NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia [ID765]

The following documents are made available to the consultees and commentators:

1. **Consultee and commentator comments on the Appraisal Consultation Document 1** from:
   - Amgen's ACD1 comments plus new evidence
   - HEART UK
   - Royal College of Pathologists
   - Merck Sharp & Dohme

   'No comment' response received from the Department of Health

2. **Comments on the Appraisal Consultation Document 1 from experts:**
   - **Professor A Wierzbicki – clinical expert**, nominated by HEART UK

3. **Comments on the Appraisal Consultation Document 1 received through the NICE website**

4. **NICE request and Amgen's response: additional information**

5. **Evidence Review Group critique of the new evidence**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

Response to appraisal consultation document

Prepared by:

8th December 2015

File name	Version	Contains confidential information	Date
		Redacted version	December 2015

Contents

Executive Summary

We welcome the opportunity to comment on the Appraisal Consultation Document (ACD) for the single technology appraisal (STA) of evolocumab for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia [ID765]. We are disappointed with the preliminary recommendation and acknowledge that the Committee considered there to be a high degree of uncertainty in the cost-effectiveness evidence in order to be able to make recommendations about evolocumab.

We welcome the Committee's recognition of the clinical need for alternative treatments and their acknowledgement that evolocumab is a first-in-class therapy with a novel mechanism of action, which consistently reduced low-density lipoprotein cholesterol (LDL-C) concentrations compared with the current standard of care, while also being well tolerated by patients. We also share the Committee's conclusion that evolocumab will likely be reserved for patients who are at particularly high risk of cardiovascular disease (CVD), including patients with heterozygous-familial hypercholesterolaemia (HeFH) and those in whom LDL-C is not adequately controlled who are at the highest residual risk and are most vulnerable to CV events.

Revised cost-effectiveness evidence and analysis

In order to provide the Committee with increased certainty in the cost-effectiveness evidence, amendments have been made in recognition of the Committee's specific preferences for evidence and cost-effectiveness analyses. These are summarised in Table 1 and described further in Section 1. We have amended the evidence and analyses with regards to baseline CVD risk in patients with HeFH, in patients with statin intolerance, inclusion of the NICE-recommended QRISK2 for primary prevention, and subgroup modelling based on actual patient-level characteristics. We have also provided further information regarding long-term treatment effects and drug acquisition cost for evolocumab based on FP10 prescribing to support further discussion at the next Appraisal Committee meeting. Additionally, we have supplemented the assessment of CVD risk by obtaining patient-level characteristics for the secondary prevention (non-familial) and HeFH populations using the Clinical Practice Research Datalink (CPRD). We hope this provides greater certainty regarding the external validity of the cost-effectiveness results for evolocumab in the modelled high-risk populations.

Table 1 Summary of Appraisal Committee preferences

Committee's preference for cost-effectiveness	Amgen response
Long-term treatment effects with evolocumab	Additional information provided (Section 1.1).
Baseline CVD risk – inclusion of GAUSS-2 baseline characteristics for the statin intolerant population	Amended as per the Committee's preference (Section 1.2).
Baseline CVD risk – modelling HeFH separately based on CVD history	Amended as per the Committee's preference (Section 1.3).
CVD risk equation – implementation of QRISK2 for primary prevention	Amended as per the Committee's preference (Section 1.1).

Committee's preference for cost-effectiveness	Amgen response
Baseline CVD risk – HeFH and risk of CVD	Amended as per the Committee's preference (Section 1.5)
Background health-related quality of life – use of updated equation based on Health Survey of England	Amended as per the Committee's preference (Section 1.6).
Subgroups – model based on actual patient characteristics	Amended as per the Committee's preference (Section 1.7).
Drug acquisition – consideration of FP10 prescribing in primary care	Additional information provided (Section 1.8).
CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia	

Revised cost-effectiveness analyses

Base case cost-effectiveness results

We have updated the cost-effectiveness analyses for primary hypercholesterolaemia (heterozygous familial non-familial) and mixed dyslipidaemia populations based on the amendments described. The revised cost-effectiveness results and comparison with the previous results considered by the Committee are presented in Table 2. Furthermore, full details of the cost-effectiveness results (sensitivity, scenario and probabilistic analyses) are provided in Section 2 and Appendix I.

Additional subgroup cost-effectiveness analyses – secondary prevention (non-familial)

The Committee agreed that evolocumab might be cost effective in specific higher risk subgroups with CVD. They concluded that the subgroups reflecting all the characteristics of the actual subgroups in the clinical trials should be modelled given the potential correlation between some variables in different subgroups. As such, we have included subgroups based on actual patient-level characteristics from the evolocumab clinical trials and additionally assessed CVD risk based on patient-level characteristics from actual subgroups from CPRD with clinically appropriate risk factors.

In summary, the revised analyses indicate an improved cost-effectiveness for evolocumab compared to our previous analyses, except for patients with HeFH with statin intolerance or contraindication. The general improvement in the cost-effectiveness of evolocumab is due to increased background HRQoL, and increased baseline CVD risk in patients with statin intolerance/contraindication and increased baseline CVD risk in high-risk secondary prevention (non-familail) subgroups based on actual patient-level characteristics.

The worsened cost-effectiveness of evolocumab for patients with HeFH who are statin tolerant is due to the adjustment and reduction of the CV rate ratio (from 7.1 to 6.1). Importantly, the adjusted rate ratio of 6.1 translates to a lifetime modelled rate ratio (accounting for CV and non-CV mortality) of 5.5 and 3.9 for primary prevention and secondary prevention populations, respectively.

Table 2 Summary of revised base case cost-effectiveness results (deterministic) including comparison with previous manufacturer estimates based on LAPLACE-2, GAUSS-2 and RUTHERFORD-2

Analysis	Population characteristics and comparison	Evolocumab		Ezetimibe		Incremental				
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER (revised)	ICER (previous)	Change
Primary prevention (non-familial) population (LAPLACE-2/GAUSS-2)										
Analysis A	Evo+statins vs. eze+statins (statin tolerant)	12.67	[redacted]	12.33	£9,928	0.34	[redacted]	£69,249	£74,331	-£5,082
Analysis B	Evo vs. eze (statin intolerant/contraindicated)	11.85	[redacted]	11.28	£9,849	0.57	[redacted]	£38,458	£78,879	-£40,421
Analysis C	Evo+eze vs. eze (statin intolerant/contraindicated)	11.93	[redacted]	11.28	£9,849	0.64	[redacted]	£41,911	£84,354†	-£42,443
Analysis D	Evo+eze+statins vs. eze+statins (statin tolerant)	12.70	[redacted]	12.33	£9,928	0.37	[redacted]	£78,459	£84,218†	-£5,759
Secondary prevention (non-familial) population (LAPLACE-2/GAUSS-2)										
Analysis E	Evo+statins vs. eze+statins (statin tolerant)	8.43	[redacted]	8.03	£21,408	0.40	[redacted]	£45,439	£46,005	-£566
Analysis F	Evo vs. eze (statin intolerant/contraindicated)	8.01	[redacted]	7.48	£19,216	0.53	[redacted]	£30,985	£49,278	-£18,293
Analysis G	Evo+eze vs. eze (statin intolerant/contraindicated)	8.09	[redacted]	7.48	£19,216	0.61	[redacted]	£33,814	£52,811	-£18,997
Analysis H	Evo+eze+statins vs. eze+statins (statin tolerant)	8.48	[redacted]	8.03	£21,408	0.45	[redacted]	£50,257	£50,880	-£623
HeFH primary prevention population (RUTHERFORD-2)										
Analysis I	Evo+statins vs. eze+statins (statin tolerant)	13.57	[redacted]	12.61	£16,246	0.96	[redacted]	£23,536	£21,975†	£1,561
Analysis J	Evo vs. eze (statin intolerant/contraindicated)	13.31	[redacted]	12.32	£16,881	1.00	[redacted]	£21,921	£22,982†	-£1,061
Analysis K	Evo+eze vs. eze (statin intolerant/contraindicated)	13.48	[redacted]	12.32	£16,881	1.16	[redacted]	£23,602	£24,602†	-£1,000
Analysis L	Evo+eze+statins vs. eze+statins (statin tolerant)	13.71	[redacted]	12.61	£16,246	1.10	[redacted]	£25,583	£23,831†	£1,752
HeFH secondary prevention population (RUTHERFORD-2)										
Analysis M	Evo+statins vs. eze+statins (statin tolerant)	9.56	[redacted]	8.97	£25,773	0.59	[redacted]	£29,910	£24,866†	£5,044
Analysis N	Evo vs. eze (statin intolerant/contraindicated)	9.01	[redacted]	8.37	£27,089	0.64	[redacted]	£25,293	£25,856†	-£563
Analysis O	Evo+eze vs. eze (statin intolerant/contraindicated)	9.12	[redacted]	8.37	£27,089	0.74	[redacted]	£27,390	£27,659†	-£269
Analysis P	Evo+eze+statins vs. eze+statins (statin tolerant)	9.65	[redacted]	8.97	£25,773	0.68	[redacted]	£32,698	£26,919†	£5,779

†Additional analyses not initially included that have been conducted retrospectively with previous model for comparative purposes

Evo, evolocumab; eze, ezetimibe; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Proposed populations and conclusions

Based on the revised cost-effectiveness analyses, evolocumab demonstrates cost-effectiveness versus ezetimibe (ICER less than £30,000 per QALY gained) in the populations described in Table 3 below, i.e.

- Secondary prevention (non-familial) patients who are statin tolerant, with additional risk factors and a minimum LDL-C,
- Secondary prevention (non-familial) patients who are statin intolerant/contraindicated, with or without additional risk factors and a minimum LDL-C,
- Patients with HeFH.

Table 3 Summary of populations where evolocumab demonstrates cost-effectiveness versus ezetimibe

Population	Modelled subgroup	Minimum LDL-C (mmol/L)	Cohort ICER (£ per QALY gained)	Detailed table
Secondary prevention (non-familial) statin tolerant[a]	Diabetes mellitus	4.5 mmol/L	£28,859	Table 3-9
	Atrial fibrillation	4.5 mmol/L	£27,669	Table 3-9
	Two vascular beds affected	4.5 mmol/L	£28,573	Table 3-9
	History of ACS	4.5 mmol/L	£27,036	Table 3-9
	Three vascular beds affected	3.5 mmol/L	£24,899	Table 3-9
	Two or more of the following risk factors: - Diabetes mellitus - Atrial fibrillation - Two or more vascular beds affected - History of ACS	3.0 mmol/L	£21,111 to £30,524 depending on combination of risk factors	Table 3-11
Secondary prevention (non-familial) statin intolerant	None	5.5 mmol/L	£28,916	Table 3-8
	Diabetes mellitus	4.0 mmol/L	£27,409	Table 3-10
	History of ACS	4.0 mmol/L	£28,690	Table 3-10
HeFH[b]	None	None	£21,733 to £27,220	Table 3-5

[a]Secondary prevention (non-familial) modelled results based on patient-level characteristics from CPRD.
[b]HeFH (primary and secondary prevention) results based on HeFH primary prevention and HeFH secondary prevention analyses in RUTHERFORD-2 and CPRD and subsequently derived using a weighted cost-effectiveness analysis (Table 3-2 and Table 3-4).

Notes: Reported cohort ICERs based on evolocumab and statin versus ezetimibe and statin for statin tolerant population, and evolocumab versus ezetimibe for statin intolerant/contraindicated population.

ACS, acute coronary syndrome; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year

It is notable that in our original evidence submission, we also included other risk factors such as moderate to severe chronic kidney disease (eGFR < 60mL/min/1.73m^2), progressive CVD evidenced by ≥2 documented acute ischaemic CV events or revascularisation procedures or elevated plasma Lp(a) ≥ 77 mg/dL (≥ 90% centile) which were deemed equivalent to diabetes mellitus based on clinical expert opinion. It was not possible to assess populations with these specific risk factors (and potential correlation with other variables).

Conclusion

We believe this response will provide the Committee with sufficient information and increased certainty to allow recommendation of evolocumab for patients who are at the highest residual risk and are most vulnerable to CV events in line with clinical expectations, and where evolocumab represents a cost-effective treatment option for the NHS. We propose evolocumab is recommended as an option in primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia populations with elevated LDL-C, in the following specific populations:

1. Secondary prevention (non-familial primary hypercholesterolaemia or mixed dyslipidaemia) patients who are statin tolerant, with:

- LDL cholesterol ≥ 4.5 mmol/L and at high residual risk due to the presence of one or more of the following:
  - Diabetes mellitus
  - History of acute coronary syndrome
  - Two vascular beds affected
  - Atrial fibrillation

- LDL cholesterol ≥ 3.5 mmol/L and at high residual risk due to the presence of one or more of the following:
  - Three vascular beds affected

- LDL cholesterol ≥ 3.0 mmol/L and at high residual risk due to the presence of two or more of the following:
  - Diabetes mellitus
  - History of acute coronary syndrome
  - Two or more vascular beds affected
  - Atrial fibrillation

2. Secondary prevention (non-familial primary hypercholesterolaemia or mixed dyslipidaemia) patients who are statin intolerant or contraindicated, with:

- LDL cholesterol ≥ 5.5 mmol/L,

- LDL cholesterol ≥ 4.0 mmol/L and at high residual risk due to the presence of one or more of the following:
  - Diabetes mellitus

  History of acute coronary syndrome

3. Patients with heterozygous familial hypercholesterolaemia

1 Committee preferences for cost-effectiveness evidence

The Committee's preferences regarding the cost-effectiveness evidence and analyses are stated within the ACD (Section 4.27, pages 55-56). These preferences, our response and associated amendments to the cost-effectiveness analyses are summarised in Table 1-1.

Table 1-1 Appraisal Committee preferences for cost-effectiveness evidence

Element	Committee Preference	Comments
Long-term treatment effects with evolocumab	Considering alternative scenarios to reflect different assumptions about future treatment effects. These should include assuming that evolocumab does not give further benefit after a certain duration of treatment, or that its treatment effect tapers in the long term.	Refer to Section 1.1. We have provided additional information regarding this preference.
Baseline CVD risk – statin intolerant population	Using the baseline characteristics of the population in GAUSS-2 to model patients who cannot tolerate statins.	Amended as per the Committee's preference. Refer to Section 1.2– baseline characteristics from GAUSS-2 used to model non-FH patients who cannot tolerate statins.
Baseline CVD risk – HeFH and CVD history	Modelling the HeFH population with or without CVD separately.	Amended as per the Committee's preference. Refer to Section 1.3 – HeFH population modelled separately based on CVD history.
CVD risk equation -QRISK2 versus Framingham	Using the QRISK2 assessment tool to estimate the level of CVD risk in people without CVD (non-familial or HeFH). For the variables for which data were not collected, the average value for the specific UK population that reflects this variable could be used.	Amended as per the Committee's preference. Refer to Section 1.1 – QRISK2 has been used to estimate the level of CVD risk people without CVD (non-familial or HeFH).
Baseline CVD risk – HeFH and risk of CVD	Adjusting the risk of CVD in people with HeFH, with sensitivity analyses, based on a well-conducted systematic review of the literature, and taking into account the studies identified by the ERG about the natural history of HeFH.	Amended as per the Committee's preference. Refer to Section 1.5 – CVD risk for patients with HeFH assessed in further detail based on a literature review. CVD risk adjusted and further sensitivity analyses provided.
Background health-related quality of life	Using the equation from the Health Survey for England to inform the relationship between age and background health-related quality of life.	Amended as per the Committee's preference. Refer Section 1.6 – background health-related quality of life adjusted using Ara et al 2010 equation based on the Health Survey for England.
Subgroup analyses	Modelling subgroups reflecting all the characteristics of the actual subgroup in clinical trials.	Amended as per the Committee's preference. Refer Section 1.7
Drug acquisition	Taking into account FP10 prescribing of evolocumab in primary care to reflect the true cost of evolocumab to the NHS.	Refer to Section1.8. We have provided additional information regarding this preference.

CV, cardiovascular; ERG, Evidence Review Group; HeFH, heterozygous familial hypercholesterolaemia; NHS, National Health Service

1.1 Long-term treatment effects

- We believe doubts regarding the long-term effects of evolocumab are unfounded and are a misinterpretation of the clinical expert comments from which they were derived. As such, we do not feel further modelling to account for a theoretical tapering of effect to be appropriate.

Context

The ACD (Section 4.10, page 41) states, *'The Committee discussed the long-term effects of evolocumab. It heard from the clinical experts that the treatment effect was more likely to gradually lessen when people start treatment with relatively low LDL-C concentrations. However, the Committee also noted the statement from clinical experts suggesting that with evolocumab, neutralising antibodies can develop and treatment may lose its effectiveness. The Committee was aware that long-term data were limited, but what data there were did not show that the effect of evolocumab weakened over long treatment durations.'*

As such, the Committee concluded that the effect of evolocumab over time was still unknown and that they would prefer to see analysis including assumptions that the effect of evolocumab ceases after a certain duration of treatment or tapers over time.

We believe the two key issues raised here by the Committee represent a misinterpretation of the clinical expert comments in both cases.

Gradual lessening of treatment effect in people with low LDL-C

With regards a gradual lessening of effect in patients with low starting LDL-C levels:

- We understand this comment to be a mathematical point; with lower starting LDL-C, the relative reduction will be consistent with that of higher starting LDL-C levels but the absolute reduction in LDL-C (the key driver of risk reduction) will be smaller. We do not believe the clinical experts were inferring a lessening effect over time in patients with low starting LDL-C, as there is no evidence that this is the case.
- As evolocumab is aimed at high risk patients with a LDL-C > 3.0 mmol/l, uncertainties due to a lack of data around the benefits of LDL-C lowering to a very low level (less than approximately 1 mmol/l), are not of relevant to this appraisal, and no further treatment effect was modelled below 1.03 mmol/L (40mg/dL).

Gradual lessening of treatment effect due to neutralising antibodies

We believe the clinical experts comment does not represent a specific concern related to evolocumab (a fully human monoclonal antibody) but is a general point that there is a theoretical potential for neutralising antibodies to occur with monoclonal antibody therapy.

The data from a robust trial programme with frequent dosing including patients treated for over 2 years is very reassuring: only 7 (0.1%) of 4846 patients who received at least one dose of evolocumab developed binding anti-drug antibodies. Analysis of these patients showed no effect on the efficacy or safety of evolocumab, and none tested positive for neutralising antibodies. The potential for neutralising antibodies cannot be categorically ruled

out, however evidence from other monoclonal antibodies would strongly support the assertion that if there was potential for their occurrence in a significant number of patients, they would very likely have occurred to some degree in the trial programme to date. Thus if they did arise, it would certainly be in a very small fraction of the treated population, may be transient, and have uncertain (if any) impact on efficacy.

Of note, the risk management plan for evolocumab, endorsed by the Committee for Medicinal Products for Human (CHMP) use of the European Medicines Agency (EMA), does not include neutralising antibodies or immunogenicity as an important identified risk (no important identified risks were listed).

A statistically significant tapering of effect has not been seen in the evolocumab trial programme, the trial programmes of other monoclonal antibodies to PCSK9 or in the extensive statin data accumulated (apart from due to patient adherence).

Conclusion

We believe doubts regarding the long-term effects of evolocumab are unfounded and are a misinterpretation of the clinical expert comments from which they were derived. As such, we do not feel further modelling to account for a theoretical tapering of effect to be appropriate.

1.2 Baseline CVD risk – statin intolerance

- We have included baseline patient-level characteristics from GAUSS-2 for the purposes of baseline CVD risk estimation for patients with statin intolerance (or contraindication) in these revised analyses.
- We have also implemented the ERG's assessment that the REACH registry equation (recurrent CV events) variable for whether the individual is receiving stating treatment should be set to "no" for patients with existing CVD and statin intolerance or contraindication.
- Implementation of these amendments reduces the ICER in favour of evolocumab since the baseline CVD risk is increased compared with the original analyses in patients with statin intolerance.

Context

The ACD (Section 4.13, pages 42-43) states, *'The Committee was aware that GAUSS-2 only included people who could not tolerate statins, although the company chose not to use it to source data for this group. The Committee heard from the clinical experts that separating out these 2 groups would have been desirable because the risk of CVD was likely to be affected by whether or not the person can tolerate statins.'*

The Committee considered that assuming that the risk of CVD was independent of whether or not the person can tolerate statins could be considered implausible. Therefore, the Committee concluded that using the baseline characteristics of the population in GAUSS-2 (as opposed to LAPLACE-2 in the evidence submission) to model patients who cannot tolerate statins would be preferable.

Implementation

Inclusion of GAUSS-2 baseline characteristics

We have included baseline patient-level characteristics from GAUSS-2 for the estimation of baseline CVD risk. For the purposes of the patient-level risk estimation, patients with LDL-C > 2.5 mmol/L were included from LAPLACE-2. In GAUSS-2, all patients (n = 309) had a baseline LDL-C > 2.5 mmol/L. It is notable that the population in GAUSS-2 had a high baseline LDL-C of 5.08 mmol/L and 4.85 mmol/L for primary prevention and secondary prevention patients, respectively.

Patients from GAUSS-2 have been stratified on the basis of CVD history for primary prevention (n = 191) and secondary prevention (n = 118) to inform the CVD risk as done for LAPLACE-2 population. Additionally, the subgroups of secondary prevention patients with diabetes mellitus (n = 21) and patients with a history of acute coronary syndrome (ACS) (n = 37) have also been presented. A summary of the baseline characteristics are presented in Table 1-2. No additional subgroups have been explored such as those with diabetes mellitus and history of ACS given the small patient numbers to robustly estimate baseline CVD risk (n = 7).

Table 1-2 GAUSS-2: baseline population characteristics

Characteristic	All patients	Primary prevention	Secondary prevention	Secondary prevention and diabetes mellitus	Secondary prevention and history of ACS
Number	309	191	118	21	37
Age (mean, years)	61.5	59.9	64.0	62.8	63.0
Female	45.9%	51.1%	37.6%	52.4%	32.4%
Smoking	7.8%	8.9%	6.0%	9.5%	8.1%
Diabetes mellitus	20.2%	21.6%	17.9%	100.0%	16.2%
Hypertensive therapy	59.0%	56.8%	62.4%	95.2%	51.4%
Acetylsalicylic acid	33.2%	19.5%	55.6%	47.6%	48.7%
SBP (mg Hg) (mean)	132.8	132.3	133.6	136.1	134.1
BMI < 20 kg/m^2	0.7%	1.1%	0.0%	0.0%	0.0%
LDL-C (mmol/L) (mean)	4.99	5.08	4.85	4.60	5.17
Total-C (mmol/L) (mean)	7.22	7.33	7.04	6.86	7.39
HDL-C (mmol/L) (mean)	1.34	1.36	1.31	1.17	1.27
Triglycerides (mmol/L) (mean)	1.94	1.95	1.92	2.35	2.10
Secondary prevention	38.1%	0.0%	100.0%	100.0%	100%
History of ECVD	53.0%	-	53.0%	52.4%	0.0%
History of ACS	33.3%	-	33.3%	33.3%	100.0%
History of IS	6.8%	-	6.8%	9.5%	0.0%
History of HF	1.7%	-	1.7%	4.8%	0.0%
History of ACS and IS	1.7%	-	1.7%	0.0%	0.0%
History of ACS and HF	3.4%	-	3.4%	0.0%	0.0%
History of IS and HF	0.0%	-	0.0%	0.0%	0.0%
History of ACS, IS and HF	0.0%	-	0.0%	0.0%	0.0%
Number of vascular beds[a]	-	-	1.212	1.212	1.212
Atrial fibrillation[b]	-	-	11.7%	11.7%	11.7%

[a,b] Vascular beds (number) and atrial fibrillation (%) included based on the REACH registry baseline characteristics for recurrent CV events due to unavailability of data from the study for secondary prevention.
ACS, acute coronary syndrome; BMI; body mass index; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HDL-C, high-density lipoprotein-cholesterol; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; Total-C, total cholesterol

Application of the statin indicator variable in the REACH registry equation

The REACH registry equation includes a statin indicator variable. The hazard ratio for patients receiving statins for CV death and next CV event is 0.80 (95% CI: 0.70-0.91) and 0.75 (95% CI: 0.69-0.82), respectively.[1] Since we assumed that CVD risk is independent of statin tolerance, this variable was set to "yes" for all populations regardless of actual background statin treatment.

With respect to our application of the REACH equation for secondary prevention patients with statin intolerance, the ERG review (ERG Report, page 121) stated that, '*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.'*

In Addendum 2, we added functionality to the model to allow amendment to the statin indicator variable ("yes" or "no"). This variable was retained as "yes" for all populations in the updated cost-effectiveness analyses based on our ongoing assumption that CVD risk is independent of statin tolerance.

The ERG (ERG critique of Addendum 2 and PAS submission, Section 2.4.2) again noted; *'As suggested within the ERG report, the company's amended model includes a statin indicator variable for the REACH registry equations to account for differential CV event risk in patients who are or are not able to take statins. However, as per the company's original analyses, this variable is set to "yes" for all analyses presented using the corrected model. Consequently, this amendment has no impact on the company's new analyses. The ERG considers that this variable should have been set to "no" for all analyses in which patients are unable to take statins.*'

Whilst this aspect of the ERG assessment was not specified by the Committee as a preference in the ACD for the cost-effectiveness analysis, it was recognised that considering the risk of CVD as being independent of whether or not the person can tolerate statins could be considered implausible. Therefore, we have also made the following amendment for the estimation of CVD risk in secondary prevention patients with and without statin intolerance to appropriately estimate differential CVD risk and ensure consistency between baseline characteristics and application of the REACH registry risk equation:

- Secondary prevention statin tolerant (familial and non-familial patients) – statin variable for the REACH equation set to "yes".
- Secondary prevention statin intolerant (familial and non-familial patients) – statin variable for the REACH equation set to "no".

An additional scenario analysis is presented whereby the statin variable for the REACH equation is set to "yes" (original assumption) for secondary prevention statin intolerant patients (familial and non-familial patients).

Comparison of baseline CVD risk

To support the conclusion by the Committee that assuming the risk of CVD is independent of statin tolerance is implausible, we have also included the calculated 10 year CVD risk of one or more CV events, and the 20-month CV event rate for those with existing CVD for GAUSS-2 population in comparison with LAPLACE-2 for transparency (Table 1-3). This indicates that the statin intolerant population (GAUSS-2) have a numerically higher baseline CVD risk compared with patients treated with statins (LAPLACE-2) for both first and recurrent CV events.

