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Title:

Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: An Evidence Review Group perspective of a NICE Single Technology Appraisal

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Running title:

Evolocumab for primary hypercholesterolaemia and mixed dyslipidaemia

This article contains a number of corrections to the Online First version of the paper.

Abstract

As part of its Single Technology Appraisal (STA) process, the National Institute for Health and Care Excellence (NICE) invited the manufacturer of evolocumab (Amgen) to submit evidence on the clinical effectiveness and cost-effectiveness of evolocumab. The appraisal assessed evolocumab as monotherapy or in combination with a statin with or without ezetimibe, or in combination with ezetimibe (without statin therapy), in adult patients with primary hypercholesterolaemia (which includes mixed dyslipidaemia), for whom statins do not provide optimal control of their low-density lipoprotein cholesterol (LDL-C) levels and/or for whom statins are contraindicated or not tolerated. The School of Health and Related Research Technology Appraisal Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). The ERG produced a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology, based on the company's submission to NICE. The evidence was derived mainly from four randomised controlled trials comparing evolocumab either with ezetimibe or placebo in adults with primary familial or non-familial hypercholesterolaemia, who were either able to take statins or who were statin-intolerant. The clinical effectiveness review found that evolocumab is efficacious at lowering LDL-C, but that there was uncertainty regarding its impact on cardiovascular disease (CVD) outcomes. In response to the ERG's critique of the submitted health economic model, the company submitted an amended model, which also included a Patient Access Scheme (PAS). Based on this, the deterministic ICERs for evolocumab against ezetimibe were above £74,000 and £45,000 per QALY gained within the non-familial primary and secondary prevention population, respectively, whilst the ICERs within the Heterozygous Familial Hypercholesterolaemia (HeFH) population were approximately £23,000 per QALY gained. The final determination was that evolocumab would be a clinically and cost-effective use of NHS resource in certain patient subgroups.

Key points for decision-makers:

- Guidance on lipid-lowering therapies emphasises managing cardiovascular disease (CVD) risk rather than targeting cholesterol concentrations.
- Evolocumab is efficacious and safe in reducing low-density-lipoprotein cholesterol (LDL-C) in adults with primary familial and non-familial hypercholesterolaemia, but there is uncertainty regarding the impact of evolocumab on CVD, apheresis and health-related quality of life: there is little or no direct evidence on these key outcomes.
- Inferences have had to be made regarding the impact of evolocumab on CVD risk reduction, based on the evidence for statins and ezetimibe, because of high clinical unmet need and high risk of CVD in patient groups with inadequately-controlled LDL-C.
- The Evidence Review Group had doubts regarding the validity of the company's model results. In the final guidance, the Appraisal Committee agreed that evolocumab would be a clinically and cost-effective use of NHS resource in certain patient subgroups. Guidance is to be reviewed when a current, ongoing trial reports on the relationship between evolocumab and CVD outcomes.

1. **INTRODUCTION**

Health technologies must be shown to be clinically effective and to represent a cost-effective use of National Health Service (NHS) resources to be recommended for use within the NHS in England and Wales. The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health, and preventing and treating ill health, in priority areas with significant impact. The NICE Single Technology Appraisal (STA) process usually covers new technologies soon after they have received UK marketing authorisation and is specifically designed for the appraisal of a single health technology within a single indication [1].

Within the STA process, the manufacturer of a technology provides NICE with a written submission, containing relevant clinical effectiveness evidence alongside a mathematical model that summarises that company's estimates of the cost-effectiveness of the technology. This submission is reviewed by the Evidence Review Group (ERG), an external academic organisation independent of NICE, with advice from clinical specialists, and an ERG report is produced. After consideration of the company's submission (CS), the ERG report, and testimony from experts and other stakeholders, the NICE Appraisal Committee (AC) formulates the preliminary guidance, the appraisal consultation document (ACD), which indicates the initial decision of the AC regarding the recommendation (or not) of the intervention. Stakeholders are then invited to comment on the submitted evidence and the ACD, after which a subsequent ACD may be produced or a final appraisal determination (FAD) is issued, which is open to appeal. An ACD is not produced when the intervention is recommended without restriction; in such instances, a FAD is produced directly.

