear.

8.1 Implications for research

Future research should seek to address the following key areas of uncertainty:

- The efficacy of evolocumab in reducing the risk of CVD in all populations (adults with familial and non-familial primary hypercholesterolaemia), especially in comparison with ezetimibe.
- The efficacy of evolocumab in combination with ezetimibe compared with ezetimibe alone in all populations (adults with familial and non-familial primary hypercholesterolaemia).
- The impact of evolocumab on HRQoL and apheresis in the short- and long-term.

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