Table 1-3 Baseline CVD risk for patients in LAPLACE-2 and GAUSS-2 based on actual patient-level characteristics

Population (non-familial)	Study	10 year risk of ≥1 CV events	Next event male (20-month rate) [SD]	Next event female (20-month rate) [SD]
Primary prevention	LAPLACE-2	9.9%	-	-
	GAUSS-2	16.9%	-	-
Secondary prevention	LAPLACE-2	46.7%	0.0399 [0.0129]	0.0396 [0.0124]
	GAUSS-2	53.3%	0.0411 [0.0120]	0.0412 [0.0117]
Secondary prevention and diabetes mellitus	LAPLACE-2	55.8%	0.0549 [0.0128]	0.0502 [0.0179]
	GAUSS-2	63.1%	0.0565 [0.0111]	0.0498 [0.0121]
Secondary prevention and history of ACS	LAPLACE-2	47.1%	0.0367 [0.0107]	0.0354 [0.0089]
	GAUSS-2	60.4%	0.0415 [0.0125]	0.0373 [0.0086]

ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; SD, standard deviation

RUTHERFORD-2: Patients with HeFH and statin intolerance/contraindication

The decision problem includes presentation of cost-effectiveness results for evolocumab versus ezetimibe either alone or in combination with background statins. RUTHERFORD-2 compared evolocumab versus placebo in patients with HeFH receiving stable background lipid-lowering therapy (statins ± other lipid-lowering therapies). As such, there are no specific statin intolerant patients for estimation of CVD risk in this population. Therefore, only consideration of the statin indicator variable (set to “no”) is made for HeFH patients (secondary prevention) to reflect. Otherwise, the same patient-level characteristics were used for both statin tolerant and statin intolerant or contraindicated patients.

Summary

We have included baseline patient-level characteristics from GAUSS-2 for the purposes of baseline CVD risk estimation for patients with statin intolerance (or contraindication) in these revised analyses. We have also implemented the ERG’s assessment that the REACH registry equation (recurrent CV events) variable for whether the individual is receiving stating treatment should be set to “no” for patients with existing CVD and statin intolerance or contraindication. Implementation of these amendments reduces the ICER in favour of evolocumab since the baseline CVD risk is increased compared with the original analyses in patients with statin intolerance.

1.3 Baseline CVD risk – HeFH and CVD history

- We have expanded the cost-effectiveness reporting for the HeFH population from the entire cohort to primary and secondary prevention separately as per the Committee's preference.

Context

The ACD (Section 4.13, page 43) states, '*HeFH: the Committee noted that the company modelled patients with or without CVD together, which the ERG did not consider to be clinically appropriate. The Committee heard from the clinical experts that in clinical practice, people with CVD are treated more intensively than those without, and so it would be useful to separate the results for each of these groups. The Committee concluded that splitting the HeFH by whether or not people had CVD would better reflect clinical practice.'*

The Committee considered that assuming that the risk of CVD was independent of whether or not patients with HeFH have CVD could be considered implausible. Therefore, the Committee concluded that modelling the HeFH with or without CVD separately would be preferable.

Implementation

We acknowledge the Committee's preference for the cost-effectiveness modelling of the HeFH population to be presented based on CVD history as opposed to the entire cohort.

The model used for the original analyses had the functionality to consider the HeFH populations based on CVD history. Patient-level characteristics from RUTHERFORD-2 were stratified on the basis of CVD history (Evidence Submission, Table 5-5, and page 183) and also included in the model.

The model now utilises QRISK2 to estimate risk for patients without existing CVD as opposed to Framingham (Section 1.4 regarding implementation of QRISK2). For the primary prevention population, once a CV event has occurred, the secondary prevention (based on REACH) CVD rate is utilised for recurrent CV events.

We have expanded the cost-effectiveness reporting (Section 2) for the HeFH population from the entire cohort to primary and secondary prevention separately as per the Committee's preference.

1.4 CVD risk equation – QRISK2 versus Framingham

- We have implemented the QRISK2 assessment tool to estimate the level of CVD risk in primary prevention (non-familial or HeFH) patients.

Context

The ACD (Section 4.15, pages 44-45) states, *'The Committee discussed whether the risk equations used by the company to predict the risks of CVD at baseline were appropriate. It noted that the company used the Framingham Heart Study risk equations for patients without CVD, and the REACH registry risk equations for patients with CVD.'* The Committee concluded, *'that the QRISK2 assessment tool would have been more appropriate than Framingham risk equations to estimate the risks of CVD in people without CVD.'*

Furthermore, with respect to the HeFH population, the Committee concluded (ACD Section 4.16, page 46), *'that the REACH registry and QRISK2 assessment tool could be used for heterozygous-familial hypercholesterolaemia in this appraisal, but only for the subsets in RUTHERFORD-2 with or without CVD respectively.'*

Implementation

QRISK2 assessment tool

We have implemented the QRISK2 assessment tool to estimate risk in people without CVD (non-familial or HeFH) using the most recent 2015 equations.[2] The QRISK2 risk assessment scores were used for analyses of the calibration factor to cross-walk between the QRISK2 risk and the actual risk in the CPRD study population, and to derive an age-adjustment factor to facilitate estimating age-specific rates in the model. These analyses are discussed in more detail below.

All patients in whom the QRISK2 equations could be calculated were included in the analyses. This was a total of 6,341 (83.2%) primary prevention patients from the overall 7,626 patient dataset from the CPRD study (Evidence submission, Appendix XI).

The only recommended input limit applied to the data was to exclude patients with total cholesterol to HDL-cholesterol ratio of greater than 12 because of out-of-range errors in subsequent calibration and regression analyses (9 patients out of 6,224 dataset). Smoking status in QRISK2 was changed to a 5-level covariate in the more recent QRISK2 equations (non-, ex, light, moderate, and heavy smoker) from the original 2-level covariate in the QRISK2 2008 equations (non-smoker, smoker). For our analyses we retained smoking as a 2-level covariate (non-smokers and smoker). We mapped our definition of non-smokers to non-smokers in the 2015 QRISK2 risk equations, and our definition of smokers to the category of "light" smokers. The light smoker category was chosen because its associated relative risk was virtually identical to the relative risk for all smokers in the original QRISK2 2008 publication. All patients in the dataset were given the mean Townsend deprivation score (derived from the published risk algorithm code). Race and family history categories were estimated from the data using all relevant READ codes that could be identified. Patients with missing values were assumed to be in the reference group (white or not reported). Patients with type 1 diabetes mellitus were identified from the set of all diabetes

mellitus patients (which were identified based on both READ codes and medication use). Patients with at least one diagnosis of type 1 diabetes mellitus were assumed to be type 1, and all others were assumed to be type 2 diabetes mellitus. All definitions were aligned between the non-FH population and non-FH population (described later).

For all analyses, we estimated the 10-year risk of events using the QRISK2 2015 equations. This risk (probability) was converted to a rate by using the following equation below. All results are reported using the rates.

$$rate = -\log(1 - risk)$$

QRISK2 calibration - methods

As done previously for the REACH registry and Framingham equations, we calibrated the QRISK2 rates to ensure alignment with the rates actually observed in the CPRD study. The reason we estimated a calibration factor was three-fold:

- to account for the specific CV events in the economic model which were different from the outcomes used to derive the QRISK2 risk equations,
- to adapt the QRISK2 predicted rates for use in a high-risk population managed with high-intensity statins,
- to derive a less complicated relationship between risk and age than the one used in QRISK2 for the economic model.

We replicated the calibration methods as described fully in Appendix XI of our evidence submission (Amgen Study: Estimation and calibration of CV event rates). Briefly, we constructed a Poisson regression model that predicted the ratio of the observed CV event rate versus the QRISK2 predicted CV event rate for each person in the population. This allows the derivation of a rate ratio that can be used to convert a QRISK2 risk for a person based on the QRISK2 model to an annual event rate for application in the economic model.

QRISK2 includes a narrower definition of CV events compared with that in economic models designed to model the natural course of CVD. QRISK2 was developed to assess the risk of the following CV outcomes: myocardial infarction, angina, coronary heart disease (CHD), stroke, or transient ischemic stroke. These CV events are a subset of the outcomes used in the economic model (and our analyses of CPRD data). Primarily, we also included heart failure, peripheral arterial disease (PAD), abdominal aortic aneurysm, and carotid stenosis. We also included percutaneous coronary intervention and coronary artery bypass grafting, but these are primarily used in patients with coronary heart disease, so it is likely that they are capturing the same coronary heart disease and angina patients as QRISK2. Therefore, the calibration of the QRISK2 results allows us to account for differences in outcome definitions between QRISK2 and the economic model.

While QRISK2 included a broad range of patients, it is possible that in high risk sub-populations there could be even more complex interactions than those captured in QRISK2. Hence, QRISK2 could be less accurate in some sub-populations, even though these sub-populations were included in the original cohorts on which the QRISK2 model was developed. The calibration process accounts for any differences in our high-intensity statin treated high-risk primary prevention population to the extent that such differences exist.

Most of the complexity of the QRISK2 score is related to its use of interaction terms of age with body mass index (BMI), Townsend score, systolic blood pressure (SBP), history of CHD, smoking status, diabetes mellitus and atrial fibrillation. Because of this, it was difficult to convert the 10-year rates to 1-year rates, while also correcting for the effect of aging over the 10-year time horizon for QRISK2. Therefore, we estimated a simpler relationship between risk and age using the CPRD high-risk primary prevention cohort. We constructed a generalised linear model using the high-risk primary prevention population to assess the relationship between the 10-year rate and age. The model was fit using a log link and normal errors. Models were fit separately by gender to align with the gender-specific QRISK2 scoring algorithms. No other covariates were used in the model. Only patients between age 45 and 84 were included in the analyses to align with the economic model inputs. The results using all patients resulted in slightly higher rate ratios for each year of age, so this subset analysis can be considered to be conservative (not in favour of evolocumab).

QRISK2 calibration - results

The coefficients from the model are provided below (Table 1-4), as well as a plot (Figure 1-1) of the 10-year rate from QRISK2 with the fitted regression line superimposed on the data. The rate ratio for age was [redacted] for females and [redacted] for males per 1-year increase.

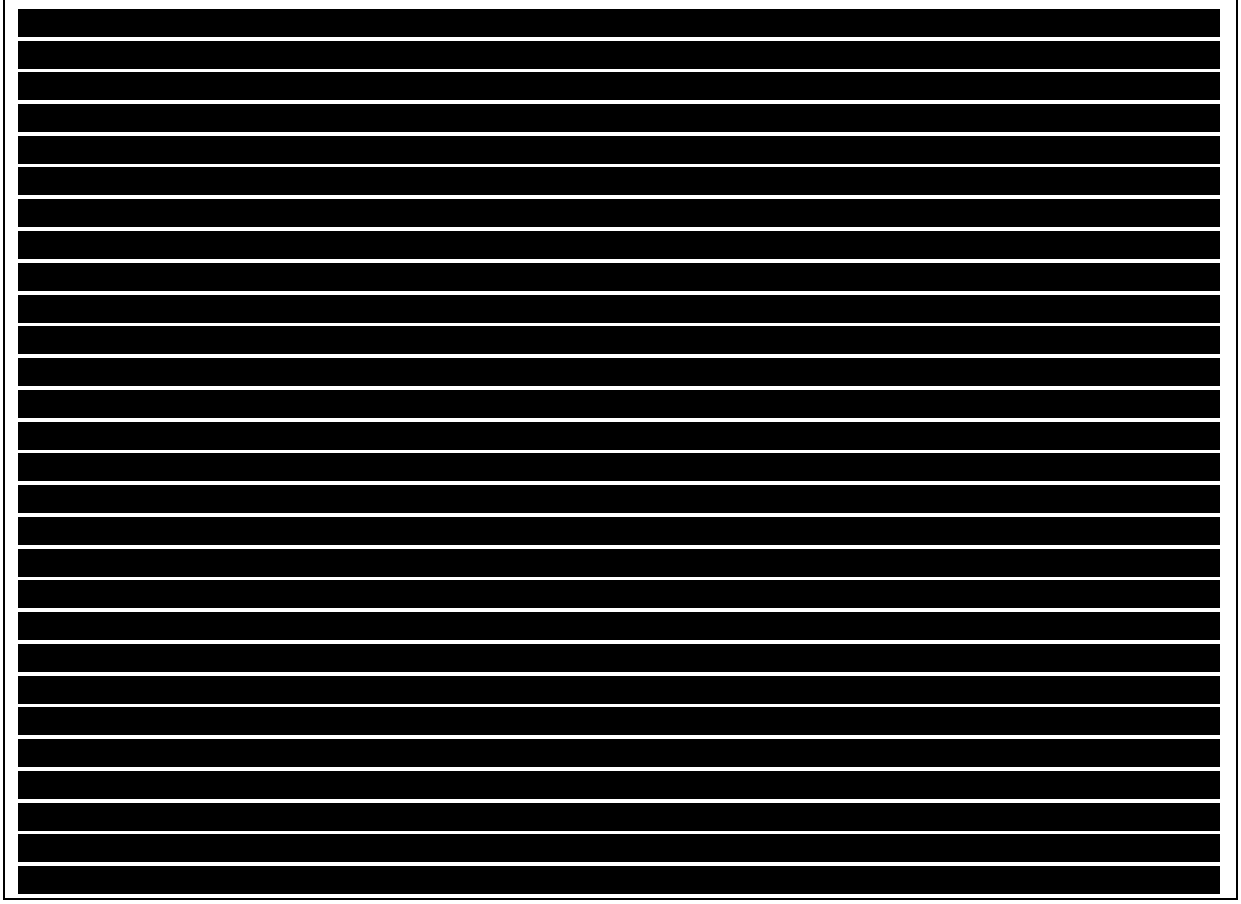
Table 1-4 Regression Model Results

Parameter	Estimate	Standard Error	t-statistic	p-value
Female (aged 45-84)				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Male (aged 45-84)				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]

Note: Models including all ages had very similar but slightly higher coefficients for age (female = 0.0561, male = 0.0444) and were not used.

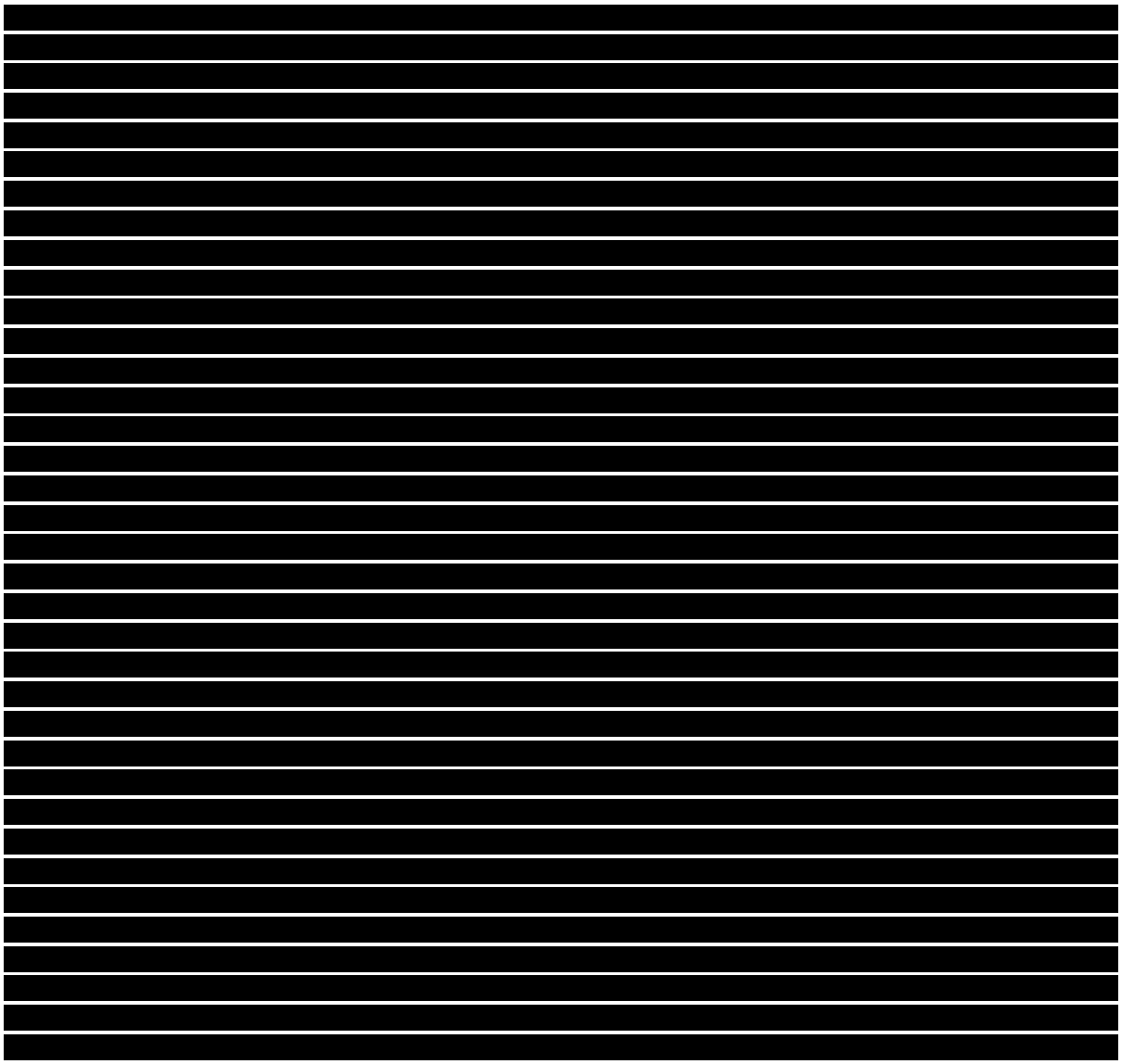
The calibration factor (broader definition of CV outcomes) for QRISK2 was derived as [redacted]. This indicates that the observed rates were approximately [redacted]% higher than the rates predicted by QRISK2. This is in contrast to the Framingham calibration factor that was [redacted], i.e. Framingham slightly over-estimated the rates.

Figure 1-1 [redacted]



This can be visualised by comparing the Framingham and QRISK 10-year rates (without calibration) using data from primary prevention population. In Figure 1-2, it is evident that the use of Framingham results in a higher event rate across much of the relevant age range in the cohort (45 to 84 years).

Figure 1-2 [redacted]



Importantly, this calibration should be considered in the context of the rate adjustment used in NICE CG181. QRISK2 includes a narrower definition of CV events compared with that in economic models designed to model the natural course of CVD. For example, the QRISK2 definition of a first CV event does not include PAD or HF. As such, previous economic evaluations such as that for NICE CG181 have amended the CVD risk estimated from QRISK2 to a 'total CVD risk'. For example, a QRISK2 derived absolute 10-year CVD risk of 10% has been calculated as being equivalent to a 'total CVD risk' of 14.7% (NICE CG181 Appendices, pages 597-598).[3] Notably, the adjustment of CV rates used in the model (Table 1-5) was 1.37 to 1.69 to derive a 'total CVD rate' compared to [redacted] from our calibration.

Table 1-5 CV event rates used in NICE CG181[4]

Sex	Age	Stable angina	Unstable angina	MI	TIA	Stroke	Heart failure	PAD	CV death	Total CVD
Male	40-44	0.30731	0.10711	0.29530	0.06006	0.12913	0.07143	0.53571	0.10110	1.60714
	45-54	0.30731	0.10711	0.29530	0.06006	0.12913	0.07143	0.53571	0.10110	1.60714
	55-64	0.32800	0.07100	0.17200	0.08900	0.20600	0.12409	0.38321	0.13400	1.50730
	65-74	0.21400	0.08300	0.17300	0.10000	0.27000	0.16049	0.25720	0.16000	1.41770
	75-84	0.19119	0.08108	0.16116	0.08008	0.34334	0.26133	0.12667	0.14314	1.38800
	85+	0.21400	0.09600	0.18600	0.01600	0.35100	0.39437	0.11150	0.13700	1.50587
Sex	**Age**	**Stable angina**	**Unstable angina**	**MI**	**TIA**	**Stroke**	**Heart failure**	**PAD**	**CV death**	**Total CVD**
Female	40-44	0.32435	0.11677	0.07984	0.15968	0.22854	0.06250	0.62500	0.09082	1.68750
	45-54	0.32435	0.11677	0.07984	0.15968	0.22854	0.06250	0.62500	0.09082	1.68750
	55-64	0.34600	0.07300	0.09200	0.09500	0.28800	0.10606	0.45455	0.10600	1.56061
	65-74	0.20180	0.05195	0.12088	0.07293	0.38162	0.18548	0.30242	0.17083	1.48790
	75-84	0.14915	0.03403	0.10210	0.09810	0.46446	0.25214	0.11752	0.15215	1.36966
	85+	0.13600	0.02900	0.10000	0.08700	0.50100	0.29179	0.08359	0.14700	1.37538

Note: data presented in this table is derived from the economic model used for NICE CG181 following prior permission from the National Clincial Guidelines Centre, Royal College of Physicians.

CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease

Evolocumab studies (LAPLACE-2, GAUSS-2 and RUTHERFORD-2)

The QRISK2 score was estimated in patients from the relevant evolocumab studies. The available baseline data was used to estimate the 10-year risk scores (which were converted to 10-year rates). There were missing inputs; therefore, we imputed mean values from the UK population as published by the QRISK2 authors in the most recent update.[5] This imputation was done for BMI, renal disease, and family history of CHD. The proportion of patients with rheumatoid arthritis and the distribution of type 1 and 2 diabetes mellitus were not available from this publication and, instead, were taken from our high-risk primary prevention CPRD population. Ethnicity was assumed to be the reference group (white or not reported). The population mean Townsend scores were provided as part of the code for the QRISK2 risk model and were used.

Familial Hypercholesterolaemia

Analysis of patients with FH was conducted using the same READ code sets as the non-FH population. The primary difference between the cohort selection was that the FH population was enrolled based on the first FH diagnosis after 2008, whereas the high-risk primary prevention (non-FH) cohort was selected as a prevalent cohort as of January 1, 2005. Also, the FH primary prevention population included all patients without evidence of CVD, including both diabetic and non-diabetic patients. In contrast, in the high-risk (non-FH) primary prevention cohort, all patients were required to have evidence of diabetes (either a READ code or prescription).

1.5 Baseline CVD risk – HeFH and risk of CVD

- A literature review was undertaken to determine the CVD risk associated with FH.
- Fourteen publications based on population-based (n = 1), registry-based (n = 7) and hospital- and family-based studies (n = 6) were identified and assessed for risk of bias to determine the least biased estimate for the rate of increased CVD in patients with FH compared with non-FH patients.
- Selection bias for registry-based and hospital/family-based studies included in the review is a major source of bias affecting estimates of CVD risk in FH from these studies, making generalisability highly limited. In addition, some of these studies lacked a non-FH comparator group or included only non-fatal or fatal events, further limiting generalisability.
- In contrast, the only population-based study (Benn et al. 2012), a population level survey of patients undertaken in Denmark that compared risk of coronary artery disease in patients with FH versus patients without FH, showed a low degree of bias and was the only study that included both fatal and non-fatal CV events. This study was therefore deemed to represent the best available literature-based estimate of CVD risk in FH. Compared with non-FH patients not on lipid-modifying therapy, the study reported an odds ratio for coronary artery disease in FH patients of 10.3 (95% CI: 7.8-13.8) and 13.2 (95% CI: 10.0-17.4) in subjects treated and not treated with lipid lowering therapy, respectively.
- The rate ratio from Benn et al. (2012) was adjusted to derive an estimate reflecting treatment with LMT in both the general population and FH population with a derived rate ratio of 6.1 (range 4.9 to 7.5). Additionally, we have conducted sensitivity analyses for the HeFH primary prevention and secondary prevention population based on a range of alternative rate ratios (range of 2-10) and baseline LDL-C (3.5 mmol/L to 6 mmol/L).
- Importantly, a rate ratio of 6.1 translates to a lifetime modelled rate ratio (accounting for CV and non-CV mortality) of 5.5 (10-year CVD risk of 28%) and 3.9 (10-year CVD risk of 62%) for primary prevention and secondary prevention populations, respectively.
- Scenario analyses also indicate the cost-effectivness results are not sensitive to assumptions regarding the rate of stroke events in patients with HeFH.
- Whilst we have assessed the cost-effectiveness in HeFH based on CVD history, as described in our response (and subgroup analyses), CVD risk is multi-factorial, therefore decision-making for the HeFH population on the basis of CVD history alone is inappropriate given the potential for the presence of additional risk factors (e.g. diabetes mellitus).

Context

The ACD (Section 3.30, page 20-21) states, *'…the company used the study by Benn et al. (2012) to adjust the risk of CVD at baseline in patients with HeFH. The ERG noted that this study compared the risk of CV events between the general population and patients with HeFH. However, in the model, the relative risk was not applied to the general population, but to the RUTHERFORD-2 trial population that was already at high risk of CVD. This was likely to overestimate the risk of CVD, and produce more favourable ICERs for evolocumab. The ERG also highlighted other studies, which suggested that the relative risk derived from Benn et al. was likely to be an overestimate.'*

The Committee was concerned about how we estimated the risk of CVD, particularly by what was deemed an unrealistically high factor to adjust the risk of CVD in people with HeFH. Therefore, the Committee concluded we should take into account the studies identified by the ERG, and that:

- the risk of CVD in people with HeFH should be adjusted (with sensitivity analyses),
- the analyses should be based on a well-conducted systematic review of the literature.

We have provided an overview of the literature review and subsequent analyses informed by the findings of this review.

Implementation – Literature review

A literature review was undertaken to determine the CVD risk associated with familial hypercholesterolaemia (FH) as described in our evidence submission (Baseline CV rate calibration for the HeFH population, page 191 and Appendix XII). A summary of the findings are provided in this section and further details are also available in Appendix II. A top-line overview of the methods and results of this literature review were presented at the ISPOR 18th Annual European Congress in November 2015.[6] In addition, this literature review is planned to be submitted for peer-reviewed publication imminently, with publication anticipated in Q2 2016. As such, content related to the review of the studies, discussion and conclusions are academic in confidence.

Medline searches

Searches using Medline (PubMed) were performed on 12 August 2014 spanning 10 years (i.e. from 2 August 2004 to 12 August 2014); to identify potentially relevant publications using the following advanced PubMed search string:

- ((((Cardiovascular Disease Risk + Familial Hypercholesterolaemia) NOT Nursing) AND English[Language])NOT randomized controlled trials) NOT reviews[Publication Type]

Previous review of FH registries

Publications identified in a previously-conducted, Amgen-sponsored literature review of available FH registries (and publications from these registries) were also screened for eligibility. This previous FH registry literature review included the following searches (conducted in October 2013):

- Internet (Google Search): Searches were conducted using "familial hypercholesterolaemia" + "registry" as search terms Articles found through the internet search were hand searched and the reference lists from each article were reviewed to locate additional papers.
- Medline (PubMed): Searches were conducted using the names of key investigators identified in the searches above (Raul Santos from Brazil, Dev Datta from Wales, Fernando Civeira from Spain, Frederick Raal from South Africa, and Mariko Harada-Shiba from Japan) + "familial hypercholesterolaemia" as search terms. No date limits were applied to the search.