This paper presents a summary of the ERG report [2] and FAD [3] for the STA of evolocumab for adult patients with primary familial and non-familial hypercholesterolaemia (which includes mixed dyslipidaemia), for whom statins do not provide optimal control of their low-density lipoprotein cholesterol (LDL-C) levels and/or for whom statins are contraindicated or not tolerated. It also covers the subsequent development of the NICE guidance for the use of this drug in England. Full details of all relevant appraisal documents can be found on the NICE website [4].

2. DECISION PROBLEM

Hypercholesterolaemia, a type of hyperlipidaemia, specifically refers to an excessive total plasma cholesterol concentration in the blood of approximately $\geq$3mmol/L, especially LDL-C [5]. Primary hypercholesterolaemia can be familial or non-familial. The former population is principally composed of the heterozygous familial hypercholesterolaemia (HeFH) subgroup, which is most commonly diagnosed in the UK using the Simon Broome criteria [6, 7], with diagnosis increasingly confirmed with genetic mutation test [8]. LDL-C levels in people with HeFH are typically two to three times higher than normal [9, 10]. The prevalence of HeFH within primary hypercholesterolaemia in the UK is traditionally stated as 0.2% [5], but recent surveys suggest that up to one in every 300 people are affected worldwide [11]. Non-familial primary hypercholesterolaemia is defined as elevated LDL-C produced by a combination of effects caused by a variety of genes allied with nutritional and lifestyle factors

[5]. The exact role of genetic inheritance in producing elevated LDL-C levels is unclear [12]. 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 [5]. "Mixed dyslipidaemia" is a type of lipid disorder which is termed in the literature as "combined hyperlipidaemia", a disorder which is characterised by elevated LDL-C and high triglycerides (>1.7 mmol/L) and/or reduced or elevated high-density lipoprotein cholesterol (HDL-C). Like primary non-familial hypercholesterolaemia, it is also relatively common; approximately 10% of people with raised cholesterol in the UK have "mixed dyslipidaemia"[5]. Elevated LDL-C is one of the risk factors for cardiovascular disease (CVD) [13]. CVD can have major health and economic implications both for people and for health services; it remains the most common cause of mortality in women and the second most common cause of mortality in men in England [14].

2.1 Current treatment

The principal lipid-lowering therapies currently prescribed for hypercholesterolaemia are statins, most commonly atorvastatin (dose based on risk of CVD, with a maximum dose of 80mg) and ezetimibe (based on inadequate LDL-C control by statins or statin intolerance or contraindication) [15, 16]. Recent years have seen consistent increases in prescription rates for lipid-lowering therapies in England, with the aim of reducing CVD risk [14].

Evolocumab (Repatha®) 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-C from the blood [17]. By binding to PCSK9, evolocumab increases the number of LDL receptors expressed by the liver, thereby reducing serum LDL-C levels. The benefits of evolocumab are its ability to reduce the level of serum LDL-C in patients who are unable to control their cholesterol despite taking a maximum tolerated dose of statins, or in patients who cannot tolerate or take statins. Evolocumab is given as either one dose (140mg) every 2 weeks (Q2W) or three doses (420mg) every month (QM), administered by subcutaneous injection via a prefilled pen or syringe. The intervention is designed to be self-administered by the patient after proper training. Evolocumab is indicated in adults with primary hypercholesterolaemia (HeFH and non-familial) or mixed dyslipidaemia, as an adjunct to diet. It is to be used in combination, either with a statin or with a statin plus other lipid lowering therapies, in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or it is to be used, either as monotherapy or in combination with other lipid-lowering therapies, in patients who are statin-intolerant, or for whom a statin is contraindicated [17]. It is also indicated for use in populations with homozygous familial hypercholesterolaemia (HoFH).

The CS in this STA proposed evolocumab as an alternative to ezetimibe 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. Evolocumab is also proposed as a treatment, in combination with ezetimibe, when response to monotherapy is considered inadequate. Eligible patients are therefore considered to be those at high-risk of a CVD event on account of inadequately-controlled LDL-C levels due either to the inappropriateness of statin therapy or

due to the failure of a maximum-tolerated dose of statins. This includes people with HeFH; people with HoFH were not covered by this appraisal.