- Additional Medline (PubMed): Searches were conducted to locate additional publications and information for each country of interest*. For these searches, the country name + "Familial hypercholesterolemia" were used as search terms. No date limits were applied to the search.

Reference searches

In addition, reference lists from publications identified as relevant for inclusion in the above searches were hand searched to identify additional relevant publications. A comprehensive literature review by Austin et al. (2004) [7] on the association between FH and coronary heart disease (CHD) was identified and hand searched to identify additional relevant publications published prior to 2004.

Study selection and screening

The review focussed on publications of studies that included an FH patient population and reported a CVD risk estimate. A full list of eligibility criteria is provided in Table 1-6.

Table 1-6 Inclusion and exclusion criteria for the literature review

	Inclusion criteria	Exclusion criteria
Population	FH	Non-FH Non-human or animal
Intervention	n/a	n/a
Comparators	any	n/a
Outcomes	CVD risk estimate	• No CVD risk estimate • Biomarkers • Genomic • Mechanistic endpoint • Laboratory endpoint
Study design	Any apart from those meeting exclusion criteria	• No data described e.g. opinion, commentary, meeting reports • Randomised controlled study
Language	English	Non-English

CV, cardiovascular; FH, familial hypercholesterolaemia; n/a, not applicable

Publication titles and abstracts were screened for content and the resulting articles deemed potentially relevant for inclusion were retrieved for full-text review. Screening of both publication titles/abstracts and full-text articles was conducted by 2 reviewers independently with any discrepancies reconciled by mutual agreement and discussion.

*Asia (general search term but also searched specific countries within Asia as listed below), Australia Austria, Brazil, Canada, China, Czech Republic, Denmark, France, Germany, Iceland, Ireland, Italy, Japan, Korea, Malaysia, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Scotland, Singapore, Slovak Republic, Slovenia, South Africa, Spain, Switzerland,Taiwan, Thailand, UK, USA

Data extraction

Data for CVD risk estimates and other study characteristics were extracted for publications included in the review by one reviewer to an extraction grid and accuracy checked by a second reviewer, with any discrepancies reconciled by mutual agreement and discussion.

Quality assessment

To assess the quality and potential for bias of each study, a bias assessment form based on the Cochrane Handbook report of low risk, unclear risk, and high risk of bias was developed.[8] As the studies within this search were non-RCTs, the Newcastle-Ottawa criteria (Appendix II) were adapted for inclusion in the risk of bias assessment.

The Newcastle-Ottawa criteria for cohort studies broadly assess how subjects are selected, the comparability of the cohorts, and how outcomes are assessed. These broad categories are divided into six areas of potential bias:

- Selection bias: assesses if eligibility criteria is explicitly described, the selection of the eligible population from the target population, similarities in exposed and unexposed groups, and exclusion of participants
- Performance bias: assesses ascertainment of exposure and outcomes, temporal sequence, and concurrent interventions or unintended exposures
- Detection bias: assesses the blinding of assessors, valid and reliable measure of exposure status and outcomes, and exposure durations
- Attrition bias: assesses missing data across exposed and unexposed groups
- Confounding bias: assesses valid and reliable measurement of confounders, and controlling for confounders
- Reporting bias: assesses post-hoc analyses

A further category of 'other biases' was also included to allow for the capture any bias not captured in the defined categories.

The bias assessment form included guided questions for the reviewers to assess bias risk with 17 individual criteria assessed for each study as described in (Appendix II).

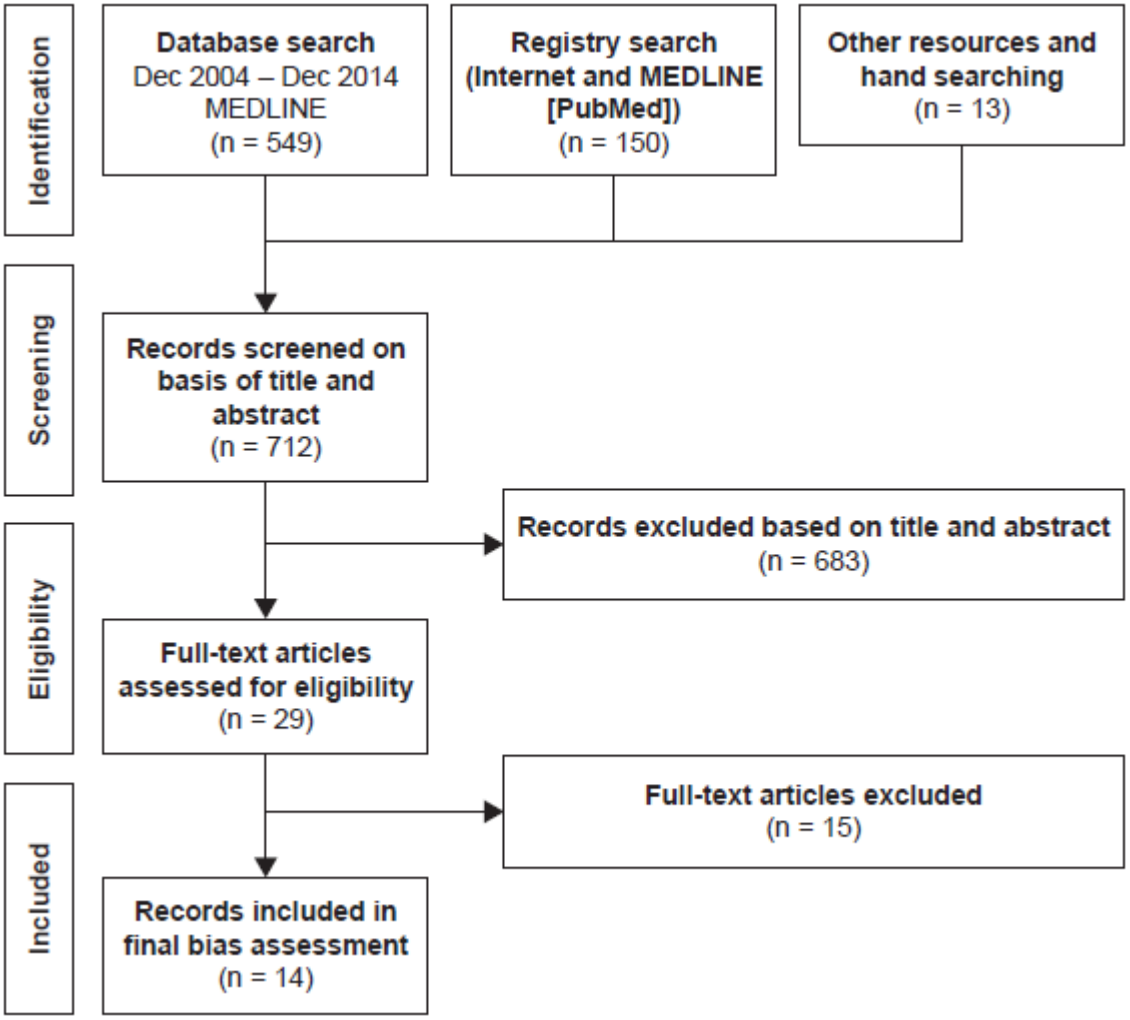
Bias risk assessments were coded as high risk, low risk, and unclear risk for each bias risk assessment criterion. The bias risk assessments were performed by 2 reviewers independently with any discrepancies reconciled by mutual agreement and discussion. Reviewers conducted the bias risk assessments with reference to the specific objective of estimating the CVD risk, even if there were multiple objectives within the paper and when the primary reason for the research was for a different purpose. This is especially relevant for registries where the primary objective is one of patient management rather than formal risk calculation. Bias criteria and assessment levels were discussed between the reviewers prior to starting the project during the development of the excel spreadsheet template for the independent collection of bias criteria to improve concordance of reviews.

Search results

The complete literature search identified 712 potential publications which included 549 from PubMed (Medline), 150 from the registry search and 13 from reference sources. Following

title and abstract review, 29 publications were identified as likely to contain CVD risk estimates and were retrieved for full text review. Of these 29 publications, 14 met the inclusion criteria of containing estimates of the rate of increased CVD risk in FH and were included in the review. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram providing a summary of the searching, screening, and assessment process is provided in Figure 1-3 .

Figure 1-3 PRISMA flow diagram for the literature review



A list of publications excluded during assessment of full-text articles for eligibility and reason for exclusion is provided in Appendix II.

Overview of included studies

An overview of the 14 included studies in the review is provided in Table 1-7. Examining the data source and methodology for the 14 studies, 8 were based on registries in the UK, Netherlands, Norway, and Spain; 5 from single hospitals or families in Japan, Denmark, Netherlands, and UK; and 1 was based on a population survey in Denmark.

Table 1-7 Overview of population and registry-based studies identified in the literature review

Study	Country/ ethnicity	Study sample	CVD risk measure	FH risk estimate	Exposure group	Comparison group
Population survey-based studies						
Benn et al. (2012)[a9]	Denmark	Population survey of 69,016 patients in Denmark	OR for CAD (fatal or non-fatal)	10.3 (7.8-13.8)	LMT-treated	Random sample of Danish population
				13.2 (10.0-17.4)	No LMT	
Registry-based studies						
Mabuchi et al. (1989)[10]	Japan	Cohort (Konazawa Hospital) of 527 vs. Japanese population	PMR for CHD (fatal)	10.9 (7.95-15.03)	No LMT	Japanese population
Simon Broome (1991)[b11]	British	526 registry patients vs. England and Wales population	SMR for CHD (fatal)	3.74 (1.8-6.89)	Males (age 0-79 years) LMT-treated	Population of England and Wales
				4.13 (1.34-9.64)	Females (age 0-79 years) LMT-treated	
				3.86 (2.1-6.39)	All 0-79 LMT-treated	
Simon Broome (1999)[b11]	British	1185 registry patients (1980 – 1995) vs. England and Wales population	SMR for CHD (fatal)	2.6 (1.7-3.8)	Males (0-79 years of age) LMT-treated	Population of England and Wales
Alonso et al. (2008)[12]	Spanish	811 registry patients vs. Spanish population	% premature CVD (non-fatal)	8.4 (21.9%/2.6%)	80% of patients on LMT	Spanish Population

Neil et al. (2008)[13]	British	Simon Broome Registry, 3413 patients vs. England and Wales population. 1980 - 1991 patients	SMR for CHD (fatal)	1.98 (1.02 - 3.46)	Primary prevention (age 20-79 years) LMT-treated	Population of England and Wales
				5.15 (3.35-7.64)	Secondary prevention (age 20-79 years) LMT-treated	
		Simon Broome Registry, 3413 patients vs. England and Wales population. 1992 - 2006 patients	SMR for CHD (fatal)	1.03 (0.75-1.38)	Primary prevention (age 20-79 years) LMT-treated	
				3.88 (3.18-4.68)	Secondary prevention (age 20-79 years) LMT-treated	
Versmissen et al. (2008)[14]	Dutch	Dutch lipid clinic patients age > 55 years, N=1950	HR for MI (non-fatal)	8.7 (4.77-15.82)	No LMT Not taking statin for more than 1 month prior to their MI	Rotterdam Study in the elderly, age-sex matched sub-group to FH patients.
				1.44 (0.80 - 2.60)	Primary prevention LMT-treated	
Besseling et al. (2013)[15]	Dutch	High-severity FH vs. low-severity FH. (Defining high severity in a novel way, using data from one subgroup and applying that to the whole cohort). Does not provide a risk estimate vs. non-FH.	HR for CVD (non-fatal)	1.25 (1.05-1.51)	High severity group LMT-treated	Low severity FH group
Mundal et al. (2014)[16]	Norway	Norway Registry 4688 patients (1992-2010) vs. Norwegian population	SMR for CVD (fatal)	2.29 (1.65-3.19)	89.1% of patients on LMT	Norwegian population

Hospital-based and family-based studies						
Jensen et al. (1967)[17]	Denmark	Family study 11 families (1944-64 vs. Danish population)	SMR (fatal)	2.88 (1.73-4.46)	LMT-treated	Danish population
Slack et al. (1969)[18]	British	104 patients with clinical FH vs. 41 patients with type III, IV or V hyperlipoproteinaemia	1st MI (fatal and non-fatal)	60% increased risk	LMT-treated	Type III, IV or V hyperlipoproteinaemia
Sijbrands et al. (2000)[19]	Dutch	Family study 855 first degree relatives vs. Dutch population	SMR (fatal)	1.34 (1.16-1.55)	LMT-treated	Dutch population
Sijbrands et al. (2001)[20]	Dutch	Pedigree analysis to a single pair of ancestors. 250 descendants vs. Dutch population	SMR (fatal)	1.32 (1.03-1.67)	LMT-treated	Dutch population
Mohrschladt et al. (2004)[21]	Dutch	Leiden lipid clinic patients N=400 - all patients treated with statins.	RR IHD (fatal)	2.6 (0.6-3.3)	No history of CHD LMT-treated	Dutch population

[a] Only population-based estimate

[b] Simon Broome SMR results have been expressed as absolute risk increases (SMR/100)

CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; HR, hazard ratio, IHD, ischaemic heart disease; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; OR, odds ratio; PMR, proportional mortality ratio; RR, relative risk; SMR, standardised mortality ratio

Quality assessment

A summary of the quality/risk of bias assessment results is provided in Figure 1-3. Generally more dark grey boxes for a particular study indicates a greater degree of bias for that study; however, the criteria are not weighted as to their overall importance to the interpretation of the results and a single dark grey box for bias could be sufficient to render that papers results uninterpretable. For example, if it is determined that there is a high risk of bias in patient selection, then all other criteria become moot – as even if these patients are studied well, the results remain highly biased.

Trends in the risk assessment were observed by bias type. When bias risk was examined across the studies, selection bias was the largest potential threat with 35/56 (63%) of the selection bias criteria categorised as high risk. Performance bias was also an issue where 6/42 (14%) of the criteria were high risk and 11/42 (26%) were unclear risk. Unclear risk was prevalent in both detection bias and confounding bias, with 19/56 (34%) of the detection bias criteria and 18/28 (64%) of the confounding bias criteria identified as unclear risk. In contrast, attrition bias and confounding bias were not a concern in most studies, with 24/28 (86%) of the attrition bias criteria and 13/14 (93%) of the confounding bias identified as low risk.

Figure 1-4 Summary of quality/risk of bias assessment of the included studies

Bias Category		Selection				Performance			Detection				Attrition		Confounding		Reporting	Other	
Study	Publication year	Eligibility criteria explicitly described	Selection of eligible population from the target population	Similarities of exposed and unexposed groups	Exclusion of participants from analysis of the outcome	Ascertainment of exposure and outcome	Temporal sequence	Concurrent interventions or unintended exposures	Blinding of assessors	Valid and reliable measurement of exposure status	Valid and reliable measurement of outcomes	Exposure durations	Missing data across exposed and unexposed groups	Accounting for missing data	Control for confounders	Valid and reliable measurement of confounders	Post hoc Analyses	Other biases	High bias count x study
Population-Survey Based Studies																			
Benn et al.	2012																		0
Registry-Based Studies																			
Mabuchi et al.	1986																		6
Simon Broome et al	1991																		4
Simon Broome et al	1999																		4
Alonso et al.	2000																		11
Neil et al.	2008																		4
Versmissen et al.	2008																		3
Besseling et al.	2014																		4
Mudnal et al.	2014																		5
Hospital-Based and Family-Based Studies																			
Jansen et al.	1967																		3
Slack et al.	1969																		9
Sijbrands et al.	2000																		2
Sijbrands et al.	2001																		2
Morcschladt et al	2004																		3
High Bias Assessment count x bias type		9	13	11	2	0	0	6	1	1	3	1	1	0	3	3	1	5	

White, low risk of bias; light grey, unclear risk of bias, dark grey, high risk of bias

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Implementation - Cost-effectiveness analysis

HeFH CVD risk adjustment and cost-effectiveness assessment

Based on the literature review, we believe that the estimates from Benn et al. (2012) report credible estimates of the increase in CVD risk in FH patients and have the least amount of bias compared to the other publcicaitons.

We recognise and acknowledge a limitation of this study. The ACD (Section 4.17, pages 46-47) states, '*Benn et al. compared the risk of CV events between the general population and patients with HeFH. However, the company applied the relative risk from the study to the RUTHERFORD-2 trial population, who were already at high risk of CVD.'* As such, the Committee concluded a preference for the risk of CVD in people with HeFH to be adjusted with appropriate sensitivity analyses.

In Benn et al. (2012), it is notable that the general population (unlikely FH) had a LDL-C level of 3.2 mmol/L (interquartile range: 2.7-3.8 mmol/L) and a total cholesterol of 5.6 mmol/L (interquartile range 4.9-6.3 mmol/L). Furthermore, only 48% of subjects with definite/probable FH were taking LMT in the study. This is evident, since the LDL-C levels were 6.5 mmol/L (interquartile range: 5.1-6.8 mmol/L) and 4.7 mmol/L (interquartile range: 3.8-5.1 mmol/L) for those taking LMT and those not taking LMT.

We have undertaken an exercise to estimate a revised rate ratio based on simulating the CV event reduction if all patients from Benn et al. (2012) were actually receiving LMT. The adjustment is based on assuming that the patients without LMT achieve the same LDL-C as those receiving LMT. For example, the definite/probable FH cohort LDL-C is reduced from 6.5 mmol/L to 4.7 mmol/L, thereby achieving an absolute reduction of 1.8 mmol/L reduction. This absolute reduction is then translated into CV event reduction based on the CTTC meta-analysis.[24] The CV event reduction (0.72 per mmol/L of LDL-C) based on the '*more versus less intensive statin therapy'* is used for the FH cohort, and the CV event reduction for *'statins versus placebo'* used for the general population (0.78 per mmol/L of LDL-C). This was also reported for the ranges based on the original confidence intervals reported in Benn et al. (2012).[9] These calculations are presented in Table 1-8. We have therefore adjusted the rate ratio from 7.1 (range 5.7-8.7) to 6.1 (range 4.9-7.5) used in the model.

We have conducted sensitivity analyses for the HeFH primary prevention and secondary prevention population based on a range of alternative rate ratios (range of 2-10) and baseline LDL-C (3.5 mmol/L to 6 mmol/L). These are presented in Figure 1-5 and Figure 1-6 for patients without and patients with existing CVD, respectively.

The analyses have the following elements included to support further interpretation:

- FH rate ratio (input): the rate ratio used for CVD rate adjustment in the model
- FH rate ratio (modelled): this is the computed rate ratio for CV events based on HeFH populations with and without the adjustment over the modelled lifetime for the backbone arm. The modelled FH rate ratio is less than the inputted rate ratio due to CV and non-CV mortality. This is calculated as the ratio of the rates of any CV event at baseline for a HeFH population versus HeFH population without CVD rate adjustment.
- 10-year risk: this is calculated as the risk of 1 or more CV events over a 10 year time frame.

For example, in the HeFH primary prevention, the inputted HeFH CV rate ratio of 6.1 translates to a modelled rate ratio of approximately 5.5 over the lifetime which is also equivalent to a 10-year CVD risk of approximately 28% for one or more CV events. In HeFH secondary prevention, this translates to a modelled rate ratio of 3.9 over the lifetime which is also equivalent to a 10-year CVD risk of approximately 62%.

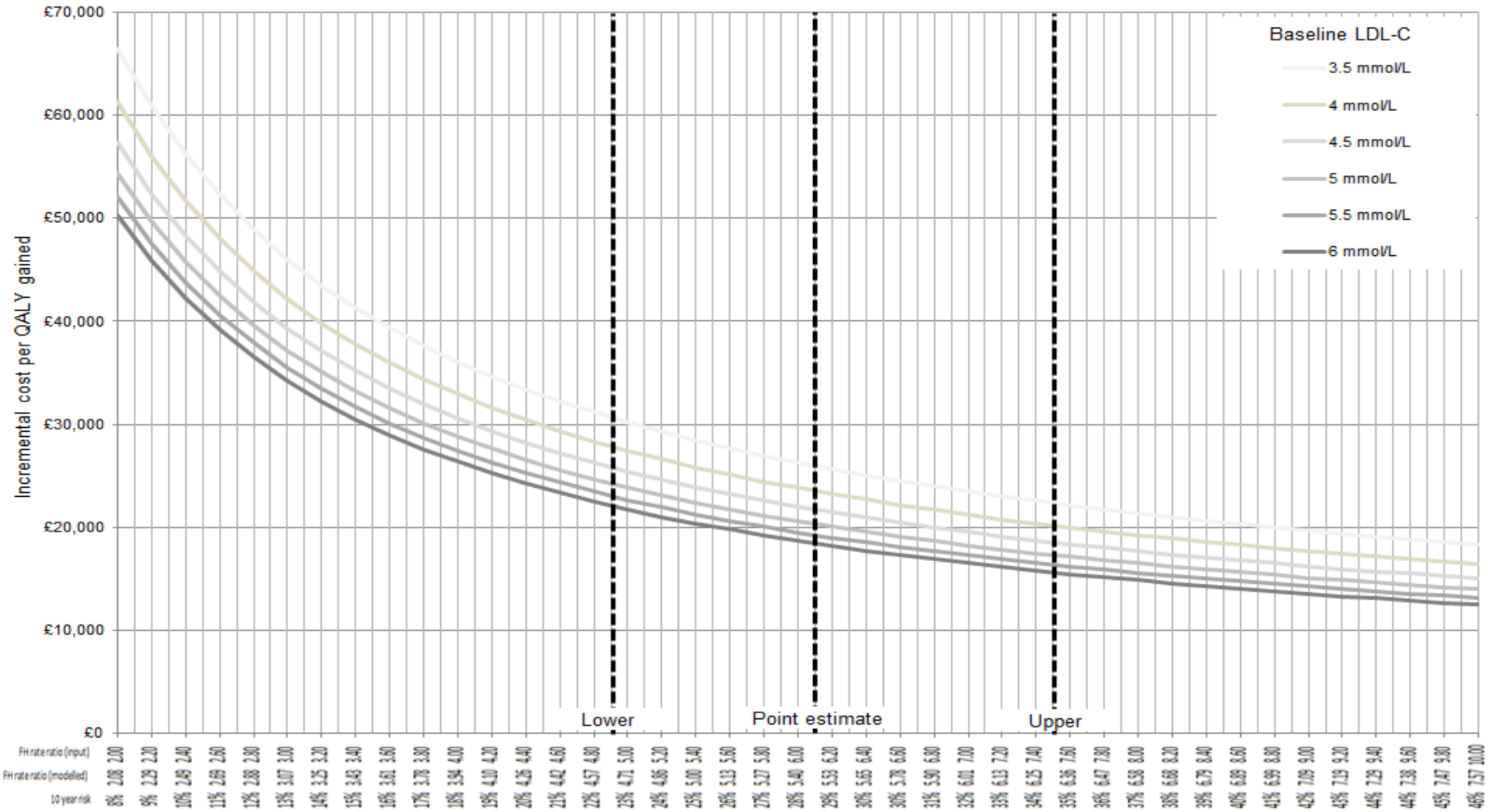
Additionally, the ACD (Section 4.17, page 46) states, *'the estimate from Benn et al. was not event-specific, so it increased the risk of all CV events by a factor of 7.1.'* As stated earlier, the effects of accelerated atherosclerosis in FHare not limited to the coronary arteries. We recognise that Benn et al. (2012) specifically reported coronary artery disease events. Therefore, we have also explored a conservative scenario whereby the rate ratio for stroke events is assumed to be 1, whilst retaining the adjusted value for coronary events (Table 6-3 and Table 6-4).These scenario analyses indicates the results are not sensitive to this variable even when a conservative assumption is adopted.

Table 1-8 Adjustment of rate ratio report in Benn at al. (2012)

Point estimate	n	Odds ratio	Odds	Rate	Baseline LDL-C (mmol/L)	Adjusted LDL-C (mmol/L)	Adjusted rate (LMT treated)	Risk	Pooled risk	Pooled rate	Rate ratio
Unlikely FH (Off LMT)	58158	1 (reference)	0.0466	0.0456	3.2	2.3	0.0365	0.0358	0.0520	0.0534	6.1
Unlikely FH (On LMT)	6061	5.6	0.2612	0.2321	2.3	2.3	0.2321	0.2071			
Definite or probable FH (Off LMT)	260	13.2	0.6157	0.4798	6.5	4.7	0.2656	0.2333	0.2773	0.3247	
Definite or probable FH (On LMT)	242	10.3	0.4805	0.3924	4.7	4.7	0.3924	0.3245			
Lower bound	**n**	**Odds ratio**	**Odds**	**Rate**	**Baseline LDL-C (mmol/L)**	**Adjusted LDL-C (mmol/L)**	**Adjusted rate (LMT treated)**	**Risk**	**Pooled risk**	**Pooled rate**	**Rate ratio**
Unlikely FH (Off LMT)	58158	1 (reference)	0.0466	0.0456	3.2	2.3	0.0365	0.0358	0.0508	0.0522	4.9
Unlikely FH (On LMT)	6061	5.2	0.2426	0.2172	2.3	2.3	0.2172	0.1952			
Definite or probable FH (Off LMT)	260	10	0.4665	0.3829	6.5	4.7	0.2120	0.1910	0.2275	0.2582	
Definite or probable FH (On LMT)	242	7.8	0.3638	0.3103	4.7	4.7	0.3103	0.2668			
Upper bound	**n**	**Odds ratio**	**Odds**	**Rate**	**Baseline LDL-C (mmol/L)**	**Adjusted LDL-C (mmol/L)**	**Adjusted rate (LMT treated)**	**Risk**	**Pooled risk**	**Pooled rate**	**Rate ratio**
Unlikely FH (Off LMT)	58158	1 (reference)	0.0466	0.0456	3.2	2.3	0.0365	0.0358	0.0531	0.0545	7.5
Unlikely FH (On LMT)	6061	6.0	0.2799	0.2468	2.3	2.3	0.2468	0.2187			
Definite or probable FH (Off LMT)	260	17.8	0.8303	0.6045	6.5	4.7	0.3346	0.2844	0.3361	0.4096	
Definite or probable FH (On LMT)	242	13.8	0.6437	0.4970	4.7	4.7	0.4970	0.3916			

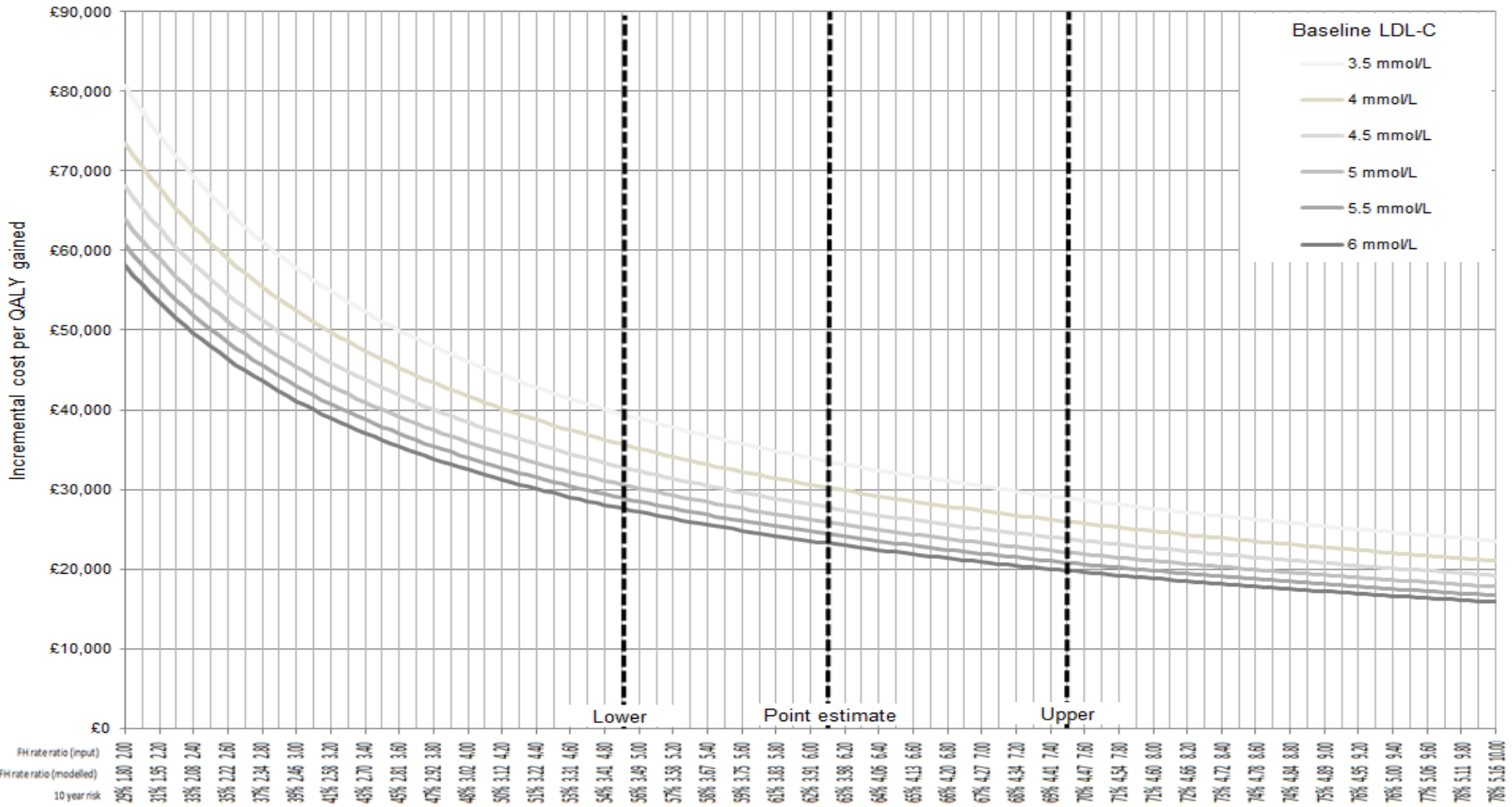
FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LMT; lipid-modifying therapy

Figure 1-5 HeFH primary prevention – cost-effectiveness results based on alternative FH rate ratios and baseline LDL-C for evolocumab and statins versus ezetimibe and statins



Notes: Dashed vertical lines represent the adjusted Benn et al. (2012) CV rate ratio of 6.1 (range 4.9-7.5)
LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year

Figure 1-6 HeFH secondary prevention – cost-effectiveness results based on alternative FH rate ratios and baseline LDL-C for evolocumab and statins versus ezetimibe and statins



Notes: Dashed vertical lines represent the adjusted Benn et al. (2012) CV rate ratio of 6.1 (range 4.9-7.5)
LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year

Summary

A literature review was undertaken to determine the CVD risk associated with FH. Fourteen publications based on population-based (n = 1), registry-based (n = 7) and hospital- and family-based studies (n = 6) were identified and assessed for risk of bias to determine the least biased estimate for the rate of increased CVD in patients with FH compared with non-FH patients.

The publications reported variable definitions of CVD outcomes and measurement either non-fatal or fatal (detection bias), lack of non-FH comparator group within the same study (selection bias) were the most common limitations for registries. Individual hospital-based studies and family-based studies lack generalisability (selection bias).

Selection bias for registry-based and hospital/family-based studies included in the review is a major source of bias affecting estimates of CVD risk in FH from these studies, making generalisability highly limited. In addition, some of these studies lacked a non-FH comparator group or included only non-fatal or fatal events, further limiting generalisability.

In contrast, the only population-based study (Benn et al. (2012)), a population level survey of patients undertaken in Denmark that compared risk of coronary artery disease in patients with FH versus patients without FH, showed a low degree of bias and was the only study that included both fatal and non-fatal CV events. This study was therefore deemed to represent the best available literature-based estimate of CVD risk in FH. Compared with non-FH patients not on lipid-modifying therapy, the study reported an odds ratio for coronary artery disease in FH patients of 10.3 (95% CI: 7.8-13.8) and 13.2 (95% CI: 10.0-17.4) in subjects treated and not treated with lipid lowering therapy, respectively.

The rate ratio from Benn et al. (2012) was adjusted to derive an estimate reflecting treatment with LMT in both the general population and FH population with a derived rate ratio of 6.1 (range 4.9 to 7.5). Additionally, we have conducted sensitivity analyses for the HeFH primary prevention and secondary prevention population based on a range of alternative rate ratios (range of 2-10) and baseline LDL-C (3.5 mmol/L to 6 mmol/L). Importantly, a rate ratio of 6.1 translates to a lifetime modelled rate ratio (accounting for CV and non-CV mortality) of 5.5 (10-year CVD risk of 28%) and 3.9 (10-year CVD risk of 62%) for primary prevention and secondary prevention populations, respectively.

Whilst we have assessed the cost-effectiveness in HeFH based on CVD history, as described in our response (and subgroup analyses), CVD risk is multi-factorial, therefore decision-making for the HeFH on the basis of CVD history alone is inappropriate given the potential for the presence of additional risk factors (e.g. diabetes mellitus).

1.6 Background health-related quality of life

- We have amended the background utility values in the model using the equation from the HSE by Ara et al. (2010) as per the Committee's preference.
- Implementation of this amendment reduces the ICER marginally in favour of evolocumab since the background HRQoL is estimated to be slightly higher using the equation from Ara et al. (2010) compared to Dolan et al. (1996).

Context

The ACD (Section 4.19, page 47) states, *'The Committee also noted that the relationship assumed between age and utility was based on a study by Dolan et al. (1996), which the ERG considered to be crude and outdated by a more recent equation based on the Health Survey for England.'*

The Committee considered that the utility values in the model did not reflect the best available evidence. The Committee concluded that the equation from the Health Survey for England (HSE) should be used to inform the relationship between age and background health-related quality of life (HRQoL).

Implementation

We have amended background HRQoL based on data from the HSE by using the more recent equations which have been published by Ara et al. (2010)[25] to inform the relationship between age and background HRQoL.

The following equations have been implemented in the model from Ara et al (2010) are recommended by the authors for modelling patients with and without existing CVD.

- The utility for patients without existing CVD is based on the equation for individuals with no history of CVD (defined as angina, heart attack or stroke)
- The utility for patients with existing CVD is based on the equation for individuals in the general population.

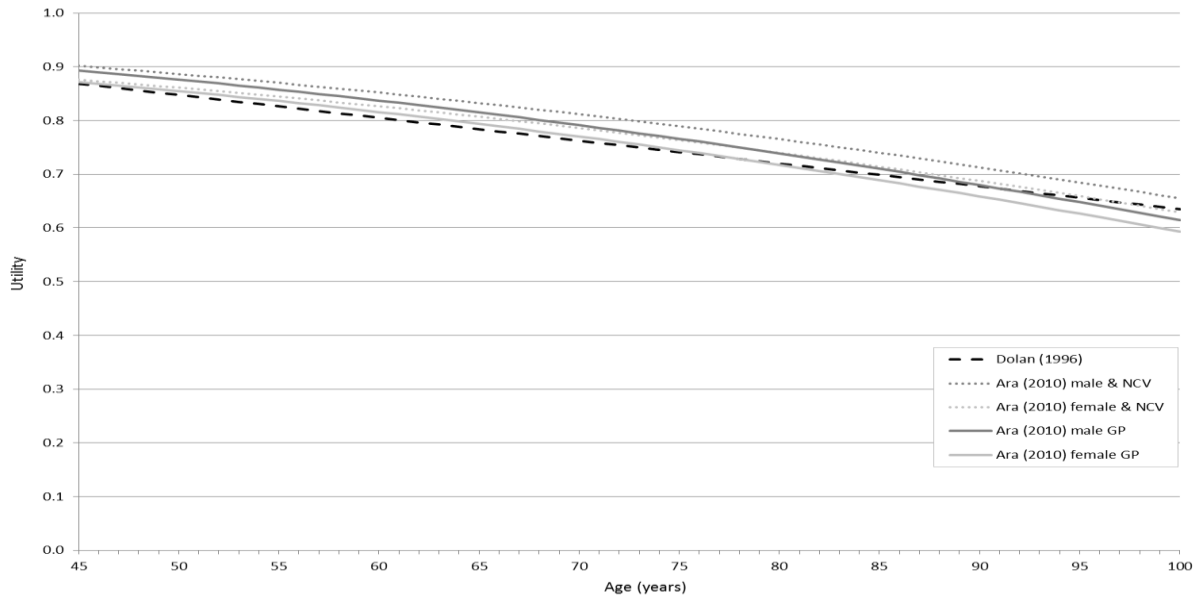
These equations are described below:

$$Utility_{NCV} = 0.9454933 + (0.0256466 \times male) - (0.0002213 \times age) - (0.0000294 \times age^2)$$
$$Utility_{GP} = 0.9508566 + (0.0212126 \times male) - (0.0002587 \times age) - (0.0000332 \times age^2)$$

Where NCV = no history of CVD, and GP = general population

For comparative purposes, the background utilities based on the original source (Dolan et al. 1996)[26] and the updated source (Ara et al. 2010) in the model are illustrated in Figure 1-7.

Figure 1-7 Background HRQoL based on Dolan et al (1996) and Ara et al (2010)



GP, general population; NCV, no history of cardiovascular disease

Additionally, for illustrative purposes, the cumulative quality-adjusted life year (QALY) gains for the alternative approaches for individuals from age 60 to 99 (40 years) are presented in Table 1-9. These indicate that application of the equations based on Ara et al. (2010) yield slightly greater cumulative QALYs compared to Dolan et al. (1996) in all populations except for general population for females (secondary prevention). As such, implementation of this amendment reduces the incremental cost-effectiveness ratio (ICER) marginally in favour of evolocumab.

Table 1-9 Cumulative QALYs based on alternative approaches for background HRQoL from ages 60 to 99 (40 years)

	Dolan (1996)	Ara (2010)			
	All	Male NCV	Female NCV	Male GP	Female GP
Cumulative QALYs	28.89	30.55	29.53	29.49	28.64

GP, general population; NCV, no history of cardiovascular disease; QALYs, quality-adjusted life years

1.7 Subgroups

- We have modelled subgroups based on actual patient-level characteristics from the evolocumab studies (LAPLACE-2, GAUSS-2 and RUTHERFORD-2) to account for correlation between variables to derive accurate estimations of CVD risk.
- We have additionally obtained patient-level characteristics for the subgroups (e.g. additional risk factors) based on appropriate high-risk populations from CPRD studies allowing accurate estimation of CVD risk in more subgroups than feasible from the evolocumab studies given the larger data-set.

Context

The ACD (Section 4.22, pages 50-51) states, *'The Committee was aware that these analyses had the same limitations as the primary analysis (see section 4.21). Also, the ERG highlighted additional methodological limitations in that the company manually changed the subgroup variable for the entire population and held the other characteristics at their observed values, instead of modelling the subgroups that actually had these characteristics in the trial. The Committee was aware that some variables may be correlated in subgroups, and so within-trial subgroups would reflect the subgroup characteristics more accurately.'*

The Committee agreed that evolocumab might be cost effective in specific subgroups with CVD; the analyses presented had several limitations, which made it unsure about the reliability of the results. Therefore, the Committee concluded that the subgroups reflecting all the characteristics of the actual subgroups in the clinical trials should be modelled.

Implementation

We adopted this approach for the subgroup analysis to allow presentation of hypothetical profiles given the insufficient patient numbers to allow a robust estimation of baseline CVD risk. We agree with the limitations of this equation based approach since there may be correlation between some variables in the different subgroups.

We acknowledge the Committee's preference to assess subgroups based on patients that had the actual characteristics in the evolocumab trials. Therefore, we have included actual patient-level characteristics where possible. This has allowed assessment of patients with the presence of one additional risk factor in LAPLACE-2 and GAUSS-2. These are secondary prevention patients with diabetes mellitus and secondary prevention patients with a history of ACS. To supplement the analyses, we have also used patient-level characteristics of actual subgroups from Clinical Practice Research Datalink (CPRD). This allowed increased patients numbers to robustly estimate baseline CVD risk for patients with diabetes mellitus, two or three vascular beds, atrial fibrillation and those with a history of ACS.

Use of patient-level characteristics from CPRD has also allowed assessment of combination of two or more additional risk factors given the larger overall dataset (n = 10,061) compared to LAPLACE-2 (n = 330) GAUSS-2 (n = 117). A comparison of the data availability to conduct subgroup analysis between our original approach and the revised approach based on patient-level characteristics from LAPLACE-2/GAUSS-2 and CPRD are summarised in

Table 1-10. The subgroup cost-effectiveness analyses for differing baseline LDL-C were based on manual amendments to define cohort minimum LDL-C levels (intervals of 0.5 mmol/L). It would not have been possible to robustly estimate patient-level risk for the subgroups if we held a requirement for specific LDL-C levels for patients for each LDL-C interval. Since we are manually increasing baseline LDL-C, it is plausible that the approach is conservative given no adjustment of other variables that could be correlated. This approach is also consistent with a previous NICE technology appraisal (NICE TA132)[27] and a clinical guideline (NICE CG181)[3].

Table 1-10 Comparison of data sources to support subgroup analyses

Subgroup	Original approach	Revised approach		
		LAPLACE-2	GAUSS-2	CPRD
LDL-C	Equation	Equation	Equation	Equation
Sex	Actual	Actual	Actual	Actual
Diabetes mellitus	Mixed	Actual	Actual	Actual
Vascular beds	Equation	Unable	Unable	Actual
Atrial fibrillation	Equation	Unable	Unable	Actual
History of ECVD	Equation	Unable	Unable	Not assessed
History of ACS	Equation	Actual	Actual	Actual
History of IS	Equation	Unable	Unable	Not assessed
History of HF	Equation	Unable	Unable	Not assessed

ACS, acute coronary syndrome; CPRD; Clinical Practice Research Datalink; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol

It is notable that in our original evidence submission, we also included other risk factors such as moderate to severe chronic kidney disease (eGFR < 60mL/min/1.73m^2), progressive CVD evidenced by ≥2 documented acute ischaemic CV events or revascularisation procedures or elevated plasma Lp(a) ≥ 77 mg/dL (≥ 90% centile) which were deemed equivalent to diabetes mellitus based on clinical expert opinion. It was not possible to assess populations with these specific risk factors (and potential correlation with other variables).

Clinical Practice Research Datalink – non-familial hypercholesterolaemia

The CPRD study (evidence submission, Appendix XI) dataset for primary prevention (diabetes mellitus, non-familial) and secondary prevention (non-familial) was used to support further subgroup analyses. The populations appropriately represented high-risk patients receiving high-intensity statins for who evolocumab would be considered in accordance with its marketing authorisation. Subgroup datasets based on Table 1-10 for one or more additional risk factors were analysed. Summary descriptive statistics of the patient-level characteristics are provided in Appendix III for each of the subgroups.

Clinical Practice Research Datalink – familial hypercholesterolaemia

We have previously conducted a study in CPRD (Amgen Study: Prevalence and clinical management of familial hypercholesterolaemia: a retrospective UK database pilot study; Study 20140465). This study was based on a FH dataset of 8,646 patients diagnosed with

FH between 1st August 2008 and 31st July 2013. FH patients were identified via the CPRD diagnostic codes for FH presented in Table 1-11.

Table 1-11 Familial Hypercholesterolaemia READ codes

Code	Term
C3200.	Familial hypercholesterolaemia
C3201.	Hyperbetalipoproteinaemia
C3203.	Low-density-lipoprotein-type hyperlipoproteinaemia
C3204.	Fredrickson's hyperlipoproteinaemia, type Iia
C3205.	Familial defective apolipoprotein B-100
C3220.	Familial combined hyperlipidaemia
Source: HSCIC-QOF (2014) Prevention (CVD-PP) Indicator Set. HSCIC	

Fur the purposes of the subgroup analyses, FH patients have been stratified on the basis of CVD history. Summary descriptive statistics of the patient-level characteristics are provided in Appendix III. These dataset have been used to support risk estimation in the context of the UK patient-level characteristics and associated CVD risk. Scenario cost-effectiveness analyses based on CPRD are presented in Section 2.

Summary

We have modelled subgroups based on actual patient-level characteristics from the evolocumab studies (LAPLACE-2, GAUSS-2 and RUTHERFORD-2) to account for correlation between variables to derive accurate estimations of CVD risk.

We have additionally obtained patient-level characteristics for the subgroups (e.g. additional risk factors) based on appropriate high-risk populations from CPRD studies allowing accurate estimation of CVD risk in more subgroups than feasible from the evolocumab studies given the larger data-set.

1.8 Drug acquisition cost based on FP10 prescribing

- We believe that basing the cost of evolocumab on list price via FP10 does not reflect the true cost to the NHS since, A) we do not plan to operate differential pricing based on care setting, B) NHS commissioners will not proactively pay list price where the technology is only recommended in conjunction with a PAS within NICE guidance, and, C) we plan to replicate a primary care rebate model to prevent CCGs from paying the list price.
- We recommend that any guidance recommending the use of evolocumab should include appropriate direction that the technology is cost-effective only when considered in conjunction with the PAS proposed by the manufacturer regardless of care setting to ensure appropriate procurement.

Context

The Committee discussed whether the ICERs it considered reflected the cost of evolocumab to the NHS. It understood that the actual discount received by the NHS may be less than the percentage discount offered in the patient access scheme. This was because people may move from secondary to primary care after 2–3 years, and simple discounts do not apply when drugs are prescribed through FP10 prescriptions.

The Committee noted the company's sensitivity analyses to explore different assumptions about the implementation of the patient access scheme (PAS) (Section 3.52). It considered that most people would self-administer at home, with the repeat prescriptions being provided by primary care, although people are likely to continue to be followed up in secondary care.

The Committee agreed that up to 90% of people may have evolocumab through FP10 prescriptions in primary care after 2 years. Therefore, the Committee concluded that the modelling should take into account FP10 prescribing of evolocumab in primary care to reflect the true cost of evolocumab to the NHS.

Implementation

We believe that basing the cost of evolocumab on list price via FP10 does not reflect the true cost to the NHS. Under no circumstances would we implement differential pricing based on alternative distribution or prescribing settings. Nor do we envisage NHS commissioners proactively paying list price in the presence of a confidential discount, especially when the cost-effectiveness has not been demonstrated at list price.

In previous correspondence, we outlined our intention to provide evolocumab to the NHS at the same acquisition cost regardless of the care setting (secondary or primary care). As noted, savings associated with lower acquisition costs for medicines with simple PAS discounts compared to the list price cannot be realised by the NHS when prescribed through FP10 prescriptions due to the current financial flows.

We have experience with regards implementation of parallel simple PAS (secondary care) and an equivalent confidential commercial discount (primary care) for an existing medicine that has been recommended through a NICE Technology Appraisal (NICE TA265:

Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours).

We acknowledge the feedback that since routine lipid management is an area of standard GP practice, there may be a potential transition of patients from secondary to primary care after 2 to 3 years. We would plan to follow the same process if evolocumab prescribing was to transition to primary care in the future for some patients.

The primary care rebate model for denosumab was designed in collaboration with the NHS to ensure minimal administrative burden for NHS staff. Therefore, CCG representatives (e.g. pharmacists) are only required to complete a single contract agreement at the outset and then provide routinely available ePACT data via email to ensure realisation of the equivalent simple PAS price in primary care. The primary care rebate model has been noted for its ease of administration. We are currently in process for approval of an identical primary care rebate model for evolocumab with PrescQIPP Pharmaceutical Industry Scheme Governance Review Board.

Summary

We recommend that any guidance recommending the use of evolocumab should include appropriate direction that the technology is cost-effective only when considered in conjunction with the PAS proposed by the manufacturer regardless of care setting.

2 Additional comments - Composite health states

- We have provided additional information to reassure the Committee regarding the use of the composite health states.
- The implementation of composite health states prevents the occurrence of clinically implausible scenarios, whereby a patient will benefit (improved HRQoL, reduced CV management cost or reduced risk) from experiencing a specific sequence of events which can occure in a memory-less Markov model.
- The assumptions underpinning costs, utilities and risks have been supported by clinical and economic advisors as reasonable and conservative in the absence of data.

Context

The ACD (Section 4.11, page 41) states, *'The Committee agreed that the composite states reflected specific combinations of CV events, which were unlikely to be robustly modelled given the existing evidence. Because the effect of using the composite states was unclear, the Committee expressed its concern about the internal validity of the model.'*

Response

We have provided additional information to reassure the Committee regarding the use of the composite health states. As noted in our response to clarification questions (B11), previous economic evaluations have attempted to account for combined health states by ensuring the appropriate application of risks, utilities and costs to prevent patients from benefiting from specific sequences of CV events which would not be clinically plausible.

Our economic model has included the full set of possible composite health states and has applied the same principles to introduce memory of prior CV events for risk, utilities, and costs, as implemented only partially in earlier economic evaluation studies. Furthermore, during the economic model development, clinical and economic advisors supported these assumptions as reasonable and conservative in the absence of robust data.

Additionally, we have provided some examples of the counter-factual/clinically implausible scenarios associated with a memory-less Markov model and hence our approach for composite health states.

Worked example - utilities, costs and risks

The health-related quality of life of a patient is anticipated to remain the same or worsen by experiencing further CV events; therefore the lowest utility is used. Table 2-1 provides an overview of the potential transitions when a Markov model with and without composite health states are used. The example is based on the utility multiplers used in the model. A memory-less model will result in clinically implausible scenarios whereby patients' health can improve by experiencing a certain sequence of events. For example (Table 2-1, grey cells):

- A patient transitioning from a history of IS to ACS, IS to HF, or HF to ACS will experience an improvement in health-related quality of life.

Table 2-1 Utilities: Example of clinically implausible scenarios due to a memory-less Markov model

First CV event	First CV event utility	Next CV event	Utility		Markov model		Markov model inc. composite health states		Markov model Clinically plausible	
			Acute (next event)	Long-term (next event)	Acute (next event)	Long-term (next event)	Acute (next event)	Long-term (next event)	Acute	Long-term
ACS	0.880	ACS	0.770	0.880	0.770	0.880	0.770	0.880	Yes	Yes
ACS	0.880	IS	0.628	0.628	0.628	0.628	0.628	0.628	Yes	Yes
ACS	0.880	HF	0.683	0.683	0.683	0.683	0.683	0.683	Yes	Yes
IS	0.628	ACS	0.770	0.880	0.770	0.880	0.628	0.628	No	No
IS	0.628	IS	0.628	0.628	0.628	0.628	0.628	0.628	Yes	Yes
IS	0.628	HF	0.683	0.683	0.683	0.683	0.628	0.628	No	No
HF	0.683	ACS	0.770	0.880	0.770	0.880	0.683	0.683	No	No
HF	0.683	IS	0.628	0.628	0.628	0.628	0.628	0.628	Yes	Yes
HF	0.683	HF	0.683	0.683	0.683	0.683	0.683	0.683	Yes	Yes

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

Table 2-2 Costs: Example of clinically implausible scenarios due to a memory-less Markov model

First CV event	Long-term cost (first CV event)	Next CV event	Long-term cost (next event)	Markov model Long-term cost	Markov model inc. composite health states	Markov model Clinically plausible
ACS	£522.34	ACS	£522.34	£522.34	£522.34	Yes
ACS	£522.34	IS	£887.33	£887.33	£887.33	Yes
ACS	£522.34	HF	£1,078.26	£1,078.26	£1,078.26	Yes
IS	£887.33	ACS	£522.34	£522.34	£887.33	No
IS	£887.33	IS	£887.33	£887.33	£887.33	Yes
IS	£887.33	HF	£1,078.26	£1,078.26	£1,078.26	Yes
HF	£1,078.26	ACS	£522.34	£522.34	£1,078.26	No
HF	£1,078.26	IS	£887.33	£887.33	£1,078.26	No
HF	£1,078.26	HF	£1,078.26	£1,078.26	£1,078.26	Yes

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

Example - costs

The long-term CV management cost is anticipated to remain the same or increase by experiencing further CV events; therefore, we utilise the maximum cost of the individual CV events.

The similar trend is observed when considering long-term costs (Table 2-2). A memory-less model will allow clinically implausible scenarios whereby the medical costs can reduce by experiencing certain sequence of events. For example (Table 2-2, grey cells):

- A patient transitioning from a history of IS to ACS, HF to ACS or HF to IS will generate a cost-saving when comparing long-term costs.

Example – risks

We have also provided a hypothetical example based on a secondary prevention (non-familial) patient aged 62 in Table 2-3. A memory-less model will allow clinically implausible scenarios whereby the long-term risks can reduce by experiencing certain sequence of events.

- A patient transitioning from a history of ACS to IS, HF to ACS or HF to IS will experience a reduction in long-term CVD risk.

Table 2-3 CVD risk: Example of clinically implausible scenarios due to a memory-less Markov model

First CV event	First CV event long-term cost	Next CV event	Long-term cost (next event)	Markov model	Markov model inc. composite health states	Markov model Clinically plausible
ACS	0.0878	ACS	0.0878	0.0878	0.0878	Yes
ACS	0.0878	IS	0.0645	0.0645	0.0878	No
ACS	0.0878	HF	0.1436	0.1436	0.1436	Yes
IS	0.0645	ACS	0.0878	0.0878	0.0878	Yes
IS	0.0645	IS	0.0645	0.0645	0.0645	Yes
IS	0.0645	HF	0.1436	0.1436	0.1436	Yes
HF	0.1436	ACS	0.0878	0.0878	0.1436	No
HF	0.1436	IS	0.0645	0.0645	0.1436	No
HF	0.1436	HF	0.1436	0.1436	0.1436	Yes

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

The model is based on 13 composite health states that follow the same principles of these examples for utilities, costs and risks.