In May 2015, NICE issued a final scope to appraise the clinical effectiveness and cost-effectiveness of evolocumab for the treatment of patients with primary familial and non-familial hypercholesterolaemia [4]. The principal efficacy outcomes for consideration were plasma lipid and lipoprotein levels, including LDL-C, non-HDL-C, HDL-C, triglycerides (TG), apolipoprotein B (ApoB) and lipoprotein(a) (Lp(a)). 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 CVD events, citing the meta-analyses of the Cholesterol Treatment Trialists' Collaboration (CTTC), which found that a reduction of 1mmol/L might lead to 22% reduced risk of CVD events [18-21]. CVD events include myocardial infarction (MI) and unstable angina (collectively referred to as Coronary Heart Disease [CHD]), stroke, transient ischaemic attack (TIA) and peripheral artery disease (PAD) [22]. However, the optimal LDL-C level required to minimise CVD risk is not known. The principal safety outcomes were all also considered and reported in the CS: nasopharyngitis, upper respiratory tract infection, headache and back pain. The company submitted a de novo health economic model which assessed the cost-effectiveness of evolocumab in terms of the incremental cost per quality-adjusted life-year (QALY) gained [4].

3. INDEPENDENT EVIDENCE REVIEW GROUP (ERG) REPORT

The ERG report comprised a critical review of the clinical and cost-effectiveness evidence presented in the CS, and assessed the appropriateness of the company's analysis and interpretation of the evidence. In accordance with the STA process, the ERG had the opportunity to seek clarification on specific points in the CS, which resulted in the company providing additional information [1].

3.1 Clinical evidence submitted by the company

The clinical evidence submitted by the company consisted of: (i) a review of the clinical efficacy evidence from randomised controlled trials (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 non-randomised studies. The principal clinical efficacy review included four relevant RCTs. Two trials compared evolocumab with ezetimibe in adults with primary non-familial hypercholesterolaemia, who were either able to take statins (LAPLACE-2) [23] or who were statin-intolerant (GAUSS-2) [24]. The other two trials were placebo-controlled: one was undertaken in adults with primary non-familial hypercholesterolaemia (DESCARTES) [25] and one trial was undertaken in adults with HeFH (RUTHERFORD-2) [26]. 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 low risk of bias by the company and ERG following quality assessment using the Cochrane risk of bias 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-up durations. Both of these values were reported for follow-up at 10 and 12 weeks; 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 statin and comparator treatments).

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, compared with ezetimibe (fixed effects model), of -46.9 (95% confidence interval [CI], -53.0 to -40.7, p<0.001) and -42.5 (95% CI, -47.9 to -37.0, p<0.001), respectively, for the Q2W and QM doses of evolocumab. 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, compared with ezetimibe, 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.

In the placebo-controlled RUTHERFORD-2 trial, at 12 weeks, patients with HeFH on background statin therapy (intensive and non-intensive doses) had a treatment difference in mean percentage change compared with placebo of -60.6 (95% CI, -66.7 to -54.5, p<0.001) and -60.3 (95% CI, -67.8, -52.9, p<0.001), respectively, for the Q2W and QM doses of evolocumab. The ERG received clinical advice that the proportion of the HeFH population in the RUTHERFORD-2 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. Clinical advisors to the ERG also noted 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 an HeFH population, and was also 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 treatment difference in mean percentage change compared with placebo of -59.3 (95% CI, -63.8 to -54.9, p<0.001) at 52 weeks.

Detailed results were also provided in the main submission and appendices for other lipid parameters, as well as pre-specified and post hoc subgroup analyses based on key covariates. The CS reported that evolocumab provided consistent and intensive reductions in LDL-C compared with ezetimibe and placebo, regardless of patient population, dosing regimen, CVD risk, and presence or type of background lipid-lowering therapy. The results presented within the CS were based on the full analysis set (FAS) of the trials rather than the data reported in the original publications. The CS also provided additional efficacy evidence from two open-label extension (OLE) studies, which included some slightly different populations in terms of baseline LDL-C and ethnicity (OSLER 1 and 2) [27], and a single non-RCT (TAUSSIG) undertaken within the HeFH subgroup [28]. 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. The CS 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 CVD events and non-coronary revascularisations, where such evidence was available. The CS concluded that the AEs were overall balanced between groups in all three periods of the integrated safety data set (12 weeks, 1 year and 2 years), as well as across populations and therapeutic settings, and that most AEs were mild to moderate in severity. It also concluded that 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: OSLER 1 and 2 [27], FOURIER [29] and EBBINGHAUS [30].