Summary

The implementation of composite health states prevents the occurrence of clinically implausible scenarios, whereby a patient will benefit (improved HRQoL, reduced CV management cost or reduced risk) from experiencing a specific sequence of events which can occure in a memory-less Markov model.

3 Cost-effectiveness results and sensitivity analyses

3.1 Summary of revised cost-effectiveness results

Updated economic model

The main changes in the model are summarised below and the anticipated impact on the cost-effectiveness results are summarised in Table 3-1:

Table 3-1 Appraisal Committee preferences for cost-effectiveness evidence

Element	Comments
Background HRQoL	▪ Inclusion of equation by Ara et al. (2010): Expected to reduce ICERs in favour of evolocumab due to higher background HRQoL.
REACH registry equation statin variable	▪ Set to "no" for statin intolerant/contraindicated: Expected to reduce ICERs in favour of evolocumab due to increased baseline CVD risk.
CVD risk	▪ QRISK2 used to predict PP risks: Expected to increase ICERs for evolocumab in FH due lower baseline CV rates estimated versus Framingham and to provide similar ICERs in non-FH as QRISK2 is calibrated versus real-world event rates. ▪ Non-familial PP patients experiencing events switch to the corresponding SP risks: Expected to reduce ICERs in favour of evolocumab due to increased overall CVD risk. ▪ REACH registry used to predict SP (non-familial) risks with no link PP and SP (non-familial) CVD risks: Expected to increase ICERs for evolocumab in FH due to lower baseline rates estimated versus Framingham and to provide similar ICERs in non-FH (PP risks lower than SP after calibration).
FH rate ratio	▪ Adjustment of rate ratio to 6.1 (4.9, 7.5): Expected to increase ICERs for evolocumab in FH due to lower baseline CVD risk.
Subgroups based on CPRD patient-level characteristics	▪ Expected to reduce ICERs in favour of evolocumab due to correlation between risk factors.

CV, cardiovascular; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PP, primary prevention; SP, secondary prevention

This section presents updated cost-effectiveness results and sensitivity analyses based on a revised model with implementation of the Committee's preferences. For brevity, results are described only for the comparison of evolocumab (with or without statins) versus ezetimibe (with or without statins) for the statin tolerant and statin intolerant/contraindicated populations. Full base case results are presented in Table 3-2.

Table 3-2 Summary of revised base case cost-effectiveness results (deterministic) including comparison with previous manufacturer estimates based on LAPLACE-2, GAUSS-2 and RUTHERFORD-2

Analysis	Population characteristics and comparison	Evolocumab		Ezetimibe		Incremental				
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER	ICER (previous)	Change
Primary prevention (non-familial) population (LAPLACE-2/GAUSS-2)										
Analysis A	Evo+statins vs. eze+statins (statin tolerant)	12.67	[redacted]	12.33	£9,928	0.34	[redacted]	£69,249	£74,331	-£5,082
Analysis B	Evo vs. eze (statin intolerant/contraindicated)	11.85	[redacted]	11.28	£9,849	0.57	[redacted]	£38,458	£78,879	-£40,421
Analysis C	Evo+eze vs. eze (statin intolerant/contraindicated)	11.93	[redacted]	11.28	£9,849	0.64	[redacted]	£41,911	£84,354†	-£42,443
Analysis D	Evo+eze+statins vs. eze+statins (statin tolerant)	12.70	[redacted]	12.33	£9,928	0.37	[redacted]	£78,459	£84,218†	-£5,759
Secondary prevention (non-familial) population (LAPLACE-2/GAUSS-2)										
Analysis E	Evo+statins vs. eze+statins (statin tolerant)	8.43	[redacted]	8.03	£21,408	0.40	[redacted]	£45,439	£46,005	-£566
Analysis F	Evo vs. eze (statin intolerant/contraindicated)	8.01	[redacted]	7.48	£19,216	0.53	[redacted]	£30,985	£49,278	-£18,293
Analysis G	Evo+eze vs. eze (statin intolerant/contraindicated)	8.09	[redacted]	7.48	£19,216	0.61	[redacted]	£33,814	£52,811	-£18,997
Analysis H	Evo+eze+statins vs. eze+statins (statin tolerant)	8.48	[redacted]	8.03	£21,408	0.45	[redacted]	£50,257	£50,880	-£623
HeFH primary prevention population (RUTHERFORD-2)										
Analysis I	Evo+statins vs. eze+statins (statin tolerant)	13.57	[redacted]	12.61	£16,246	0.96	[redacted]	£23,536	£21,975†	£1,561
Analysis J	Evo vs. eze (statin intolerant/contraindicated)	13.31	[redacted]	12.32	£16,881	1.00	[redacted]	£21,921	£22,982†	-£1,061
Analysis K	Evo+eze vs. eze (statin intolerant/contraindicated)	13.48	[redacted]	12.32	£16,881	1.16	[redacted]	£23,602	£24,602†	-£1,000
Analysis L	Evo+eze+statins vs. eze+statins (statin tolerant)	13.71	[redacted]	12.61	£16,246	1.10	[redacted]	£25,583	£23,831†	£1,752
HeFH secondary prevention population (RUTHERFORD-2)										
Analysis M	Evo+statins vs. eze+statins (statin tolerant)	9.56	[redacted]	8.97	£25,773	0.59	[redacted]	£29,910	£24,866†	£5,044
Analysis N	Evo vs. eze (statin intolerant/contraindicated)	9.01	[redacted]	8.37	£27,089	0.64	[redacted]	£25,293	£25,856†	-£563
Analysis O	Evo+eze vs. eze (statin intolerant/contraindicated)	9.12	[redacted]	8.37	£27,089	0.74	[redacted]	£27,390	£27,659†	-£269
Analysis P	Evo+eze+statins vs. eze+statins (statin tolerant)	9.65	[redacted]	8.97	£25,773	0.68	[redacted]	£32,698	£26,919†	£5,779

†Additional analyses not initially included that have been conducted retrospectively with previous model for comparative purposes
Evo, evolocumab; eze, ezetimibe; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Primary prevention (non-familial)

Within the primary prevention (non-familial) population (Analysis A), the base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.34 QALYs at an additional cost of £[redacted] as compared against ezetimibe plus statins; the resulting ICER is estimated to be £69,249 per QALY gained. Within the secondary prevention (non-familial) statin intolerant/contraindicated population (Analysis B), the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.57 QALYs at an additional cost of £[redacted] as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £38,458 per QALY gained.

Secondary prevention (non-familial)

Within the secondary prevention (non-familial) population (Analysis E), the base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.40 QALYs at an additional cost of £18,070 as compared against ezetimibe plus statins; the resulting ICER is estimated to be £[redacted] per QALY gained. Within the non-familial secondary prevention statin intolerant/contraindicated population (Analysis F), the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.53 QALYs at an additional cost of £[redacted] as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £30,985 per QALY gained.

HeFH primary prevention

Within the HeFH primary prevention population (Analysis I), the base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.96 QALYs at an additional cost of £[redacted] as compared against ezetimibe plus statins; the resulting ICER is estimated to be £23,536 per QALY gained. Within the HeFH statin intolerant/contraindicated population (Analysis F), the company's base case analysis suggests that evolocumab monotherapy produces an additional 1.00 QALYs at an additional cost of £[redacted] as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £21,921 per QALY gained.

HeFH secondary prevention

Within the HeFH secondary prevention population (Analysis M), the base case analysis suggests that evolocumab plus statins is expected to produce an additional 0.59 QALYs at an additional cost of £[redacted] as compared against ezetimibe plus statins; the resulting ICER is estimated to be £29,910 per QALY gained. Within the HeFH secondary prevention statin intolerant/contraindicated population (Analysis N), the company's base case analysis suggests that evolocumab monotherapy produces an additional 0.64 QALYs at an additional cost of £[redacted] as compared against ezetimibe monotherapy; the resulting ICER is estimated to be £25,293 per QALY gained.

Probabilistic sensitivity analyses

The probabilistic sensitivity analysis (PSA) was run with 1,000 simulations. The results of the PSA for analyses A to M are presented in Table 3-3 in terms of ICER and probability that

evolocumab is the optimal strategy at maximum acceptable incremental cost-effectiveness ratios of £20,000 and £30,000 per QALY gained.

The deterministic and probabilistic ICERs were broadly consistent across the populations and comparisons for the analyses based on LAPLACE-2, GAUSS-2 and RUTHERFORD-2.

Additional cost-effectiveness analyses based on patient-level characteristics from CPRD

We have also conducted cost-effectiveness analyses based on patient-level characteristics for the populations where possible with data from CPRD. These results are summarised in Table 3-4. These indicate an ICER of £54,432 per QALY gained in secondary prevention (non-familial) for evolocumab and statins versus ezetimibe and statins (Analysis E). The ICERs in HeFH primary prevention and HeFH secondary prevention were £15,836 and £26,038 per QALY gained for evolocumab and statins versus ezetimibe and statins (Analyses I and M).

Table 3-3 Summary of revised base case cost-effectiveness results (probabilistic) based on LAPLACE-2, GAUSS-2 and RUTHERFORD-2

Analysis	Population characteristics and comparison	Probabilistic ICER	Probability evolocumab optimal at defined WTP threshold	
			λ=£20,000/QALY gained	λ=£30,000/QALY gained
Primary prevention (non-familial) population (LAPLACE-2/GAUSS-2)				
Analysis A	Evo+statins vs. eze+statins (statin tolerant)	£71,047	0.0%	0.0%
Analysis B	Evo vs. eze (statin intolerant/contraindicated)	£39,730	0.0%	0.0%
Analysis C	Evo+eze vs. eze (statin intolerant/contraindicated)	£43,442	0.0%	0.0%
Analysis D	Evo+eze+statins vs. eze+statins (statin tolerant)	£80,323	0.0%	0.0%
Secondary prevention (non-familial) population (LAPLACE-2/GAUSS-2)				
Analysis E	Evo+statins vs. eze+statins (statin tolerant)	£46,511	0.0%	0.0%
Analysis F	Evo vs. eze (statin intolerant/contraindicated)	£31,885	0.0%	30.1%
Analysis G	Evo+eze vs. eze (statin intolerant/contraindicated)	£34,851	0.0%	5.4%
Analysis H	Evo+eze+statins vs. eze+statins (statin tolerant)	£51,207	0.0%	0.0%
HeFH primary prevention population (RUTHERFORD-2)				
Analysis I	Evo+statins vs. eze+statins (statin tolerant)	£24,252	3.6%	94.3%
Analysis J	Evo vs. eze (statin intolerant/contraindicated)	£22,546	15.5%	97.0%
Analysis K	Evo+eze vs. eze (statin intolerant/contraindicated)	£24,396	1.1%	95.8%
Analysis L	Evo+eze+statins vs. eze+statins (statin tolerant)	£26,410	0.0%	86.9%
HeFH secondary prevention population (RUTHERFORD-2)				
Analysis M	Evo+statins vs. eze+statins (statin tolerant)	£30,890	0.0%	41.7%
Analysis N	Evo vs. eze (statin intolerant/contraindicated)	£25,775	2.3%	83.5%
Analysis O	Evo+eze vs. eze (statin intolerant/contraindicated)	£28,232	0.0%	68.7%
Analysis P	Evo+eze+statins vs. eze+statins (statin tolerant)	£33,508	0.0%	15.2%

Evo, evolocumab; eze, ezetimibe; heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; WTP, willingness-to-pay

Table 3-4 Summary of revised base case cost-effectiveness results (deterministic) including comparison with previous manufacturer estimates based on CPRD

Analysis	Population characteristics and comparison	Evolocumab		Ezetimibe		Incremental		
		QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER
Primary prevention (non-familial) population								
Analysis A	Evo+statins vs. eze+statins (statin tolerant)	Not conducted						
Analysis B	Evo vs. eze (statin intolerant/contraindicated)	Not conducted						
Analysis C	Evo+eze vs. eze (statin intolerant/contraindicated)	Not conducted						
Analysis D	Evo+eze+statins vs. eze+statins (statin tolerant)	Not conducted						
Secondary prevention (non-familial) population								
Analysis E	Evo+statins vs. eze+statins (statin tolerant)	6.68	[redacted]	6.40	£16,182	0.28	[redacted]	£54,432
Analysis F	Evo vs. eze (statin intolerant/contraindicated)	Not possible to identify statin intolerant/contraindicated patients						
Analysis G	Evo+eze vs. eze (statin intolerant/contraindicated)	Not possible to identify statin intolerant/contraindicated patients						
Analysis H	Evo+eze+statins vs. eze+statins (statin tolerant)	6.68	[redacted]	6.40	£16,182	0.28	[redacted]	£67,615
HeFH primary prevention population								
Analysis I	Evo+statins vs. eze+statins (statin tolerant)	12.36	[redacted]	11.13	£17,397	1.23	[redacted]	£15,836
Analysis J	Evo vs. eze (statin intolerant/contraindicated)	Not possible to identify statin intolerant/contraindicated patients						
Analysis K	Evo+eze vs. eze (statin intolerant/contraindicated)	Not possible to identify statin intolerant/contraindicated patients						
Analysis L	Evo+eze+statins vs. eze+statins (statin tolerant)	12.55	[redacted]	11.13	£17,397	1.42	[redacted]	£17,400
HeFH secondary prevention population								
Analysis M	Evo+statins vs. eze+statins (statin tolerant)	7.30	[redacted]	6.75	£21,894	0.55	[redacted]	£26,038
Analysis N	Evo vs. eze (statin intolerant/contraindicated)	Not possible to identify statin intolerant/contraindicated patients						
Analysis O	Evo+eze vs. eze (statin intolerant/contraindicated)	Not possible to identify statin intolerant/contraindicated patients						
Analysis P	Evo+eze+statins vs. eze+statins (statin tolerant)	7.39	[redacted]	6.75	£21,894	0.64	[redacted]	£28,359

Evo, evolocumab; eze, ezetimibe; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

HeFH (primary and secondary prevention) based on RUTHERFORD-2 and CPRD

Combined HeFH primary prevention and HeFH secondary prevention cost-effectiveness results are presented based on a weighted analysis (Table 3-5). The costs and QALYs from RUTHERFORD-2 and CPRD based analyses have been weighted based on the estimated proportion of adult diagnosed and treated HeFH primary and secondary prevention patients from the Royal College of Physicians FH audit. The FH audit cites that 559 (57.8%) of 967 adults with confirmed history of CHD in the patient notes.[28] These results indicate an ICER of £27,220 and £21,733 per QALY gained for evolocumab and statins versus ezetimibe and statins based on patient-level characteristics from RUTHERFORD-2 and CPRD, respectively.

Table 3-5 HeFH (primary and secondary prevention) based on RUTHERFORD-2 and CPRD for evolocumab and statin versus ezetimibe and statin

HeFH (primary and secondar prevention)	Evolocumab		Ezetimibe		Incremental		
	QALYs	Costs	QALYs	Costs	QALYs	Costs	ICER
RUTHERFORD-2	11.25	[redacted]	10.51	£21,753	0.75	[redacted]	£27,220
CPRD	9.44	[redacted]	8.60	£19,996	0.84	[redacted]	£21,733
CPRD, Clinical Practice Research Datalink; Evo, evolocumab; eze, ezetimibe; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

3.2 Subgroup analysis

Individual risk factors for patients with existing CVD

The impact of the individual risk factors on the cost-effectiveness (evolocumab and statin versus ezetimibe and statin) has been assessed individually based on patient-level characteristics from LAPLACE-2 (Table 3-6), CPRD (Table 3-7) and GAUSS-2 (Table 3-8).

Secondary prevention (non-familial) with additional risk factors

Table 3-6 Subgroup analysis: Secondary prevention (non-familial) with additional risk factors based on LAPLACE-2 (evolocumab and statin versus ezetimibe and statin)

Scenario	Cost Evo	Cost Eze	ΔCost	QALYs Evo	QALYs Eze	ΔQALYs	ICER	Difference
Base case	[redacted]	£21,408	[redacted]	8.43	8.03	0.40	£45,439	-
Baseline LDL-C (mmol/L)								
3.0	[redacted]	£21,639	[redacted]	8.35	8.00	0.35	£51,571	£6,132
3.5	[redacted]	£21,442	[redacted]	8.42	8.03	0.39	£46,218	£779
4.0	[redacted]	£21,253	[redacted]	8.48	8.06	0.43	£42,347	-£3,092
4.5	[redacted]	£21,071	[redacted]	8.55	8.09	0.46	£39,463	-£5,975
5.0	[redacted]	£20,897	[redacted]	8.61	8.12	0.49	£37,272	-£8,166
5.5	[redacted]	£20,729	[redacted]	8.66	8.14	0.52	£35,585	-£9,853
6.0	[redacted]	£20,569	[redacted]	8.71	8.17	0.54	£34,277	-£11,161
Sex								
Male	[redacted]	£21,104	[redacted]	8.34	7.95	0.40	£44,662	-£777
Female	[redacted]	£22,069	[redacted]	8.62	8.22	0.40	£47,045	£1,607
Diabetes mellitus								

Yes	[redacted]	£21,642	[redacted]	7.97	7.53	0.44	£38,406	-£7,033
CVD history								
ACS	[redacted]	£24,873	[redacted]	9.62	9.18	0.44	£39,471	-£5,968
ACS, acute coronary syndrome; CVD, cardiovascular disease; Evo; evolocumab; Eze, ezetimibe; LDL-C, low-density lipoprotein cholesterol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year								

Table 3-7 Subgroup analysis: Secondary prevention (non-familial) with additional risk factors based on CPRD (evolocumab and statin versus ezetimibe and statin)

Scenario	Cost Evo	Cost Eze	ΔCost	QALYs Evo	QALYs Eze	ΔQALYs	ICER	Difference
Base case	[redacted]	£16,182	[redacted]	6.68	6.40	0.28	£54,432	-
Baseline LDL-C								
3.0	[redacted]	£16,108	[redacted]	6.74	6.42	0.32	£47,936	-£6,495
3.5	[redacted]	£15,984	[redacted]	6.80	6.45	0.35	£43,190	-£11,242
4.0	[redacted]	£15,866	[redacted]	6.86	6.47	0.39	£39,758	-£14,673
4.5	[redacted]	£15,753	[redacted]	6.92	6.50	0.42	£37,205	-£17,227
5.0	[redacted]	£15,645	[redacted]	6.97	6.53	0.44	£35,266	-£19,166
5.5	[redacted]	£15,541	[redacted]	7.02	6.55	0.46	£33,775	-£20,656
6.0	[redacted]	£15,442	[redacted]	7.06	6.58	0.48	£32,622	-£21,810
Sex								
Male	[redacted]	£15,787	[redacted]	6.52	6.25	0.28	£52,525	-£1,906
Female	[redacted]	£16,737	[redacted]	6.90	6.62	0.28	£57,120	£2,688
Diabetes mellitus								
Yes	[redacted]	£17,505	[redacted]	6.47	6.17	0.30	£49,404	-£5028
Vascular beds								
Two	[redacted]	£15,640	[redacted]	5.59	5.29	0.30	£43,368	-£11,064
Three	[redacted]	£15,346	[redacted]	4.07	3.80	0.27	£37,153	-£17,278
Atrial fibrillation								
Yes	[redacted]	£14,264	[redacted]	4.58	4.33	0.25	£45,274	-£9,157
CVD history								
ACS	[redacted]	£20,028	[redacted]	6.80	6.47	0.33	£40,740	-£13,692
ACS, acute coronary syndrome; CVD, cardiovascular disease; Evo; evolocumab; Eze, ezetimibe; LDL-C, low-density lipoprotein cholesterol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year								

Secondary prevention (non-familial) statin intolerant/contraindicated with additional risk factors

Table 3-8 Subgroup analysis: Secondary prevention (non-familial) statin intolerant/contraindicated with additional risk factors based on GAUSS-2 (evolocumab versus ezetimibe)

Scenario	Cost Evo	Cost Eze	ΔCost	QALYs Evo	QALYs Eze	ΔQALYs	ICER	Difference
Base case	[redacted]	£19,216	[redacted]	8.01	7.48	0.53	£30,985	-
Baseline LDL-C (mmol/L)								
3.0	[redacted]	£19,890	[redacted]	7.75	7.37	0.38	£43,180	£12,194
3.5	[redacted]	£19,701	[redacted]	7.82	7.40	0.42	£38,455	£7,470
4.0	[redacted]	£19,517	[redacted]	7.90	7.43	0.47	£35,017	£4,031
4.5	[redacted]	£19,339	[redacted]	7.97	7.46	0.50	£32,437	£1,451
5.0	[redacted]	£19,167	[redacted]	8.03	7.49	0.54	£30,458	-£528
5.5	[redacted]	£19,000	[redacted]	8.09	7.52	0.57	£28,916	-£2,069
6.0	[redacted]	£18,839	[redacted]	8.15	7.55	0.60	£27,703	-£3,282
Sex								

Male	[redacted]	£18,889	[redacted]	7.92	7.40	0.52	£30,765	-£221
Female	[redacted]	£19,809	[redacted]	8.17	7.63	0.55	£31,331	£346
Diabetes mellitus								
Yes	[redacted]	£20,319	[redacted]	7.85	7.23	0.63	£25,004	-£5,981
CVD history								
ACS	[redacted]	£22,815	[redacted]	8.55	7.93	0.62	£24,007	-£6,798
ACS, acute coronary syndrome; CVD, cardiovascular disease; Evo; evolocumab; Eze, ezetimibe; LDL-C, low-density lipoprotein cholesterol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year								

Secondary prevention (non-familial) with combination of additional risk factors, baseline LDL-C, age, and sex (based on LAPLACE-2 and CPRD patient-level characteristics)

The impact of combining one of the risk factors with varying age (+5 and +10 years) and sex (male or female) was assessed (Table 3-9). The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000.

Table 3-9 Secondary prevention (non-familial) with specific CVD risk factors: cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin

Baseline LDL-C	Sex	Age (years)	LAPLACE-2			CPRD					
			SP cohort	DM	ACS	SP cohort	DM	ACS	VB2	VB3	AF
3.5 mmol/L	Cohort	Cohort	£46,218	£36,746	£41,509	£43,190	£33,631	£32,105	£33,259	£24,899	£32,270
		+5	£43,185	£34,454	£37,720	£42,662	£32,860	£30,578	£33,330	£25,172	£33,222
		+10	£41,632	£33,331	£35,056	£44,280	£33,561	£30,364	£35,279	£26,970	£36,814
	Male	Cohort	£45,429	£36,839	£40,944	£41,650	£32,439	£31,371	£31,812	£24,172	£31,442
		+5	£42,474	£34,559	£37,218	£41,159	£31,724	£29,890	£31,901	£24,471	£32,377
		+10	£40,965	£33,449	£34,598	£42,702	£32,410	£29,676	£33,746	£26,215	£35,823
	Female	Cohort	£47,850	£36,460	£44,370	£45,360	£35,386	£33,185	£35,530	£27,232	£33,539
		+5	£44,670	£34,147	£40,273	£44,803	£34,550	£31,602	£35,598	£27,495	£34,540
		+10	£43,046	£33,006	£37,402	£46,559	£35,299	£31,409	£37,745	£29,516	£38,388
Baseline LDL-C	**Sex**	**Age (years)**	**LAPLACE-2**			**CPRD**					
			SP cohort	**DM**	**ACS**	**SP cohort**	**DM**	**ACS**	**VB2**	**VB3**	**AF**
4.0 mmol/L	Cohort	Cohort	£42,347	£33,645	£37,748	£39,758	£30,893	£29,195	£30,571	£22,774	£29,635
		+5	£39,594	£31,577	£34,307	£39,296	£30,213	£27,823	£30,665	£23,067	£30,540
		+10	£38,195	£30,578	£31,896	£40,804	£30,882	£27,649	£32,481	£24,746	£33,865
	Male	Cohort	£41,619	£33,728	£37,230	£38,334	£29,788	£28,519	£29,231	£22,109	£28,866
		+5	£38,937	£31,671	£33,847	£37,905	£29,160	£27,190	£29,341	£22,415	£29,754
		+10	£37,578	£30,683	£31,475	£39,343	£29,814	£27,014	£31,060	£24,045	£32,945
	Female	Cohort	£43,852	£33,386	£40,366	£41,766	£32,518	£30,189	£32,673	£24,944	£30,813
		+5	£40,967	£31,302	£36,648	£41,277	£31,779	£28,768	£32,765	£25,222	£31,764
		+10	£39,504	£30,289	£34,049	£42,913	£32,493	£28,614	£34,764	£27,106	£35,325
Baseline LDL-C	**Sex**	**Age (years)**	**LAPLACE-2**			**CPRD**					
			SP cohort	**DM**	**ACS**	**SP cohort**	**DM**	**ACS**	**VB2**	**VB3**	**AF**
4.5 mmol/L	Cohort	Cohort	£39,463	£31,340	£34,960	£37,205	£28,859	£27,036	£28,573	£21,203	£27,669
		+5	£36,917	£29,437	£31,777	£36,787	£28,244	£25,780	£28,681	£21,501	£28,537

		+10	£35,631	£28,528	£29,551	£38,209	£28,887	£25,634	£30,395	£23,089	£31,659
	Male	Cohort	£38,783	£31,417	£34,478	£35,867	£27,822	£26,405	£27,313	£20,578	£26,945
		+5	£36,301	£29,524	£31,348	£35,480	£27,254	£25,186	£27,436	£20,888	£27,797
		+10	£35,051	£28,624	£29,160	£36,837	£27,883	£25,038	£29,060	£22,429	£30,793
	Female	Cohort	£40,873	£31,101	£37,397	£39,090	£30,386	£27,965	£30,547	£23,242	£28,777
		+5	£38,204	£29,186	£33,957	£38,648	£29,717	£26,664	£30,654	£23,527	£29,689
		+10	£36,859	£28,266	£31,559	£40,189	£30,402	£26,537	£32,539	£25,308	£33,032
ACS, acute coronary syndrome; AF, atrial fibrillation; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; DM, diabetes mellitus; disease; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention; VB2, two vascular beds; VB3, thress vascular beds											

Secondary prevention (non-familial) with combination of additional risk factors, baseline LDL-C, age, and sex (based on GAUSS-2 patient-level characteristics)

The impact of combining age (+5 and +10 years) and sex (male or female) in the statin intolerant/contraindication secondary prevention cohort and subgroups with diabetes mellitus or history of acute coronary syndrome is presented in Table 3-9. The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000.