3.1.1 Critique and interpretation of the clinical evidence

The principal efficacy review represented a good quality systematic review which identified four relevant, good quality RCTs. The trials were generally consistent with the final NICE scope. The results for LDL-C and other lipid parameters, such as non-HDL-cholesterol, were consistent, 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 (OSLER 1 and 2). However, some participants in the extension studies were recruited from 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 their longer-term evidence. The included efficacy RCTs also excluded potentially relevant patients, such as those with diabetes. A network meta-analysis (NMA) was not performed, although it was concluded by the ERG it may have been useful in order to quantify the uncertainty associated with the treatment effects, as required for subsequent health economic analyses.

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 and statin-intolerant patients who had primary non-familial hypercholesterolaemia. Similarly, AE 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 increased risk of AEs over time, although 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 were therefore needed in relevant UK populations, although it was unclear whether ongoing trials would address this.

3.2 Cost-effectiveness evidence provided by the company

The company submitted a model-based health economic analysis as part of their submission to NICE. Following the identification of programming errors and inconsistencies by the ERG, revised versions of the model were submitted by the company during the clarification process and, again, following submission of the ERG report. The analysis was undertaken from the perspective of the NHS over a lifetime horizon. Costs and health outcomes were discounted at a rate of 3.5% per annum. The company's analysis was presented for 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 with no history of CVD and patients with existing CVD (primary and secondary prevention). For all three populations, separate analyses were presented for patients who are able to take statins (hereafter denoted "ST" - statin tolerant) and for patients for whom statins are contraindicated or not tolerated (hereafter denoted "SI" – statin intolerant). The company's base case analysis assessed evolocumab with/without statins. Within all three analyses, modelled comparators included ezetimibe (both with and without statins). Additional scenario analyses were presented in which evolocumab was assumed to be used in combination with ezetimibe.

The company's base case model adopted a Markov approach, using an annual cycle length and comprised 24 mutually exclusive health states: three individual "acute" event states (acute coronary syndrome [ACS], ischaemic stroke [IS], heart failure [HF]), 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 "established" CVD (ECVD); 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).

Baseline characteristics for the non-familial primary prevention and secondary prevention populations were based on the subset of patients in the LAPLACE-2 trial who had LDL-C>2.5mmol/L [23]. Baseline characteristics for the HeFH population were based on the modified intention-to-treat (ITT) population of the RUTHERFORD-2 trial [26]. The model used risk equations from the Framingham Heart Study [31] and REduction of Atherothrombosis for Continued Health (REACH) Registry [32] to predict CVD risk (prior to evolocumab or ezetimibe) and then adjusted these using "calibration factors" derived from an analysis of data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) for the non-familial population[33], or using a calibration factor from Benn et al [34] for the HeFH population.

LDL-C reduction is used as a surrogate for a reduction in CVD events. The relationship between LDL-C reduction and CVD event reduction was taken from the CTTC meta-analysis [18]. For the ST population, LDL-C treatment effects were based on the LAPLACE-2 trial [23]. For the SI population, treatment effects were based on the GAUSS-2 trial [24]. Health utilities were based on Euroqol-5D (EQ-5D) and time trade-off (TTO) studies used in

the NICE Clinical Guideline(CG) 181 model[15]. The model included the costs 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 were not included in the company's model. All costs were valued at 2013/14 prices. Unit costs were taken from the NHS Drugs Tariff, NHS Reference Costs [35], the Personal Social Services Research Unit (PSSRU) [36] and a CPRD/HES costing analysis undertaken by the company [33].

The CS contained a large range of analyses, including cost-effectiveness analyses within whole cohorts of patients and threshold analyses to determine the 10-year CVD risk at which the incremental cost-effectiveness ratio (ICER) for evolocumab would be below £20,000 or £30,000 per QALY gained. Based on the list price analyses, the probabilistic ICERs for evolocumab versus ezetimibe were considerably higher than £30,000 per QALY gained within the non-familial population and the HeFH population. In response to the critique presented in the ERG report, the company submitted a further amended health economic model which addressed some of the ERG's concerns regarding the company's original model and included a Patient Access Scheme (PAS) for evolocumab based on a confidential simple price discount. Based on the company's amended model and including the PAS, the deterministic ICERs for evolocumab against ezetimibe were above £74,000 and £45,000 per QALY gained within the non-familial primary and secondary prevention population, respectively, whilst the ICERs within the HeFH population were approximately £23,000 per QALY gained.