Table 3-10 Secondary prevention (non-familial) statin intolerant with specific CVD risk factors: cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab versus ezetimibe

Baseline LDL-C	Sex	Age (years)	SP cohort	Diabetes mellitus	ACS
3.5 mmol/L	Cohort	Cohort	£38,455	£30,164	£31,842
		+5	£36,391	£28,438	£29,350
		+10	£35,653	£27,694	£27,786
	Male	Cohort	£38,190	£29,334	£31,194
		+5	£36,168	£27,701	£28,773
		+10	£35,454	£27,017	£27,256
	Female	Cohort	£38,867	£30,943	£33,261
		+5	£36,745	£29,135	£30,622
		+10	£35,980	£28,342	£28,967
Baseline LDL-C	**Sex**	**Age (years)**	**SP cohort**	**Diabetes mellitus**	**ACS**
4.0 mmol/L	Cohort	Cohort	£35,017	£27,409	£28,690
		+5	£33,166	£25,873	£26,461
		+10	£32,521	£25,229	£25,072
	Male	Cohort	£34,772	£26,644	£28,098
		+5	£32,958	£25,191	£25,933
		+10	£32,335	£24,601	£24,585
	Female	Cohort	£35,399	£28,128	£29,987
		+5	£33,498	£26,518	£27,627
		+10	£32,831	£25,831	£26,157
Baseline LDL-C	**Sex**	**Age (years)**	**SP cohort**	**Diabetes mellitus**	**ACS**
4.5 mmol/L	Cohort	Cohort	£32,437	£25,347	£26,326
		+5	£30,744	£23,951	£24,294
		+10	£30,167	£23,380	£23,035

	Male	Cohort	£32,207	£24,632	£25,777
		+5	£30,548	£23,312	£23,802
		+10	£29,989	£22,789	£22,581
	Female	Cohort	£32,796	£26,019	£27,530
		+5	£31,058	£24,557	£25,378
		+10	£30,462	£23,946	£24,046

ACS, acute coronary syndrome; CV, cardiovascular; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention

Secondary prevention (non-familial) with combination of two risk factors, baseline LDL-C, age, and sex (based on CPRD patient-level characteristics)

The impact of combining two of the risk factors with varying age (+5 and +10 years) and sex (male or female) was assessed (Table 3-11). The grey cells denote patient profiles whereby the incremental cost per QALY gained is less than £30,000.

Table 3-11 Secondary prevention (non-familial) with two CVD risk factors: cost-effectiveness analysis (incremental cost [£] per QALY gained) of evolocumab and statin versus ezetimibe and statin

Baseline LDL-C	Sex	Age (years)	SP cohort	DM:AF	DM:VB2	DM:VB3	AF:VB2	AF:VB3	ACS:DM	ACS:AF	ACS:VB2	ACS:VB3
3.0 mmol/L	Cohort	Cohort	£47,936	£27,111	£30,524	£23,072	£29,701	£27,315	£30,405	£28,375	£27,737	£22,864
		+5	£47,313	£27,729	£30,040	£23,192	£30,730	£27,770	£28,777	£28,774	£26,815	£22,316
		+10	£49,076	£30,342	£30,935	£24,478	£34,517	£29,948	£28,277	£31,394	£27,185	£22,901
	Male	Cohort	£46,240	£25,574	£29,444	£22,110	£29,034	£26,509	£29,230	£27,340	£26,293	£21,776
		+5	£45,658	£26,188	£29,014	£22,274	£30,060	£26,982	£27,691	£27,717	£25,445	£21,281
		+10	£47,339	£28,616	£29,895	£23,532	£33,716	£29,094	£27,223	£30,184	£25,793	£21,842
	Female	Cohort	£50,327	£29,546	£32,543	£25,363	£30,539	£32,276	£32,048	£29,783	£30,117	£26,088
		+5	£49,671	£30,206	£31,980	£25,407	£31,593	£32,715	£30,309	£30,236	£29,098	£25,419
		+10	£51,588	£33,159	£32,932	£26,809	£35,575	£35,426	£29,785	£33,094	£29,534	£26,119
Baseline LDL-C	**Sex**	**Age (years)**	**SP cohort**	**DM:AF**	**DM:VB2**	**DM:VB3**	**AF:VB2**	**AF:VB3**	**ACS:DM**	**ACS:AF**	**ACS:VB2**	**ACS:VB3**
3.5 mmol/L	Cohort	Cohort	£43,190	£24,287	£27,386	£20,591	£26,644	£24,384	£26,963	£25,205	£24,598	£20,235
		+5	£42,662	£24,888	£26,996	£20,745	£27,613	£24,846	£25,545	£25,591	£23,809	£19,780
		+10	£44,280	£27,276	£27,841	£21,944	£31,054	£26,851	£25,130	£27,942	£24,169	£20,333
	Male	Cohort	£41,650	£22,889	£26,402	£19,711	£26,033	£23,649	£25,905	£24,270	£23,298	£19,253
		+5	£41,159	£23,484	£26,059	£19,905	£26,996	£24,127	£24,565	£24,635	£22,572	£18,844
		+10	£42,702	£25,706	£26,892	£21,077	£30,319	£26,073	£24,177	£26,851	£22,913	£19,376
	Female	Cohort	£45,360	£26,500	£29,223	£22,682	£27,414	£28,889	£28,443	£26,477	£26,739	£23,140
		+5	£44,803	£27,139	£28,764	£22,771	£28,406	£29,341	£26,927	£26,911	£25,864	£22,577
		+10	£46,559	£29,833	£29,663	£24,076	£32,022	£31,825	£26,492	£29,474	£26,284	£23,234
Baseline LDL-C	**Sex**	**Age (years)**	**SP cohort**	**DM:AF**	**DM:VB2**	**DM:VB3**	**AF:VB2**	**AF:VB3**	**ACS:DM**	**ACS:AF**	**ACS:VB2**	**ACS:VB3**
4.0 mmol/L	Cohort	Cohort	£39,758	£22,250	£25,126	£18,809	£24,436	£22,269	£24,483	£22,920	£22,336	£18,343
		+5	£39,296	£22,835	£24,801	£18,986	£25,358	£22,733	£23,215	£23,295	£21,641	£17,954
		+10	£40,804	£25,056	£25,607	£20,118	£28,543	£24,610	£22,861	£25,450	£21,993	£18,483
	Male	Cohort	£38,334	£20,954	£24,214	£17,990	£23,865	£21,588	£23,510	£22,058	£21,141	£17,438

		+5	£37,905	£21,532	£23,930	£18,202	£24,781	£22,066	£22,313	£22,412	£20,503	£17,091
		+10	£39,343	£23,601	£24,724	£19,308	£28,857	£23,888	£21,982	£24,445	£20,837	£17,601
	Female	Cohort	£41,766	£24,299	£26,830	£20,751	£25,154	£26,436	£25,844	£24,093	£24,304	£21,014
		+5	£41,277	£24,920	£26,443	£20,870	£26,099	£26,893	£24,488	£24,512	£23,532	£20,529
		+10	£42,913	£27,422	£27,300	£22,101	£29,446	£29,210	£24,116	£26,860	£23,938	£21,152
ACS, acute coronary syndrome; AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; SP, secondary prevention; VB2, two vascular beds; VB3, three vascular beds												

4 Factual inaccuracies in the ACD

The following factual inaccuracies were identified in the ACD.

Table 4-1 Factual inaccuracies

Section	Statement	Comment
Section 3.26, page 19	*'...the company adjusted the predicted risks of CVD in this population using a relative risk of 7.1 (relative to patients without heterozygous-familial hypercholesterolaemia) derived from a study by Benn et al. (2012).'*	This statement is incorrect. We adjusted the predicted risks of CVD based on a rate ratio. A relative risk would have an estimate of 5.9.
Section 3.30, page 20	*'…However, in the model, the relative risk was not applied to the general population, but to the RUTHERFORD-2…'*	This statement is incorrect. We adjusted the predicted risks of CVD based on a rate ratio.
Section 3.30, page 21	*'…The ERG also highlighted other studies, which suggested that the relative risk derived from Benn et al. was likely to be an overestimate (see section 3.50).'*	This statement is incorrect. We derived a rate ratio.
Section 4.17, page 46	*'…the company applied a relative risk of 7.1, which was derived from a study by Benn et al. (2012)…'*	This statement is incorrect. We adjusted the predicted risks of CVD based on a rate ratio. A relative risk would have an estimate of 5.9.
Section 4.17, page 46	*'…However, the company applied the relative risk from the study to the RUTHERFORD-2 trial population…'* and *'…Third, the relative risk was derived from a pooled analysis of patients who could, and those who could not, tolerate statins, whereas the difference in relative risk between these 2 groups was large (1.7 and 10.5 respectively).'*	This statement is incorrect. We applied a rate ratio.
Section 4.17, page 47	*'…which implied that the model was highly sensitive to the relative risk applied for this population (see section 3.51).'* *and* *'The Committee concluded that, given the methodological limitations highlighted by the ERG and the existing evidence, the relative risk from Benn et al. highly overestimated the risk of CVD among people with heterozygous-familial hypercholesterolaemia.'*	This statement is incorrect. We applied a rate ratio.
Page 61 and page 63	Relative risk stated as summary of the comments above	This statement is incorrect. We applied a rate ratio.

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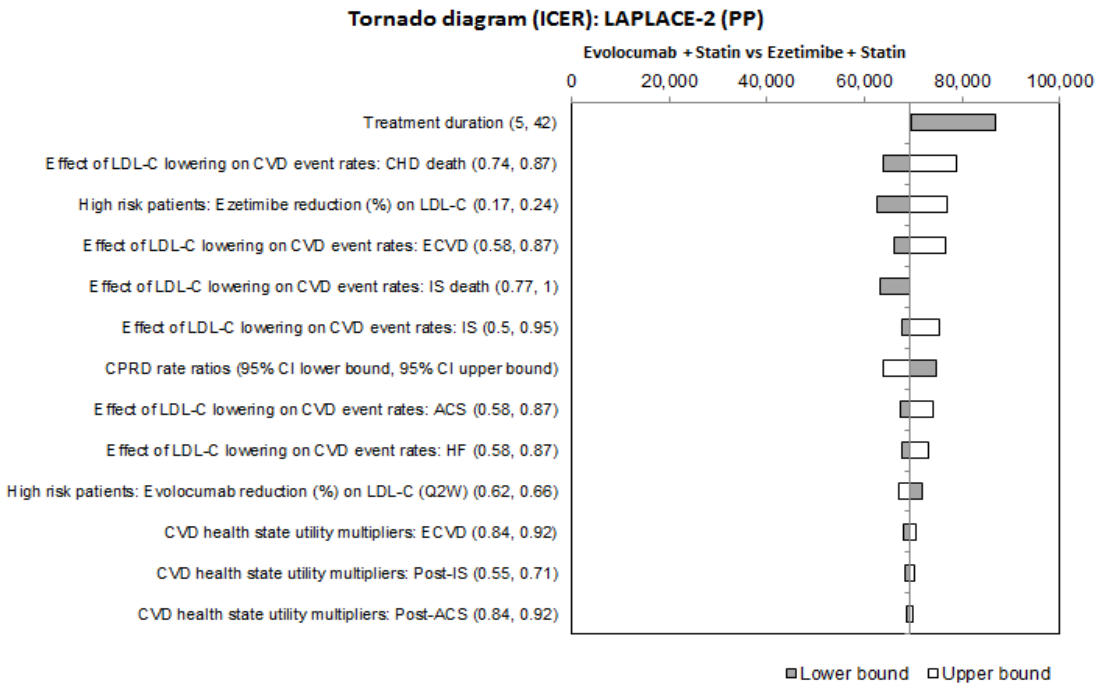
6 Appendices

6.1 Appendix I: Detailed cost-effectiveness results

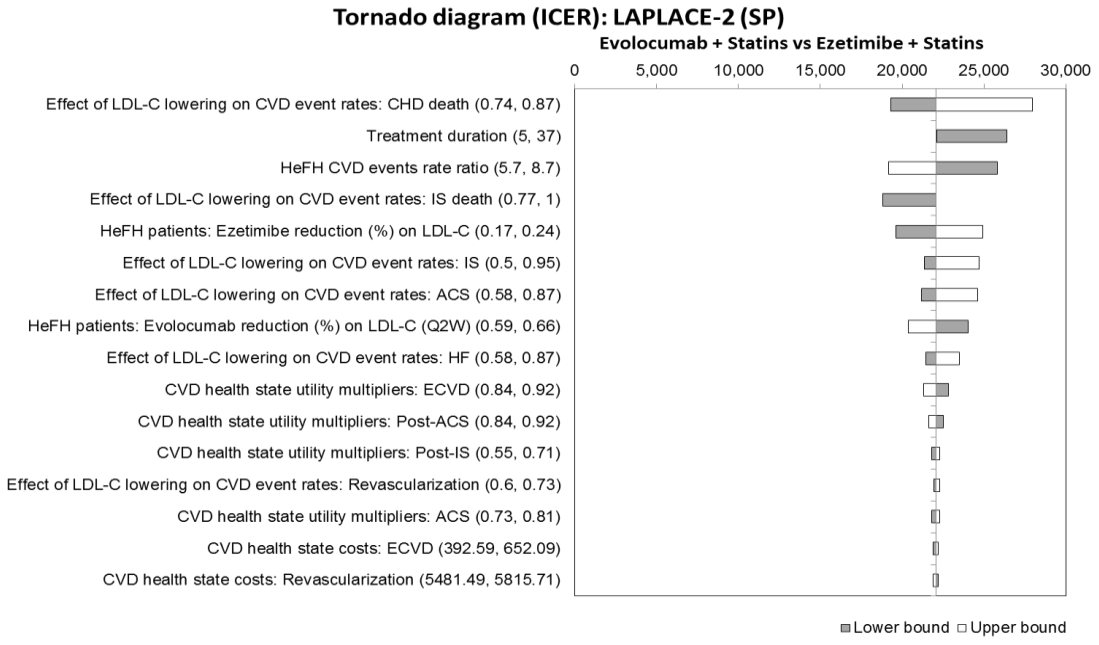
Deterministic sensitivity analyses

Figure 6-1 Tornado plot: evolocumab and statin versus ezetimibe and statin in primary prevention (non-familial)



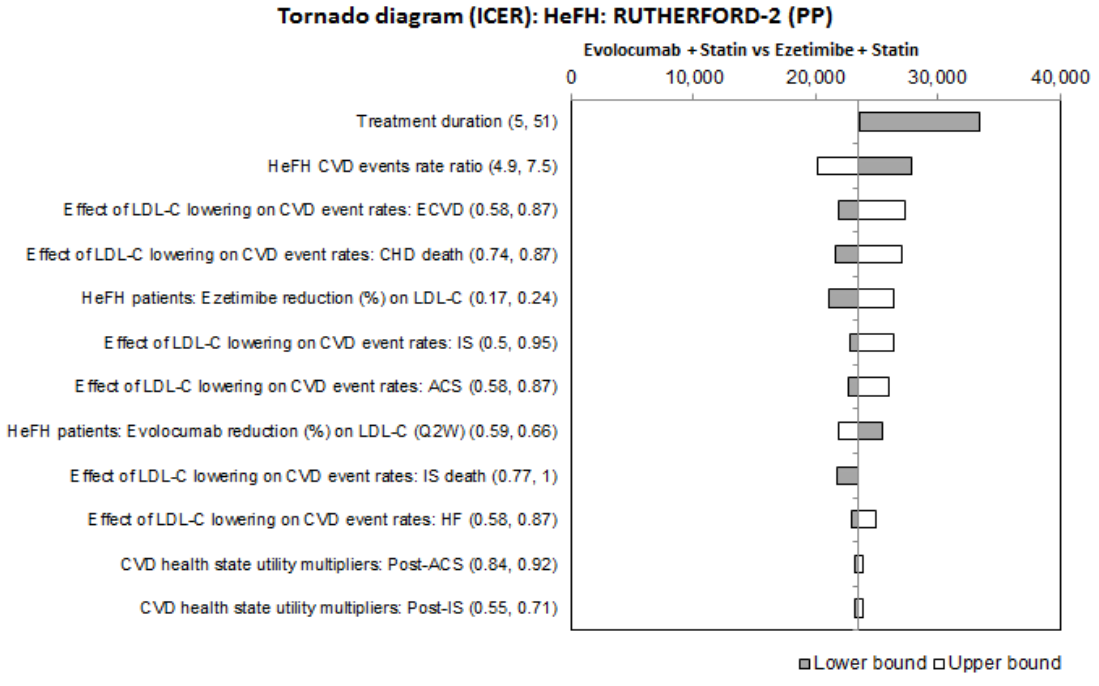
ACS, acute coronary syndrome; CI, confidence interval; CHD, coronary heart disease; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 6-2 Tornado plot: evolocumab and statin versus ezetimibe and statin in secondary prevention (non-familial)



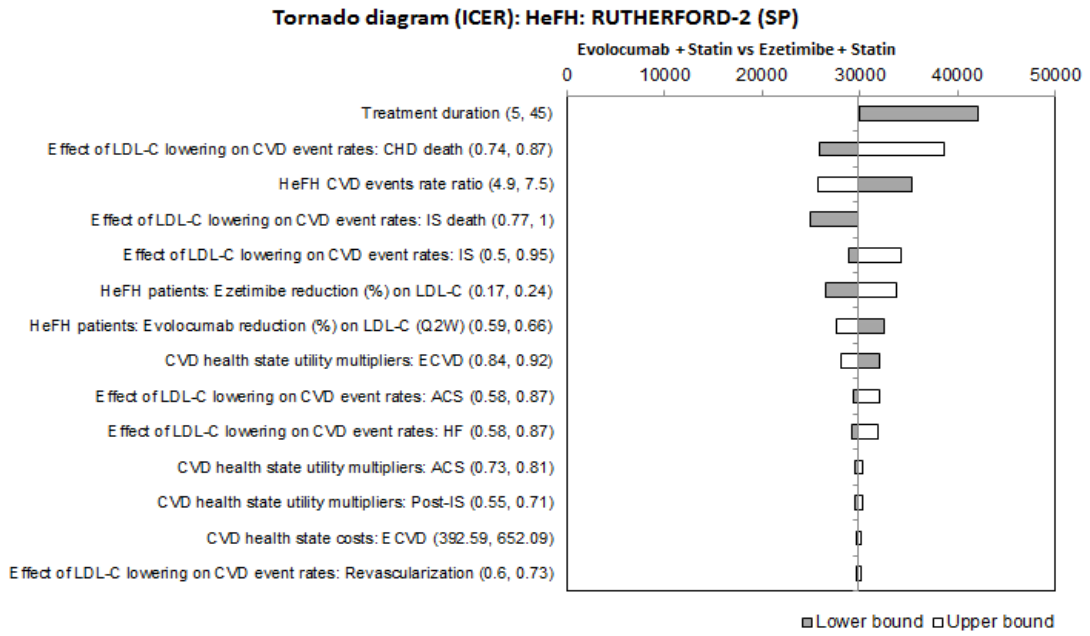
ACS, acute coronary syndrome; CI, confidence interval; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol; SP, secondary prevention

Figure 6-3 Tornado plot: evolocumab and statin versus ezetimibe and statin in HeFH primary prevention (based on RUTHERFORD-2)



ACS, acute coronary syndrome; CI, confidence interval; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol

Figure 6-4 Tornado plot: evolocumab and statin versus ezetimibe and statin in HeFH secondary prevention (based on RUTHERFORD-2)



ACS, acute coronary syndrome; CI, confidence interval; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; ICER, incremental cost-effectiveness ratio; LDL-C, low density lipoprotein cholesterol

Scenario analysis

Table 6-1 Scenario analyses: Non-familial primary prevention (evolocumab and statin versus ezetimibe and statin)

Scenario	Cost Evo	Cost Eze	ΔCost	QALYs Evo	QALYs Eze	Δ QALYs	ICER
Base case	[redacted]	£9,928	[redacted]	12.67	12.33	0.34	£69,249
LDL-C: 3.0 mmol/L	[redacted]	£9,994	[redacted]	12.62	12.31	0.32	£74,340
LDL-C: 3.5 mmol/L	[redacted]	£9,907	[redacted]	12.68	12.34	0.35	£67,797
LDL-C: 4.0 mmol/L	[redacted]	£9,824	[redacted]	12.74	12.36	0.38	£63,115
LDL-C: 4.5 mmol/L	[redacted]	£9,745	[redacted]	12.79	12.39	0.40	£59,680
LDL-C: 5.0 mmol/L	[redacted]	£9,669	[redacted]	12.84	12.42	0.42	£57,125
LDL-C: 5.5 mmol/L	[redacted]	£9,597	[redacted]	12.88	12.45	0.43	£55,216
LDL-C: 6.0 mmol/L	[redacted]	£9,528	[redacted]	12.91	12.47	0.44	£53,797
Evo QM PFP	[redacted]	£9,928	[redacted]	12.67	12.33	0.35	£101,696
5-year treatment duration	[redacted]	£5,271	[redacted]	12.23	12.16	0.08	£86,878
10-year treatment duration	[redacted]	£6,758	[redacted]	12.35	12.21	0.15	£79,921
20-year treatment duration	[redacted]	£8,751	[redacted]	12.55	12.28	0.27	£71,524
Discounting: 0% costs, 0% effects	[redacted]	£16,755	[redacted]	20.00	19.23	0.77	£49,205
Discounting: 0% costs, 6% effects	[redacted]	£16,755	[redacted]	9.74	9.54	0.21	£184,499
Risk capping 75 years	[redacted]	£9,845	[redacted]	12.73	12.40	0.32	£73,358
NICE CG181 CV costs	[redacted]	£10,170	[redacted]	12.67	12.33	0.34	£69,024
TTO study utilities	[redacted]	£9,928	[redacted]	12.83	12.56	0.27	£87,105
Nurse training 30 minutes	[redacted]	£9,928	[redacted]	12.67	12.33	0.34	£69,130
Nurse training 2 hours	[redacted]	£9,928	[redacted]	12.67	12.33	0.34	£69,249

CV, cardiovascular; Evo, evolocumab; Eze, ezetimibe; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade-off

Table 6-2 Scenario analyses: non-familial secondary prevention (evolocumab and statin versus ezetimibe and statin)

Scenario	Cost Evo	Cost Eze	ΔCost	QALYs Evo	QALYs Eze	Δ QALYs	ICER
Base case	[redacted]	£21,408	[redacted]	8.43	8.03	0.40	£45,439
LDL-C: 3.0 mmol/L	[redacted]	£21,639	[redacted]	8.35	8.00	0.35	£51,571
LDL-C: 3.5 mmol/L	[redacted]	£21,442	[redacted]	8.42	8.03	0.39	£46,218
LDL-C: 4.0 mmol/L	[redacted]	£21,253	[redacted]	8.48	8.06	0.43	£42,347
LDL-C: 4.5 mmol/L	[redacted]	£21,071	[redacted]	8.55	8.09	0.46	£39,463
LDL-C: 5.0 mmol/L	[redacted]	£20,897	[redacted]	8.61	8.12	0.49	£37,272
LDL-C: 5.5 mmol/L	[redacted]	£20,729	[redacted]	8.66	8.14	0.52	£35,585
LDL-C: 6.0 mmol/L	[redacted]	£20,569	[redacted]	8.71	8.17	0.54	£34,277
Evolocumab QM PFP	[redacted]	£21,408	[redacted]	8.44	8.03	0.40	£68,374
5-year treatment duration	[redacted]	£18,594	[redacted]	7.97	7.86	0.11	£56,171
10-year treatment duration	[redacted]	£19,697	[redacted]	8.12	7.92	0.20	£51,218
20-year treatment duration	[redacted]	£20,968	[redacted]	8.35	8.01	0.34	£46,273
Discounting: 0% costs, 0% effects	[redacted]	£31,674	[redacted]	12.32	11.55	0.77	£35,328
Discounting: 0% costs, 6% effects	[redacted]	£31,674	[redacted]	6.74	6.47	0.26	£102,785

Risk capping 75 years	[redacted]	£21,417	[redacted]	8.49	8.10	0.39	£49,926
NICE CG181 CV costs	[redacted]	£24,966	[redacted]	8.43	8.03	0.40	£45,883
TTO study utilities	[redacted]	£21,408	[redacted]	10.00	9.47	0.52	£34,450
Nurse training 30 minutes	[redacted]	£21,408	[redacted]	8.43	8.03	0.40	£45,337
Nurse training 2 hours	[redacted]	£21,408	[redacted]	8.43	8.03	0.40	£45,641
CV, cardiovascular; Evo; evolocumab; Eze, ezetimibe; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

Table 6-3 Scenario analyses: HeFH primary prevention (evolocumab and statin versus ezetimibe and statin)

Scenario	Cost Evo	Cost Eze	ΔCost	QALYs Evo	QALYs Eze	Δ QALYs	ICER
Base case	[redacted]	£16,246	[redacted]	13.57	12.61	0.96	£23,536
LDL-C: 3.0 mmol/L	[redacted]	£16,808	[redacted]	13.24	12.48	0.77	£29,304
LDL-C: 3.5 mmol/L	[redacted]	£16,521	[redacted]	13.41	12.54	0.87	£25,949
LDL-C: 4.0 mmol/L	[redacted]	£16,244	[redacted]	13.57	12.61	0.96	£23,521
LDL-C: 4.5 mmol/L	[redacted]	£15,978	[redacted]	13.72	12.68	1.04	£21,710
LDL-C: 5.0 mmol/L	[redacted]	£15,722	[redacted]	13.86	12.74	1.12	£20,331
LDL-C: 5.5 mmol/L	[redacted]	£15,476	[redacted]	13.99	12.80	1.19	£19,266
LDL-C: 6.0 mmol/L	[redacted]	£15,240	[redacted]	14.11	12.87	1.25	£18,436
Evolocumab QM PFP	[redacted]	£16,246	[redacted]	13.61	12.61	1.00	£34,717
5-year treatment duration	[redacted]	£12,855	[redacted]	12.35	12.18	0.18	£33,467
10-year treatment duration	[redacted]	£13,989	[redacted]	12.64	12.29	0.35	£30,402
20-year treatment duration	[redacted]	£15,412	[redacted]	13.14	12.47	0.66	£26,327
Discounting: 0% costs, 0% effects	[redacted]	£29,921	[redacted]	22.03	19.76	2.27	£16,414
Discounting: 0% costs, 6% effects	[redacted]	£29,921	[redacted]	10.31	9.75	0.56	£66,036
Risk capping 75 years	[redacted]	£16,227	[redacted]	13.63	12.66	0.97	£23,389
NICE CG181 CV costs	[redacted]	£16,831	[redacted]	13.57	12.61	0.96	£23,354
TTO study utilities	[redacted]	£16,246	[redacted]	13.94	13.07	0.87	£25,775
Nurse training 30 minutes	[redacted]	£16,246	[redacted]	13.57	12.61	0.96	£23,493
Nurse training 2 hours	[redacted]	£16,246	[redacted]	13.57	12.61	0.96	£23,620
Stroke rate ratio = 1	[redacted]	£16,357	[redacted]	13.94	12.99	0.94	£24,584
CV, cardiovascular; Evo; evolocumab; Eze, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

Table 6-4 Scenario analyses: HeFH secondary prevention (evolocumab and statin versus ezetimibe and statin)

Scenario	Cost Evo	Cost Eze	ΔCost	QALYs Evo	QALYs Eze	Δ QALYs	ICER
Base case	[redacted]	£25,773	[redacted]	9.56	8.97	0.59	£29,910
LDL-C: 3.0 mmol/L	[redacted]	£26,467	[redacted]	9.35	8.88	0.47	£38,133
LDL-C: 3.5 mmol/L	[redacted]	£26,133	[redacted]	9.46	8.93	0.53	£33,555
LDL-C: 4.0 mmol/L	[redacted]	£25,810	[redacted]	9.55	8.97	0.59	£30,236
LDL-C: 4.5 mmol/L	[redacted]	£25,498	[redacted]	9.65	9.01	0.64	£27,756
LDL-C: 5.0 mmol/L	[redacted]	£25,197	[redacted]	9.73	9.05	0.69	£25,863

LDL-C: 5.5 mmol/L	[redacted]	£24,905	[redacted]	9.82	9.08	0.73	£24,394
LDL-C: 6.0 mmol/L	[redacted]	£24,624	[redacted]	9.89	9.12	0.77	£23,244
Evolocumab QM PFP	[redacted]	£25,773	[redacted]	9.59	8.97	0.62	£45,089
5-year treatment duration	[redacted]	£23,610	[redacted]	8.84	8.71	0.13	£42,200
10-year treatment duration	[redacted]	£24,417	[redacted]	9.05	8.79	0.26	£37,637
20-year treatment duration	[redacted]	£25,370	[redacted]	9.37	8.91	0.46	£32,378
Discounting: 0% costs, 0% effects	[redacted]	£39,951	[redacted]	14.45	13.24	1.21	£22,876
Discounting: 0% costs, 6% effects	[redacted]	£39,951	[redacted]	7.52	7.14	0.38	£72,643
Risk capping 75 years	[redacted]	£25,788	[redacted]	9.61	9.02	0.60	£29,997
NICE CG181 CV costs	[redacted]	£27,524	[redacted]	9.56	8.97	0.59	£29,741
TTO study utilities	[redacted]	£25,773	[redacted]	10.99	10.21	0.77	£22,883
Nurse training 30 minutes	[redacted]	£25,773	[redacted]	9.56	8.97	0.59	£29,842
Nurse training 2 hours	[redacted]	£25,773	[redacted]	9.56	8.97	0.59	£30,046
Stroke rate ratio = 1	[redacted]	£26,414	[redacted]	10.02	9.39	0.63	£29,761
CV, cardiovascular; Evo; evolocumab; Eze, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PFP, prefilled pen; QALY, quality-adjusted life year; QM, monthly; TTO, time trade off							

Table 6-5 Scenario analyses: REACH registry variable "yes" for statin intolerant populations (evolocumab versus ezetimibe)

Scenario	Cost Evo	Cost Eze	ΔCost	QALYs Evo	QALYs Eze	Δ QALYs	ICER
Primary prevention (non-familial)							
Base case	[redacted]	£9,849	[redacted]	11.85	11.28	0.57	£38,458
Statin variable = "Yes"	[redacted]	£9,797	[redacted]	11.89	11.37	0.52	£42,172
Secondary prevention (non-familial)							
Base case	[redacted]	£19,216	[redacted]	8.01	7.48	0.53	£30,985
Statin variable = "Yes"	[redacted]	£18,842	[redacted]	8.32	7.89	0.43	£40,522
Evo, evolocumab; Eze, ezetimibe; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year							

6.2 Appendix II: Literature review in FH

Figure 6-5 Newcastle-Ottawa criteria

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ☐
   b) somewhat representative of the average _____ in the community ☐
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ☐
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) secure record (eg surgical records) ☐
   b) structured interview ☐
   c) written self report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes ☐
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ☐
   b) study controls for any additional factor ☐ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ☐
   b) record linkage ☐
   c) self report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ☐
   b) no
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ☐
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ☐
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ☐
   b) yes, eg record linkage or based on self reports
   c) no description
2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ☐
   b) potential for selection biases or not stated
3) Selection of Controls
   a) community controls ☐
   b) hospital controls
   c) no description
4) Definition of Controls
   a) no history of disease (endpoint) ☐
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ☐
   b) study controls for any additional factor ☐ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ☐
   b) structured interview where blind to case/control status ☐
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description
2) Same method of ascertainment for cases and controls
   a) yes ☐
   b) no
3) Non-Response rate
   a) same rate for both groups ☐
   b) non respondents described
   c) rate different and no designation

References: Wells et al.,[29]

Table 6-6 Guided questions used in the bias risk assessment

Bias type	Criterion	Guided question(s)
Selection bias	Eligibility criteria explicitly described	Were the criteria explicitly described for individuals to be eligible for inclusion in the study population and was it applied uniformly to all comparison groups?
	Selection of eligible population from the target population	Does it appear that the association of interest in the population eligible for participation in similar to the association in the target population?
	Similarities of exposed and unexposed groups	Were the exposed and unexposed populations comparable except for the intervention?
	Exclusion of participants from analysis of the outcome	Were all the participants/person-time included in the analysis of the outcome? If patients/person-time were excluded, does it appear that similar proportion of participants/person-time were/was excluded in the exposed and unexposed groups for each reason?
Performance bias	Ascertainment of exposure and outcome	Were the methods used for ascertainment of exposure status, outcome status or both were NOT susceptible to misclassification?
	Temporal sequence	Does the inability to tell the temporal sequence when the outcome and exposure data are collected at the same time NOT bias the interpretation of the results?
	Concurrent interventions or unintended exposures	Was it ruled out any impact from a concurrent intervention or an unintended exposure that might bias the results?
Detection bias	Valid and reliable measurement of exposure status	Were the interventions/exposures assessed/defined using valid and reliable measures? Does it appear that exposure status was ascertained using the same protocol and measurement tool for all participants for all time points of follow-up?
	Valid and reliable measurement of outcomes	Were the outcomes assessed/defined using valid and reliable measures? Does it appear that exposure status was ascertained using the same protocol and measurement tool for all participants for all time points of follow-up?
	Exposure durations	Did exposed prevalent cases have the same duration as non-exposed prevalent cases?
Attrition bias	Missing data across exposed and unexposed groups	If attrition (non-response) was a concern, did it occur equally across the exposed and unexposed groups?

Bias type	Criterion	Guided question(s)
	Accounting for missing data	If attrition (non-response) was a concern, does it appear that any statistical methods or other methods (e.g. appropriate samples) were used to account for missing data in order to minimise bias due to failure to follow-up and assess outcome?
Confounding bias	Control for confounders	Does it appear that analyses for the exposure-outcome association of interest have been adjusted for all relevant confounders and modifiers through matching, stratification, multivariable analysis, or other approaches?
	Valid and reliable measurement of confounders	Were the confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
Reporting bias	Post-hoc analyses	Were the potential outcomes pre-specified and were all pre-specified outcomes reported?
Other bias	Other biases	Is there any evidence of other potential biases?

Table 6-7 List of publications excluded at full-text screening and reason for exclusion

No.	Study/Publication	Reason for exclusion
1	Jensen JM, Gerdes LU, Jensen HK, et al. Association of coronary heart disease with age-adjusted aortocoronary calcification in patients with familial hypercholesterolaemia. J Intern Med 2000; 247:479-484	Study of risk factors in FH only. No FH CVD risk estimate
2	Harada-Shiba M, Sugisawa T, Makino H, et al. Impact of statin treatment on the clinical fate of heterozygous familial hypercholesterolemia. J Atheroscler Thromb 2010; 17:667-674.	Study within FH patients for the effect of Statins. No FH CVD risk estimate
3	Pijlman AH, Huigen R, Verhagen SN, et al. Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross-sectional study in the Netherlands. Atherosclerosis 2010; 209:189-194.	Study of adherence to guideline treatment in FH. No FH CVD risk estimate
4	Jansen AC, van Aalst-Cohen ES, Tanck MW, et al. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: data in 2400 patients. J Intern Med 2004; 256:482-490.	Study within FH patients of risk factors. No FH CVD risk estimate vs. non-FH
5	Frederick J. Raal, PhD; Gillian J. Pilcher, MSc; Vanessa R. Panz, PhD; Hendrick E. van Deventer, MD; Brigitte C. Brice, MD; Dirk J. Blom, PhD; A. David Marais, MDReduction in Mortality in Subjects With Homozygous Familial Hypercholesterolemia Associated With Advances in Lipid-Lowering Therapy. Circulation. 2011;124:2202-2207	Homozygous FH only and effect of Statins. No FH CVD risk estimate

No.	Study/Publication	Reason for exclusion
6	Alonso R, Mata N, Badimon L, et al. Prognostic factors of cardiovascular disease mortality and morbidity in a cohort of families with genetic diagnoses of familial hypercholesterolemia. Nature Reviews Cardiology 2009; 6:23-27.	Limited to FH patients and prognosis. No FH CVD risk estimate
7	Neil HAW, Huxley R, Hawkins MM, et al. Comparison of fatal coronary mortality in treated xanthomatous and non-xanthomatous heterozygous familial hypercholesterolaemia: results of a registry study. Atherosclerosis 2003; 170:73-78.	SMR (standardised mortality ratios) are provided for FH subgroups defined by xanthoma. No overall FH CVD risk estimate.
8	Jansen AC. van Aalst-Cohen ES. Tanck MW. Cheng S. Fontecha MR. Li J. Defesche JC. Kastelein JJ. Genetic determinants of cardiovascular disease risk in familial hypercholesterolemia. Arteriosclerosis, Thrombosis & Vascular Biology. 25(7):1475-81, 2005 Jul	Effect of genetic polymorphism on HDL-C plasma levels. No FH CVD risk estimate
9	Koeijvoets KC. Wiegman A. Rodenburg J. Defesche JC. Kastelein JJ. Sijbrands EJ. Effect of low-density lipoprotein receptor mutation on lipoproteins and cardiovascular disease risk: a parent-offspring study. Atherosclerosis. 180(1):93-9, 2005 May.	Study of risk within FH patients and off-spring. No FH CVD risk estimate vs, non-FH
10	Real JT. Chaves FJ. Martinez-Uso I. Garcia-Garcia AB. Ascaso JF. Carmena R. Importance of HDL cholesterol levels and the total/ HDL cholesterol ratio as a risk factor for coronary heart disease in molecularly defined heterozygous familial hypercholesterolaemia. European Heart Journal. 22(6):465-71, 2001 Mar	Study within FH patinents only. No FH CVD risk estimate vs. non-FH
11	Delport R. Familial hypercholesterolaemia in South Africans: tracking findings and developments over time - with reference to prevalence of hypercholesterolaemia in young Afrikaners with myocardial infarction. Ischaemic heart disease risk factors. Cardiovascular Journal of Africa. 20(1):18-22, 2009 Jan-Feb.	Primarily a review article, no data and no FH CVD risk estimate.
12	Huijgen R(1), Kindt I, Defesche JC, Kastelein JJ. Cardiovascular risk in relation to functionality of sequence variants in the gene coding for the low-density lipoprotein receptor: a study among 29,365 individuals tested for 64 specific low-density lipoprotein-receptor sequence variantsEur Heart J. 2012 Sep;33(18):2325-30. doi: 10.1093/eurheartj/ehs038. Epub 2012 Mar 4.	Comparison of CAD risk between LDL receptor variants using Dutch screening Population. No overall FH vs. non-FH CVD risk estimate
13	Hurrell C(1), Wietlisbach V, Jotterand V, Volet M, Lenain V, Nicod P, Darioli R, Paccaud F, Waeber G, Mooser V. High prevalence of major cardiovascular risk factors in first-degree relatives ofindividuals with familial premature coronary artery disease--the GENECARD project. Atherosclerosis. 2007 Sep;194(1):253-64	Study of risk factors in relatives of patients with FH. No FH CVD risk estimate
14	Hiroshi Mabuchi, MD, Junji Koizumi, MD, Masami Shimizu, MD, Ryoyu Takeda, MD, and the Hokuriku FH-CHD Study	Descriptive study of patients with FH. No overall CVD risk estimate

No.	Study/Publication	Reason for exclusion
	Group.Development of Coronary Heart Disease in Familial Hypercholesterolemia. Circulation 1989;79:225-332).	FH vs. non-FH.
15	Mattis Flyvholm Ranthe, Bo Gregers Winkel, Elisabeth Wreford Andersen, Bjarke Risgaard, Jan Wohlfahrt, Henning Bundgaard, Stig Haunsø, Mads Melbye, Jacob Tfelt-Hansen, Heather A. Boyd Risk of cardiovascular disease in family members of young sudden cardiac death victims. Eur Heart J (2013) 34 (7): 503-511	Study provides incidence ratios between in relatives of sudden cardiac death victims vs. the general population. Not a direct study of defined FH.
CAD, coronary artery disease; CV, cardiovascular; FH, familial hypercholesterolaemia; LDL, low-density lipoprotein		

6.3 Appendix III: Summary patient-level characteristics from CPRD

Table 6-8 Summary patient-level characteristics from CPRD

Population	HeFH: CPRD (PP)	HeFH: CPRD(SP)	CPRD PP (DM)	CPRD SP (all)	CPRD SP (DM)	CPRD SP (AF)	CPRD SP (VB2)	CPRD SP (VB3)	CPRD SP (ACS)
Sample size	8,166	480	7,626	10,061	2,799	693	1,081	80	1,039
Age (mean, years)	51.0540	63.4417	63.0362	68.8253	68.4284	74.1616	70.5495	72.6625	68.9220
Female (%)	0.5501	0.4479	0.4934	0.4428	0.4302	0.4170	0.4237	0.2625	0.4187
Smoking (%)	0.2661	0.3177	0.2080	0.2102	0.2190	0.1126	0.2516	0.2500	0.2445
Type 2 Diabetes Mellitus (%)	0.0254	0.1021	1.0000	0.2782	1.0000	0.2857	0.3367	0.3375	0.3927
Hypertensive therapy (%)	0.1681	0.7333	0.7703	0.8658	0.9221	0.9163	0.9029	0.9125	0.8450
Acetylsalicylic acid (%)	0.0565	0.7167	0.5231	0.8510	0.8664	0.9495	0.9390	0.9875	0.7228
SBP (mg Hg) (mean)	134.0875	137.9123	142.3562	140.9231	142.1395	140.9421	141.4923	140.0536	141.2864
BMI<20 (%)	0.0283	0.0121	0.0066	0.0224	0.0089	0.0260	0.0324	0.0500	0.0221
LDL-c (mmol/L) (mean)	4.7717	3.7089	2.6863	2.7075	2.4843	2.5458	2.6572	2.4791	2.7424
Total-c (mmol/L) (mean)	6.9276	5.9378	5.0659	4.9303	4.7458	4.6577	4.8465	4.6865	4.9181
HDL-c (mmol/L) (mean)	1.4507	1.3571	1.2989	1.3794	1.2673	1.3581	1.3422	1.2647	1.3397
Initial SP (%)	0.0000	1.0000	0.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Initial ECVD (%)	0.0000	0.4265	0.0000	0.6731	0.5895	0.4536	0.5486	0.2358	0.0000
Initial ACS (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-ACS (%)	0.0000	0.4121	0.0000	0.1652	0.2208	0.1388	0.1915	0.2602	1.0000
Initial IS (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-IS (%)	0.0000	0.0375	0.0000	0.0481	0.0603	0.0907	0.1178	0.2520	0.0000
Initial HF (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-HF (%)	0.0000	0.1239	0.0000	0.1136	0.1294	0.3169	0.1421	0.2520	0.0000
Initial Post-ACS + Post-IS (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-ACS + Post-HF (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-IS + Post-HF (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-ACS + Post-IS + Post-HF (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Number of vascular beds	0.0000	1.0375	0.0000	1.1155	1.1443	1.1919	2.0000	3.0000	1.1694
Atrial fibrillation (%)	0.0036	0.0625	0.0253	0.0689	0.0707	1.0000	0.1027	0.2125	0.0683
Age (mean, male)	47.881	61.506	60.802	67.0710	66.715	72.577	68.900	72.797	66.606
Age (mean, female)	53.649	65.828	65.330	71.0328	70.699	76.377	72.793	72.286	72.138
QRISK2 2015 (10-year rate, male)	0.1427	-	0.4053	-	-	-	-	-	-
QRISK2 2015 (10-year rate, female)	0.1209	-	0.3647	-	-	-	-	-	-
Wilson 2012 next (20-month rate, male)	0.0435	0.0435	0.0668	0.0514	0.0668	0.0835	0.0740	0.1217	0.0514
Wilson 2012 next (20-month rate, female)	0.0423	0.0423	0.0658	0.0507	0.0658	0.0814	0.0709	0.0979	0.0541

ACS, acute coronary syndrome; AF, atrial fibrillation; CPRD, Clinical Practice Research Datalink; DM, diabetes mellitus; ECVD, established cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; IS, ischaemic stroke; PP, primary prevention; SP, secondary prevention; VB2, two vascular beds; VB3, three vascular beds

Table 6-9 Summary patient-level characteristics from CPRD

Population	CPRD SP (DM ,AF)	CPRD SP (DM, VB2)	CPRD SP (DM, VB3)	CPRD SP (AF, VB2)	CPRD SP (AF, VB3)	CPRD SP (ACS, DM)	CPRD SP (ACS, AF)	CPRD SP (ACS, VB2)	CPRD SP (ACS,VB3)
Sample size	198	364	27	111	17	408	71	142	72
Age (mean, years)	74.0051	69.4121	71.7407	75.2703	73.7647	68.3848	76.3521	70.6901	72.0000
Female (%)	0.4343	0.3764	0.3333	0.4595	0.1765	0.4412	0.4507	0.4155	0.2941
Smoking (%)	0.1263	0.2637	0.2222	0.1532	0.0588	0.2230	0.0845	0.3028	0.3529
Type 2 Diabetes Mellitus (%)	1.0000	1.0000	1.0000	0.3153	0.2353	1.0000	0.3662	0.3380	0.2941
Hypertensive therapy (%)	0.9546	0.9478	0.8889	0.9820	0.9412	0.8922	0.9155	0.8662	0.9412
Acetylsalicylic acid (%)	0.9343	0.9725	1.0000	0.9820	0.9412	0.7230	0.8592	0.8944	1.0000
SBP (mg Hg) (mean)	141.0228	141.9759	139.7525	138.3952	132.5796	141.8800	142.4337	140.9161	140.4371
BMI<20 (%)	0.0101	0.0055	0.0741	0.0270	0.0588	0.0147	0.0000	0.0634	0.1177
LDL-c (mmol/L) (mean)	2.3391	2.4456	2.2597	2.5917	2.0998	2.5722	2.4276	2.7339	2.8006
Total-c (mmol/L) (mean)	4.4249	4.6690	4.6714	4.6569	4.4253	4.8095	4.5370	4.8902	4.7115
HDL-c (mmol/L) (mean)	1.2339	1.2201	1.3035	1.3555	1.3941	1.2320	1.3468	1.3839	1.4160
Initial SP (%)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Initial ECVD (%)	0.3889	0.5292	0.3000	0.3701	0.0345	0.0000	0.0000	0.0000	0.0000
Initial ACS (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-ACS (%)	0.1741	0.1922	0.2250	0.1753	0.1724	1.0000	1.0000	1.0000	1.0000
Initial IS (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-IS (%)	0.0481	0.1274	0.2000	0.1299	0.4483	0.0000	0.0000	0.0000	0.0000
Initial HF (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-HF (%)	0.3889	0.1512	0.2750	0.3247	0.3448	0.0000	0.0000	0.0000	0.0000
Initial Post-ACS + Post-IS (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-ACS + Post-HF (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-IS + Post-HF (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Initial Post-ACS + Post-IS + Post-HF (%)	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Number of vascular beds	1.2020	2.0000	3.0000	2.0000	3.0000	1.1422	1.2817	2.0000	3.0000
Atrial fibrillation (%)	1.0000	0.0962	0.1482	1.0000	1.0000	0.0637	1.0000	0.0986	0.1765
Age (mean, male)	72.420	68.079	71.611	74.650	74.429	65.566	75.897	68.337	71.750
Age (mean, female)	76.070	71.620	72.000	76.000	70.667	71.956	76.906	74.000	72.600
QRISK2 2015 (10-year rate, male)	-	-	-	-	-	-	-	-	-
QRISK2 2015 (10-year rate, female)	-	-	-	-	-	-	-	-	-
Wilson 2012 next (20-month rate, male)	0.1153	0.0904	0.1521	0.1130	0.1613	0.0625	0.0848	0.0720	0.1006
Wilson 2012 next (20-month rate, female)	0.1041	0.0875	0.1226	0.1052	0.1068	0.0653	0.0764	0.0715	0.0811

ACS, acute coronary syndrome; AF, atrial fibrillation; CPRD, Clinical Practice Research Datalink; DM, diabetes mellitus; ECVD, established cardiovascular disease; HF, heart failure; IS, ischaemic stroke; PP, primary prevention; SP, secondary prevention; VB2, two vascular beds; VB3, three vascular beds

HEART UK
THE CHOLESTEROL CHARITY

T: 01628 777046
W: www.heartuk.org.uk

TO: NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

RE: Appraisal consultation document- Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia
Healthcare professional submission

FROM: [redacted],
HEART UK- The Cholesterol Charity

DATE: 8th December 2015

Thank you for the opportunity to participate in this consultation as part of the appraisal of evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

HEART UK- The Cholesterol Charity

HEART UK is the Nation's Cholesterol Charity providing expert support, guidance and education to individuals with raised cholesterol, atherosclerosis and other lipid conditions. To this aim the charity provides high quality literature, a Cholesterol Helpline, a Patient Charter, an extensive website, a range of educational videos, the Ultimate Cholesterol Lowering Plan© and a range of electronic communication tools aimed at increasing the awareness of cholesterol. The Charity is also committed to influencing the media to report cholesterol related copy in a responsible way.

HEART UK also supports the health care professionals who work and care for patients (and their families) with raised and unhealthy patterns of high cholesterol and dyslipidaemia. HEART UK hosts a world class annual scientific conference and other networking events for clinicians, researchers, GPs, nurses and dieititians. The charity maintains a health professional membership scheme, provides resources and training to health care professionals.

In addition the charity campaigns hard to keep cholesterol and cardiovascular disease at the top of the political agenda and to help ensure better identification, diagnosis and treatment of patients with the aim of preventing deaths from early and avoidable cardiovascular disease.

HEART UK works directly with lipid experts in lipid clinics and specialist GP services where the diagnosis, treatment and the on-going management of complex lipid conditions such as Familial Hypercholesterolaemia (FH) Familial Combined Hyperlipidaemia (FCH), Type 3 Hyperlipidaemia and Lipoprotein Lipase Deficiency (LPLD) take place. In addition these centres support people with complex secondary dyslipidaeamias, secondary to and alongside other co-morbidities. Lipid clinics also support patients that have suspected statin intolerance; the aim being to identify a level of treatment and lifestyle advice that provides some protection but with minimal side effects.

HEART UK submission

HEART UK are disappointed that NICE has chosen not to recommend evolocumab (Repatha) for low density lipoprotein cholesterol (LDL-C) reduction for high cardiovascular risk patients at this time. We agree with the committee's statement that "evolocumab (Repatha®) was likely to be reserved for people who are at particularly high risk of cardiovascular disease (CVD), including people with HeFH, and those who cannot tolerate statins and in whom ezetimibe does not adequately control LDL-C".

There are several groups of patients with unmet clinical need for additional lipid lowering therapy, including:

Patients with heterozygous familial hypercholesterolaemia (HeFH) have high LDL-C from birth due to an inherited defect in LDL-C catabolism and accelerated atheroma formation. Such patients may fail to reach adequate LDL-C lowering either due to a high starting level or intolerance to statins resulting in increased mortality. A particularly high priority group are those with progression of coronary artery disease (CAD) requiring interventions.

Patients with cardiovascular disease but high LDL-C level despite maximum existing medical therapy. Evolocumab is a potential alternative treatment for patients, who meet the criteria for lipoprotein apheresis. It may allow discontinuation or less frequent apheresis.

Patients with diabetes and metabolic syndrome with high LDL-C despite maximum statin therapy and reasonable glycaemic control.

We believe that evolocumab should be recommended to these high-risk patients who fail to attain an LDL-C lower than 3mmol/L despite maximum medical therapy. We agree there is no robust evidence to support lowering LDL-C below 1 mmol/l and this is largely because there are no sufficiently potent second line medications to be used with statins to achieve such low levels. On-going studies should clarify this point. However, this is not relevant to high risk patient groups with high LDL-C despite maximum medical therapy because they are not expected to achieve LDL-C levels below 1mmol/L due to high LDL-C levels prior to deploying PCSK9 inhibitors (as proposed in evolocumab application).

There is a powerful rational for adopting a target based approach to management of patients at very high cardiovascular risk associated with high LDL-C. LDL- C is a principal driver of atherogenesis and is the key target for intervention. The lowering of LDL-C is critically related to decreased atheroma volume and improved plaque stability. Mendelian

randomisation studies and studies lowering cholesterol by diverse means, have clearly shown that the magnitude of clinical benefit in preventing cardiovascular disease (CVD) events relates to the extent of LDL-C lowering rather than the mechanism itself. Nevertheless, PCSK9 inhibitors work in the same way as statins by up-regulating the LDL receptor. The bulk of data underpinning the relationship between LDL-C lowering has been established from statin trials. We agree with NICE that LDL-C lowering is an acceptable surrogate for effectiveness in preventing CVD. Against a background of LDL-C lowering with statin and ezetimibe patients treated with PCSK9 inhibitors more often achieve acceptable LDL-C lowering targets. It should be recalled that regulatory approval has been given to evolocumab in the absence of data on outcomes. Nevertheless, meta-analysis of 24 PCSK9 inhibitor trials including 10,000 patients has shown 55% reduction in all-cause mortality, a 50% reduction in cardiovascular mortality and 51% reduction in myocardial infarction; all statistically significant. There have been no signals of harm in clinical trials although extended surveillance is needed as with all new drugs. It should be remembered that the use of monoclonal antibody medicines is a generic therapy with the nature of the monoclonal determining its site of action and that about 50 of such treatments are in use.

We believe that in their appraisal of evolocumab (Repatha®) NICE has significantly underestimated its clinical utility and the unmet clinical need. This has disadvantaged patients with heterozygous familial hypercholesterolaemia as a group and many patients at increased cardiovascular risk who cannot adequately lower their LDL-C by existing treatments. Such patients may be offered apheresis. This is invasive and inconvenient. PCSK9 treatment may substitute for this treatment and/or make it more effective. Patients currently treated by apheresis have therefore been disadvantaged. We believe that the cost effectiveness of treating patients with raised LDL-C has been significantly underestimated with the analysis focussing too much on reduction of low LDL-C. The analysis should include groups of patients with high cardiovascular risk and high LDL-C. We advocate the use of numbers needed to treat to analyse this point.