3.2.1 Critique and interpretation of the cost-effectiveness evidence

The ERG critically appraised the company's health economic analyses and the models upon which these analyses were based. The ERG identified a number of programming errors and inconsistencies, some of which were rectified by the company following the clarification process and following the submission of the ERG report. The ERG's main concerns related to four sets of issues: (a) the conceptual representation of the condition; (b) model process and logic; (c) model implementation and mis-specification of evidence inputs, and; (d) uncertainties regarding the relationship between LDL-C reduction and CVD events. The ERG also noted further concerns relating to the derivation of certain input parameters, the reporting of results, health state utilities and costs. Owing to the limitations in the company's model, the ERG had doubts regarding the validity of the results presented within the CS and advised considerable caution in their interpretation and use in informing decision-making.

(a) 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. In particular, the ERG noted that the health states used in the company's model are different from those used in the NICE CG181 model [15]. The CS did not include a description of how the health states were selected nor did it explain why these should be considered more relevant than those states included in NICE CG181 [15] or other published models. In particular, the company's model had the following features: (a) the inclusion of

HF as a health state; (b) the inclusion of IS but not haemorrhagic stroke, 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 noted the lack of evidence for the impact of cholesterol-lowering therapies on HF. Furthermore, the company did not provide any justification regarding the inclusion of only IS. Whilst it is plausible that people may experience multiple different types of CVD 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 in order to populate these cells in the transition matrix.

(b) Model process and logic

For the analysis of patients with non-familial primary hypercholesterolaemia, the company's model uses a three-step approach to estimate the risk of CVD events. This involves: (i) using the Framingham [31] and the REACH Registry [32] equations to predict the baseline risk of CVD events depending on individual characteristics in a subset of the LAPLACE-2 trial [23]; (ii) estimating calibration factors to adjust predictions from the Framingham [31] and REACH [32] equations to "real world data" estimated from the company's analysis of CPRD/HES data [33], and; (iii) adjusting the baseline risks estimated using the Framingham and REACH Registry equations by these estimated calibration factors. The ERG considered the company's approach to be circular, overly-complicated and counter-intuitive, as it required a number of assumptions and adjustments (such as removing the effect of age and sex) when estimating and applying the calibration factors. The ERG considered that it would have been more appropriate to estimate baseline CVD risk from the CPRD/HES data directly and to adjust these subsequently using relative risks from the published literature to reflect additional risk factors for subgroups, where appropriate.

(c) Model implementation and misspecification of evidence inputs

The ERG identified several inconsistencies and errors in the implementation of the company's model. First, the company's model incorrectly treated the predictions from the Framingham [31] and REACH Registry [32] risk equations as event rates rather than probabilities. Second, the model misinterpreted what the REACH Registry risk equations are predicting [32]; the model incorrectly treated predictions from the REACH Registry risk equations for "next CVD event" and "CVD death" as being independent of one another and incorrectly assumed that the risk for "next CVD event" predicted by the REACH Registry equation included only non-fatal events. Taken together with the absence of constraints, this led to mathematical inconsistencies when the risk of fatal and non-fatal CVD events was high. In addition, the ERG also noted a mismatch in evidence whereby the treatment effect used in the model did not match the baseline LDL-C level of the population from which it is estimated. With respect to the HeFH population, the company estimated the risk of CVD events using the Framingham [31] and REACH Registry [32] risk equations in the RUTHERFORD-2 trial and then adjusted these using a rate ratio estimated from Benn et al [34], calculated between the general population and patients with HeFH. The ERG considered this to be inappropriate as the baseline risk in the non-familial population used in the company's model already reflects people who are at a higher risk due to higher baseline cholesterol.

(d) Uncertainty regarding the relationship between LDL-C reduction and reductions in CVD events

The company's model applied a relationship between LDL-C reduction and reduction in CVD events, quantified in terms of the proportional reduction in specific CVD events per mmol/L reduction in LDL-C, based on the CTTC meta-analysis [18]. Owing to the lack of data, the model included a number of debatable assumptions and simplifications. Notably, the relationship estimated by the CTTC related to the first (recurrent) CVD event; it is unclear whether the relationship would be maintained for subsequent events. It is also unclear whether the relationship estimated from the CTTC meta-analysis in people receiving statins would hold for evolucumab and ezetimibe. In addition, the company's model further assumed that the relationship between LDL-C reduction and non-fatal MI would hold for HF (first event). Assumptions were also made for the effect of LDL-C reduction on ECVD. The relative reduction in fatal CVD 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 CVD events is correlated with the reduction in non-fatal events.

3.3 Additional work undertaken by the Evidence Review Group

Owing to the number of problems identified within the company's model, the ERG did not consider it appropriate or valuable to undertake additional exploratory analyses prior to the first AC meeting.

3.4 Conclusions of the Evidence Review Group Report

The ERG recognised that the CS included a good-quality systematic review of the efficacy evidence and that the four key RCTs were all good quality and at low risk of bias. Results were consistent across trials for both efficacy and safety outcomes. The clinical review found that evolocumab was efficacious at lowering LDL-C. It also found that evolocumab was safe. However, the safety evidence, though extensive, was derived in part from trial populations that did not reflect the patients likely to present in UK clinical practice, and AE rates appeared to be higher in some subgroups; the provision of more long-term safety evidence in these populations was therefore a recognised requirement. The ERG noted that the longer-term efficacy and safety evidence from the DESCARTES placebo-controlled trial (52 weeks rather than 12 weeks) related only to the evolocumab QM dose; there were no equivalent data for the Q2W dose. The ERG also noted that there was no evidence on the relative efficacy of evolocumab compared with ezetimibe in the familial hypercholesterolaemia subgroup, or for evolocumab in combination with ezetimibe compared with placebo in any population, and there was little or no direct trial evidence for evolocumab in terms of HRQoL or apheresis. The ERG also noted that, whilst LDL-C is an accepted surrogate outcome for CVD for statins, there was little direct evidence for the relationship between evolocumab and CVD events (as a safety outcome). This was the rationale behind the ongoing FOURIER trial (clinicaltrials.gov identifier, NCT01764633[29]) (Table 1), which aims to evaluate the impact of evolocumab on CVD outcomes, but only in people who have already had a CVD event.

Table 1: Relevant ongoing study of evolocumab (FOURIER)

[INSERT TABLE 1 HERE]

Based on the company model, (excluding revisions to scenarios presented by the company after the Appraisal Committee meetings), the probabilistic ICERs for evolocumab versus ezetimibe were considerably higher than £30,000 per QALY gained within both the non-familial population and the HeFH population prior to the inclusion of the PAS. Including the PAS, the deterministic ICERs for evolocumab versus ezetimibe were above £74,000 and £45,000 per QALY gained within the non-familial primary and secondary prevention population, respectively, whilst the ICERs within the HeFH population were approximately £23,000 per QALY gained. However, the ERG had doubts regarding the validity of the results presented by the company and advised caution in their interpretation and use in decision-making. As such, the expected cost-effectiveness of evolocumab in the non-familial and HeFH populations remains unclear.

4. KEY METHODOLOGICAL ISSUES

The health economic model submitted by the company was subject to a number of methodological issues, including the estimation of the risk of CVD events and the reliance on the use of a surrogate endpoint to predict the effect of evolocumab on CVD events. 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 same relationship between LDL-C and CVD events observed for statins would also hold for evolocumab and ezetimibe.

5. NATIONAL INSTITUTE OF HEALTH AND CARE EXCELLENCE (NICE) GUIDANCE

In May 2016, on the basis of the evidence available, including verbal testimony from invited clinical experts and patient representatives, the AC produced the following final guidance to the NHS in England (TA335) [3]. Evolocumab was recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:

- The dosage is 140 mg every 2 weeks (Q2W)
- LDL-C concentrations are persistently above the thresholds specified in Table 2 despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached, or further titration is limited by intolerance, as defined in NICE's guideline on the identification and management of familial hypercholesterolaemia (CG71) [37].
- The company provides evolocumab with the discount agreed in the PAS.

Table 2: LDL-C concentrations above which evolocumab is recommended

[INSERT TABLE 2 HERE]

5.1 Consideration of clinical effectiveness and cost-effectiveness issues included in the Final Appraisal Determination (FAD)

The full list of the issues considered by the AC can be found in the FAD [3]. The key issues are described in the following sections.

5.1.1 Uncertainties in the clinical evidence

The committee agreed that the included RCTs were relevant and of good quality, and noted that evolocumab effectively reduced LDL-C by 60–70% compared with placebo in patients with HeFH, and around 40% compared with ezetimibe in patients who were statin intolerant. It also noted that, despite the omission of potentially relevant patients from the trials, such as those with diabetes, the results could be generalised to clinical practice in England. However, the committee noted that current guidance on lipid-lowering therapies emphasises managing CVD risk rather than targeting cholesterol concentrations, and that the evolocumab RCTs were not powered to measure CVD outcomes. The committee considered this to be an important limitation of the evidence base. It therefore concluded that the extent to which evolocumab could reduce CVD was still uncertain, particularly with low concentrations of LDL-C at baseline (<3.5mmol/L). However, it accepted the potential impact of evolocumab on CVD risk based on the evidence for the alternative therapies, statins and ezetimibe [18, 21]. It also took into account clinical advice indicating that groups at high risk of CVD, based on inadequately-controlled LDL-C after treatment with statins and/or ezetimibe, have few alternative treatment options, and therapies such as apheresis should be avoided if possible. Furthermore, in the absence of robust, long-term data, the committee could not ascertain whether the effect of evolocumab would be maintained over time at the same level as when therapy was started. Despite these uncertainties, the committee concluded that, in clinical practice, evolocumab should therefore be reserved as an add-on therapy to statins and ezetimibe for people who are at a high risk of CVD.

5.1.2 Uncertainties in the cost-effectiveness evidence

The committee considered the internal validity of the model to be unclear owing to the absence of evidence to populate all the transitions to the health states within the model. In particular, the committee agreed that the modelling of composite health states (combination of events) was based on arbitrary assumptions with little evidence. The committee agreed that it was more appropriate to model separately people with non-familial hypercholesterolaemia who can or cannot tolerate statins. The committee further noted that using risk equations could be appropriate if these reliably predicted the risk of CVD events and considered that the use of QRISK2 [40] was more appropriate compared with the Framingham risk equations in people with non-familial hypercholesterolaemia without a history of CVD.

For the HeFH population, the committee agreed with the ERG's suggestion that the secondary and primary prevention populations should be assessed separately. The committee further recognised that the risk equations used by the company were not derived from people with HeFH and considered that using the rate ratio from Benn et al [34] was inappropriate and overestimated of the risk of CVD among these people. As a result, the committee was doubtful about the validity of the estimated cost-effectiveness of evolocumab for this population.

The committee raised some uncertainties concerning the company's model in terms of treatment duration and how long treatment would last. The committee further noted that only the cost-effectiveness for the 140mg dosage

administered every 2 weeks were presented by the company; thus was only able to make a recommendation for this dosage.

Overall, the committee considered that the ICERs presented by the company needed to be interpreted with caution owing to the limitations of the model. Despite these concerns, the committee considered that the ICERs for the non-familial population were above those that are normally considered acceptable. The committee noted that the ICERs for the HeFH population were within acceptable range but drew attention to a number of inconsistencies in the results for this population. For example, the committee noted that the ICERs in people without CVD were lower than those for people with CVD, which contrasted with findings in the non-familial hypercholesterolaemia population. The committee heard from the ERG that different CVD events were assumed for the two populations and that the calibration of CVD events for the non-familial hypercholesterolaemia population was event-specific, whereas a single rate ratio from Benn et al [34] was applied to all CVD events for the HeFH population. In light of this, the committee expressed doubts about the face validity of the resulting ICERs.

6. CONCLUSION

The evidence suggests that evolocumab is efficacious and safe in reducing LDL-C concentrations in patients with primary familial and non-familial hypercholesterolaemia. However, current guidance emphasises reduction in CVD risk as the key outcome and this was not adequately demonstrated by the available evidence for evolocumab. Nevertheless, the committee determined that evolocumab was cost-effective for primary non-familial hypercholesterolaemia patients at high or very high risk of CVD, based on prior CV events and LDL-C level, and for those with HeFH, but only as long as stated, elevated levels of LDL-C were persistent and inadequately-controlled on other appropriate therapies. However, the inferences to be drawn from the evidence for statins and ezetimibe, and the high clinical unmet need and high risk of CVD in these groups, were deemed sufficient reasons for a positive recommendation, despite the absence of direct evidence on the relationship between evolocumab and CVD risk reduction. However, the FAD stated that the guidance was to be reviewed when the ongoing FOURIER trial reported, although this trial only aims to assess the impact of evolocumab on CVD outcomes in people who have already had a CVD event.

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Compliance with Ethical Standards

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