HEART UK's consultation

Additionally, a consultation by HEART UK was undertaken to gauge opinion and views from the wider healthcare professional community. The following HEART UK committees were consulted:

- HEART UK Board of Trustees
- FH Implementation Team (FHIT)- supporting the implementation of the NICE Familial Hypercholesterolaemia Guidelines
- The Healthcare Committee- providing up-to-date information to health care professionals who care for patients and their families with lipid disorders.
- Laboratory Sub Committee- providing information about Point of Care testing and sets standards of care and best practice for health care professionals who care for patients and their families with lipid disorders
- The Lipid Interest Group- providing education, networking, promoting information and support for people with an interest in lipids

- Lipoprotein Apheresis Working Group- promulgating guidance regarding the clinical indications for undertaking lipoprotein apheresis and the criteria of its performance in the UK.
- Simon Broome Steering Committee- responsible for directing research based on a national cohort of over 3,500 patients and familial hypercholesterolaemia

A further consultation exercise was undertaken and below is listed the 107 healthcare professionals supporting this submission from HEART UK.

HEART UK
THE CHOLESTEROL CHARITY

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W: www.heartuk.org.uk

TO: NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

RE: Appraisal consultation document- Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia
Patients and public submission

FROM: [redacted]
HEART UK- The Cholesterol Charity

DATE: 8th December 2015

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HEART UK's Public and Patient Consultation

HEART UK undertook a public consultation on the appraisal consultation document on evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia.

The consultation was run in parallel to the HEART UK's consultation with healthcare professionals, also submitted with this document.

Comments received include the following statements from people who will be affected by this decision to refuse access to evolocumab:

"I really wish you would reconsider your stance on denying the access to the new modern statin treatment for patients such as myself who has Familial Hypercholestremia and also my Son who has been diagnosed with this disease in childhood.

I myself was born with this inherited disease along with inheriting the disease of Type 1 Diabetes in my childhood, as my Cardiologist tells me, genetically there could not be two worse diseases to predispose anyone to Cardiovascular disease.

I take my health very seriously, and appreciate the help I have had to keep me alive through modern medicine. I do my part in this as much as I can. I take my diet and fitness very seriously and want to fight these two diseases every step of the way. I run ten miles everyday and run Marathons when I have the time. I eat a very clean healthy diet and do not drink or smoke. When I had my first cardiac event, all the Cardiologist said I looked too fit and young to be on their wards. I am 8 stone wet through, but people cannot see the damage these terrible diseases do to me on the inside, now my Son has inherited the same disease in FH.

I deal with the side effects and pain of the medication on a daily basis, but I have no other option as the thought of a heart attack and being permanently debilitated and not being able to support my family scares me more. The choice for us with this disease when statins cannot, or cannot any longer, be tolerated would be a huge weight off my and my family's mind. I have blockages ranging from 30% to 90% in all my arteries, I stay as medication free as I can by being as ultra fit as I can be. I know it will catch me up one day soon, as most of my damage to my heart was done in my childhood and twenties before statins came out.

I just hope you will reconsider your stance on this as my Son will be starting treatment soon, and I know how hellish that was for me on the drugs when I first went onto various ones, as I

could not tolerate most of them. I wish there had been an alternative. I will cope but an option for my Boy would be invaluable for us as a family.

Please reconsider and make this new form of treatment available to patients with the Genetic disease of FH."

"As a sufferer of familial hypercholesterol I know from experience however careful I am with my diet, it can only reduce my cholesterol levels by a small amount. Thus medication is vital for me."

"As someone with a heart condition and intolerance to statins this is a matter about which I feel strongly."

"I have high cholesterol levels but can't take statins as I suffer agonising muscle pain despite trying three different brands. An alternative that wouldn't have these horrible side effects would be so good for people like me who want to do the right thing but can't."

"I think it is crucial you look for alternatives to statins, which many people like me with FH cannot take. Without alternative drugs to lower bad cholesterol I, and 2 of my 3 children, nieces and nephews, am equally at risk of premature death as my father and his siblings who all died from CHD in their 50s."

"I have FH where the gene has been identified. I currently am at my maximal medication dose for treatment of FH and my Lipidologist would like my cholesterol levels still further reduced . I suffered a heart attack at the age of 37 due to my condition which at that time was unknown to me and have passed the mutation on to my eldest daughter who is nearly 11, my youngest daughter who is 5 has yet to be tested. I have been made aware of this new treatment and the significant effect it could have to further reduce my cholesterol levels and therefore threat of a repeat attack and would urge NICE to reconsider their decision. Not only would it prove hugely beneficial to me and thousands more but would also help allay our fears of further health issues in the future, and may help me to be around for as long as possible for my family, especially my children. I am unsure if the main reason for refusing this treatment is cost, but surely preventing long stays in hospital due to coronary disease/ heart attack and their consequent expense must balance with the cost of preventing such situations."

In addition to inviting comments on the decision by NICE, we requested a response to a statement prepared by HEART UK from the public, patients and those affected by raised cholesterol. The statement reads as follows:

"We believe that the decision by NICE to refuse to recommend a new drug for patients at risk from high cholesterol is wrong. We believe that evolocumab should be recommended to these high-risk patients and NICE have disadvantaged patients with heterozygous familial hypercholesterolaemia as a group.

Many patients at increased cardiovascular risk who cannot adequately lower their LDL-C (bad cholesterol) by using existing treatments should be given access to this treatment.

Apheresis is invasive and often inconvenient. Patients currently treated with Apheresis have been disadvantaged by NICE's decision to deny access to an alternative therapy.

We believe that the cost effectiveness of treating patients with raised LDL-C has been significantly underestimated with the analysis focussing too much on reduction of low LDL-C. The analysis should include groups of patients with high cardiovascular risk and high LDL-C.

I call on NICE to reverse their decision about evolocumab."

Attached is a list of 336 individuals who support this statement and have consented to include their names. All of the individuals replied with the statement "I support the statement from HEART UK and agree to include my name in the submission to NICE". Contact details for these individuals are held with HEART UK.

The Royal College of Pathologists
Pathology: the science behind the cure

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia [ID765]

The Royal College of Pathologists would like to thank NICE for the opportunity to comment on this Appraisal consultation document.

The RCPath is concerned that the draft ACD did not recommend Evolocumab, alone or in combination with lipid-lowering therapies, within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia in adults, or for any specific sub-group of patients. We agree with the clinical expert opinion regarding the clinical unmet need and the Committee's conclusion as stated in paragraph 4.4 "that evolocumab was likely to be reserved for people who are at a particularly high risk of CVD, including people with heterozygous-familial hypercholesterolaemia, and those who cannot tolerate statins and in whom ezetimibe does not adequately control LDL-C". However this conclusion was not reflected in the recommendation.

The ERG noted (para 3.22) that the modelled heterozygous-familial hypercholesterolaemia (HeFH) population included patients with, and those without, CVD. It noted that modelling these groups separately may be more clinically appropriate. The issue of statin intolerance in FH was not adequately considered in the recommendation. It was also noted that the cost-effectiveness calculations are strongly dependent on the CVD risk of those receiving treatment and their residual pre-treatment LDL-C (or non-HDL-C). As the estimated ICER for HeFH was approximately £22K, if treatment was reserved for the highest risk FH patients as outlined below, and non-FH secondary prevention patients with equivalent residual non-HDL-C, the RCPath believes that these drugs could be used cost-effectively. Although the results of long-term studies with hard clinical endpoints with not be available until 2017 at the earliest, there are few who doubt that the changes in LDL-C as a surrogate endpoint will translate into clinical benefits in line with previous LDLR-mediated LDL-C lowering interventions, including statins and ezetimibe, perhaps with less discordance between on-treatment and intention-to-treat analyses in view of the mode of delivery and closer on-treatment monitoring.

Evolocumab is the first in a new class of "biologic" lipid modifying therapy (LMT) based on a fully human monoclonal antibody which neutralizes PCSK9, an endogenously produced plasma protein which inhibits LDL receptor mediated clearance of LDL. PSCK9 is up-regulated in patients with Familial Hypercholesterolaemia (FH) due to PCSK9 gain-of-function (GOF) mutations and by statin therapy itself, thereby attenuating the LDL-C lowering effect achieved with higher statin doses. The LDL-C lowering effect of these new drugs is not dependent on inhibition of cholesterol synthesis and is therefore not associated with the adverse effects on isoprenoid metabolism and mitochondrial function implicated in statin related muscle toxicity. Evolocumab typically achieves reductions of LDL-C of 55% and non-HDL-C of 45% by upregulation of LDL receptor mediated clearance of LDL and appears equally effective whether given as monotherapy or in addition to

statins or ezetimibe, which also exert their LDL-C lowering effect by upregulation of LDL receptor mediated clearance of LDL. These new drugs therefore represent an important therapeutic development for high risk patients who are unable to achieve satisfactory control of LDL-C (or non-HDL-C) despite maximum tolerated treatment with statins and ezetimibe.

At present the only effective alternative therapy is fortnightly LDL-apheresis, which is not only costly (approx. £30K per annum) and onerous for the patient but difficult to access, as only a small number of apheresis centres have been established in England and Wales under specialized commissioning primarily to meet the needs of homozygous FH (HoFH) patients. In the NICE FH Clinical Guideline CG71 LDL-apheresis is recommended for FH homozygotes (who respond poorly, if at all to statins and ezetimibe) and in exceptional circumstances for heterozygous FH (HeFH) when there is progressive, symptomatic coronary heart disease, and persistently high LDL-C despite maximal tolerated lipid lowering therapy. Although there are many patients who meet the accepted criteria, at present few are being treated with LDL-apheresis. The Royal College of Pathologists considers that these new drugs have a place in the management of the following patients:

1. Heterozgous Familial Hypercholesterolaemia (HeFH) patients with progressive, symptomatic coronary heart disease, and persistently high non-HDL-C >5.0 mmol/L (equivalent to LDL-C >4.0 mmol/L) despite maximal tolerated lipid lowering therapy i.e. meeting current criteria for apheresis.
2. Severe Familial Hypercholesterolaemia (HeFH) with pre-treatment LDL-C >8.0 mmol/L (>90th percentile for all FH patients) and persistently high non-HDL-C >5.0 mmol/L (equivalent to LDL-C >4.0 mmol/L) despite maximal tolerated lipid lowering therapy. Usually caused by mutations causing greatest loss of LDLR function, (including null mutations in LDLR or PCSK9 GOF mutations) LDL-C in these patients is more likely to be poorly controlled. They are recognized to be at substantially greater CVD risk than milder cases (Besserling et al. 2014). Indeed many will already be included in category 1.
3. Non-FH patients with progressive, symptomatic coronary heart disease, and persistently high non-HDL-C >5.0 mmol/L (equivalent to LDL-C >4.0 mmol/L) despite maximal tolerated lipid lowering therapy (equivalent to those in 1.).

Most of the patients in the final category and some of those in the first and second categories will be unable to achieve adequate control due to intolerance of statins, most frequently intolerable statin related muscle toxicity (SRM2-6 as defined by Alfirevic et al 2014). Repeated rechallenge may not be appropriate in those with a history of statin related myopathy associated with significant CK elevation (SRM3 >4xULN; SRM4 >10xULN), rhabdomyolysis (SRM5), autoimmune mediated polymyositis with anti- HMGCoAR antibodies (SRM6) or a pre-existing myopathy (metabolic or mitochondrial).

Of the expected 100 000-150 000 HeFH patients in the England (0.2-0.3% of the population), fewer than 20000 adult cases have been identified, and of these severe HeFH would be approximately 2000 patients. Of these the majority (60-70%) will achieve satisfactory control on statins alone or in combination with ezetimibe. Thus the expected numbers requiring these new drugs immediately should be less than 1000, potentially rising to 5000 to 10000 in future years as more severe HeFH patients are identified through cascade screening. Some of these severe HeFH and LDL-apheresis eligible patients have already been identified but no register exists to confirm their numbers. The numbers of non-FH patients in the third category is more difficult to estimate, but is unlikely to exceed the number of FH patients using these therapies.

The question of the long term efficacy and outcomes with these therapies can only be answered by the larger studies now in progress. The occurrence of neutralizing anti-drug antibodies causing loss of response as noted in paragraph 4.10 is a theoretical possibility but has not been observed in the studies reported so far with these agents which are fully human antibodies and therefore of very low immunogenicity. The evidence submitted shows that they have been found to be highly effective, well tolerated and acceptable to patients. As expected, the small number of statin

resistant patients who have FH due to PCSK9 gain-of-function (GOF) mutations respond extremely well to these agents and deserve specific mention in the final recommendations.

Kind regards

[redacted]
Royal College of Pathologists

References

1. Besseling J, Kindt I, Hof M, Kastelein JJP, Hutten BA, Hovingh GK. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. Atherosclerosis; 2014; 233:219–23.

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MSD Response to NICE ACD for evolocumab

MSD welcomes the opportunity to comment on the appraisal consultation document (ACD) for evolocumab.

MSD has comments on the following areas in the ACD, which are outlined in more detail below:

- the use of ezetimibe in clinical practice;
- data on cardiovascular event reduction;
- LDL-c concentrations of patients on statins;
- use of cholesterol targets in current clinical practice.

1. The use of ezetimibe in clinical practice

In section 4.2 of the ACD, the Committee has noted that ezetimibe is used in two populations, as follows:

"*The Committee noted that ezetimibe monotherapy is used to treat primary hypercholesterolaemia when a statin is considered inappropriate or is not tolerated, and that ezetimibe in combination with a statin is used in people when cholesterol levels are not low enough, even when the dose is increased, or if a person is unable to tolerate higher doses of the statin."*

However, the final sentence of this section states that the ezetimibe is only used in patients who are unable to have a statin, as follows:

"The Committee concluded that statins are the main option for treating primary hypercholesterol-aemia (heterozygous-familial and non-familial), and that ezetimibe is used to treat primary hypercholesterolaemia in adults who are unable to have a statin"

Ezetimibe is routinely used in two populations, which is consistent with the first statement above. UK Prescription data available for ezetimibe, in the year to January 2015, showed that 38% of the patients receiving ezetimibe were on monotherapy and 62% were co-prescribed with a statin. As such, MSD believes the final sentence in section 4.2 of the ACD should be updated to also reflect the use of ezetimibe with statins.

2. Data on cardiovascular event reduction

In section 4.9, the Committee has noted the IMPROVE-IT study[1] for ezetimibe, which showed a further reduction in cardiovascular events when ezetimibe was added to a statin compared with statins alone. However, the sentence "*By contrast, adding other lipid-modifying drugs to statins was not consistently shown to further decrease CV events*" is not consistent with the results from this study. To reflect the availability of this data which no other non-statin has demonstrated, MSD believes it would be more appropriate to update the text to the following:

"*By contrast, adding **most** other lipid-modifying drugs to statins was not consistently shown to further decrease CV events.*"

3. LDL-c concentrations of patients on statins

In section 3.20 of the ACD, there is a statement that "…most UK patients can have an LDL-C concentration of 2.0 mmol/litre on statins". MSD believes this statement is contrary to clinical practice, and a recently observational study using CPRD by van Staa *et al.*[2] found that the average LDL-c for primary prevention patients on statins was 2.7 mmol/l.

4. Use of cholesterol targets in current clinical practice

The Committee has recognised in section 4.3 of the ACD that one of the key changes in the updated NICE Clinical Guideline for Lipid Modification (CG181)[3] published in July 2014 was a greater emphasis on managing cardiovascular risk rather than meeting a specific cholesterol target. However, cholesterol targets are routinely used in clinical practice, and will remain so for the foreseeable future.

A large number of patients are still not reaching recommended cholesterol levels. In 2011, the Health Survey for England reported that 60% of men and 38% of women with CVD (the expectation is that the majority had received advice on lifestyle modification and drug treatment where deemed advisable) had TC levels below 5 mmol/L (the NICE CG675 'audit level' for those with CVD, diabetes or hypertension who are on drug treatment), while only 27% and 10% respectively had levels below 4 mmol/L (the then-NICE 'target level' for this high-risk group) in 2011[4].

The use of additional lipid-lowering medicines should be considered by the Committee in light of the common use of cholesterol targets in clinical practice.

5. Clinical-effectiveness evidence

Under section 3.6 of the ACD, it is noted that none of the trials studied evolocumab in combination with ezetimibe in any population. The DESCARTES study[5] included an arm where patients were administered evolocumab with a statin and ezetimibe.

References

1. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015
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4. Health & Social Care Information Centre (HSCIC). Cardiovascular Disease. Health & Social Care Information Centre (HSCIC); 2012
5. Blom DJ, Hala T, Bolognese M, Lillestol MJ et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014 May 8;370(19):1809-19

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Fax:
E-mail:

I, as one of the clinical experts invited by NICE TA committee C to the appraisal of evolucumab for hyperlipidaemia and familial hypercholesterolaemia, am very disappointed that the committee did not recommend Evolocumab, alone or in combination with lipid-lowering therapies, within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia in adults, or for any specific sub-group of patients in the ACD.

I repeat the clinical evidence that I gave to the committee summarized in paragraph 4.4 "that evolocumab was likely to be reserved for people who are at a particularly high risk of CVD, including people with heterozygous-familial hypercholesterolaemia (HeFH), and those who cannot tolerate statins and in whom ezetimibe does not adequately control LDL-C". This conclusion is not reflected in the recommendation.

The ERG noted (para 3.22) that the health economic model provided by the company for heterozygous-familial hypercholesterolaemia (HeFH) population did not distinguish between patients with, and those without, CVD. It noted that modeling these groups separately may be more clinically appropriate. This is correct and forms a major deficiency in the evidence presented to the committee. There is substantial differential in CVD risk (see previous evidence and CG71) between patients with and without CVD in all instances and including HeFH. There is also a substantial difference in future CVD event rates depending on the occurrence of an acute coronary syndrome compared with a diagnosis of chronic CVD- approximately 50% (18% vs. 12% over 4 years) as documented in the REACH registry[1]. This was recognised in NICE CG67 where high dose high acquisition cost statin therapy was recommended at the time for patients with ACS but not for those with chronic CVD. By the time of CG181 prices had fallen sufficiently to allow generalisation of the original ACS recommendation. Also NICE CG71 recommended that treatment should be intensified beyond the standard therapy in patients with HeFH and CVD within the text of the full guideline. In addition there is a wide spectrum of CVD risk in HeFH (see Besseling- previous evidence[2]) with patients with LDL-C >90th centile for FH having an excess risk of CVD of >30% compared to patients with HeFH and lower LDL-C. This variation within HeFH is not considered in the summary of the evidence presented and is a major deficiency in the ACD.

The issue of statin intolerance in FH was not adequately considered in the recommendation. It is specifically defined in CG71 -1.3.11 as an issue for specialist management in HeFH where additional therapies should be considered (1.3.14). The cost-effectiveness calculations in the ACD are strongly dependent on the CVD risk of those receiving treatment and their residual pre-treatment LDL-C. Thus not considering the issue of statin-intolerant HeFH given these findings and previous recommendations from NICE is a substantial omission. A small number of patients with severe residual polygenic hypercholesterolaemia (i.e. those in whom statins are contra-indicated or who are intolerant) and aggressive CVD might also qualify for

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treatment given a very high LDL-C.

The company submission does not consider the role of apheresis in patients with HeFH. This is recommended in NICE CG71 1.3.3.2 for patients with HeFH 'in exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy'. This is generally considered to represent patients with HeFH and CVD with LDL-C >4.0 mmol/L (International apheresis guidelines, UK consensus statement[3, 4]). Apheresis is expensive, time-consuming, has poorly patient uptake given its commitment requirement and is associated with severe equity issues in terms of access. There is evidence that PCSK-9 inhibitors improve lipid control, are far better tolerated and reduce the frequency and anecdotally the need for apheresis at all. A specific cost-effectiveness model needs to be performed for evolucumab in patients with HeFH in comparison with apheresis.

The committee is dubious about the efficacy of lipid-lowering interventions lacking CVD outcomes evidence. However, in the case of hypercholesterolaemia a randomized controlled trial of ileal bypass surgery (Program on Surgical Correction of Hyperlipidaemia; n=838) reduced LDL-C by 23% (from 4.32 mmol/L to 2.84mmol/L) and delivered a 35% CVD event and later a CVD mortality reduction[5, 6]. Ezetimibe, a far weaker LDL-C reducing drug than evolocumab, has also been shown to reduce CVD events when added to statin therapy in optimally controlled patients in the IMPROVE-IT trial[7]. That evidence was reviewed by the same NICE-TA committee that is evaluating evolocumab. Patients with genetic inactivating mutations in PSCK-9 show a reduced risk of CVD events (Dallas Heart Study[8]). Meta-analyses of the PCSK-9 inhibitor trials show a reduction in CVD events in initial studies[9] supporting a Bayesian hypothesis that they are unlikely to be detrimental. The results of outcome studies with PCSK-9 inhibitors in high-risk patients with good baseline LDL-C control are expected to be announced in 2017-2018. There are no outcome trials of these drugs planned in HeFH. Thus the balance of risk and benefit is potentially favourable in very high risk patients prior to the publication of CVD outcome trials.

A suggestion as the indication for evolocumab might be:-

1. Patients with HeFH with progressive, symptomatic CVD, and persistently high LDL-C >4.0 mmol/L despite maximal tolerated lipid lowering therapy i.e. those meeting current criteria for apheresis.
2. Severe HeFH with pre-treatment LDL-C >8.0 mmol/L (>90th percentile for all FH patients) and persistently high LDL-C >4.0 mmol/L despite maximal tolerated lipid lowering therapy.
3. Non-FH patients with progressive, symptomatic CVD, and persistently high LDL-C >4.0 mmol/L despite maximal tolerated lipid lowering therapy (equivalent to those in 1).

Most of the patients in the final category and some of those in the first and second categories will be limited by severe adverse reactions to statins. Repeated re-challenge may not be appropriate in those with a strong history of statin-related myopathy associated with significant CK elevation or concurrent myopathies (metabolic or mitochondrial).

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Only some of the expected 100 000-150 000 HeFH patients in the England (0.2-0.3% of the population), have been identified, and of these severe HeFH would likely amount to 2000 patients. Most (60-70%) will be satisfactorily treated with statins alone or in combination with ezetimibe. Thus the number of patients likely to require early access (prior to general CVD outcome trials) should be less than 1000, potentially rising as more severe HeFH patients are identified through implementation of CG71 and its recommended strategy of cascade screening.

The occurrence of neutralizing anti-drug antibodies causing loss of response as noted in paragraph 4.10 is a theoretical possibility but has not been observed in the studies reported so far with these agents.

The committee should review its recommendations especially with regards to patients with FH and those patients with CVD with severe hypercholesterolaemia who are intolerant to any significant dose of a statin.

Yours Sincerely

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1. Bhatt DL, Eagle KA, Ohman EM et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010; **304**: 1350-7.
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Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Chemical Pathologist
Organisation	[redacted]
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

There are many patients with clinical vascular disease in whom maximum-tolerated statins+ezetimibe does not achieve suitable LDL cholesterol. It is not safe nor reasonable to make these high risk patients wait for more data.

There is CVD end point data to show that it is clinically effective.

LDL is a valid secondary end point - statin effects, ezetimibe effects, diet effects, ileal bypass effects, cholestyramine effects, experiments of nature - so why are the authors so keen to doubt it?

A compromise might be to allow evolocumab now for secondary prevention, and after more clinical data for primary prevention.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Parent
Other role	Carer
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

I am an UK citizen and father of a UK citizen child with homozygous hypercholsterolemia. This child has already had open heart surgery at great NHS

expense to remove aortic blockages caused by high cholesterol. NHS is about to spend a large amount of ongoing money on apheresis to reduce cholesterol to prevent blockages forming again. Is this NICE suggested block on PCSK9 treatments a blanket ban? Or could it be prescribed on a case-by-case basis to reduce critically high cholesterol levels to prevent blockages forming and also reduce other NHS costs such as apheresis?

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant Medical Biochemist
Other role	NHS Professional
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

I provide a routine lipid clinic service, primarily for primary care referrals; I have a small group of patients (about 10) who are effectively without treatment but at high risk of cardiovascular disease - mainly Familial Hypercholesterolaemia and established cardiovascular disease. They have all been tried on all five available statins, including low-dose (e.g. Rosuvastatin 5mg once weekly), ezetimibe, fibrates, bile-acid sequestrants, and when it was available, nicotinic acid, and are either unable to tolerate the medication or do nopt respond adequately. I have been pllanning for years to have the chance to try them with a PCSK9 inhibitoras the alternative (CETP inhibitors) have become less likely to become available.I will need to consider applying for apheresis funding for the highest risk ones if evolocumab is not an option.Iappreciate that CVD outcome data is not yet available, but as the mechanism of action is identical to statins at the end point (increasing LDL receptor number) it would seem unlikely that this data will prove negative given the excellent surrogate response (serum LDL) seen in the trial work.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3	

(The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant
Other role	NHS Professional
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

This is for the document relating to the licencing of Evolocumab (Repatha) for the treatment of patients at high risk for the development of cardiovascular disease (CVD).

Low density lipoprotein cholesterol (LDL-C) is a major risk factor for CVD risk and atherosclerosis progression.

- Reduction of LDL-C has been shown to reduce the risk of CVD.

-There are patients in the NHS who despite treatment are still at risk

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	GP
Other role	NHS Professional
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	

I have extensive experience of using Evolocumab in clinical trials. I have found the medication to be very effective at lowering cholesterol in open label studies and patients have found it to be well tolerated with very few adverse events. The 2 weekly and 4 weekly injection regimes have been well received by patients. I support the wider use of this compound in clinical practice and feel that it has an important role to play in the treatment of hyperlipidaemia	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant chemical pathologist
Other role	NHS Professional
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: There is a clear clinical need for an additional class of LDL lowering therapy for patients who are intolerant of current drugs (statins, ezetimibe), have very high lipids (mainly familial hypercholesterolaemia) and have exisiting cardiovascular disease. Such patients would fit current criteria for LDL apheresis, which is considerably more expensive and inconvenient to the patient. At the very least, evolocumab should be available for secondary prevention in patients with elevated lipids (eg, LDL >5) despite maximally tolerated doses of conventional treatment. The LDL threshold is open for debate and review over time, but figures of 1.5 or 2 are unrealistically low.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review	

of guidance)	

Name	[redacted]
Role	Consultant Chemical Pathologist
Other role	NHS Professional
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: Consider permitting use of Evolucumab in patients on or eligible for apheresis. Evolocumab is likely to cost the NHS less than apheresis.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant in Chemical Pathology and Metabolic Medicine
Other role	NHS Professional
Organisation	[redacted]
Location	
Conflict	
Notes	
Comments on individual sections of the ACD: I would request that the committee consider the option of using evolocumab in the following selected patients: Patients whose cardiovascular (CVS) risks remain excessively high (including patients with severe heterozygous familial hypercholesterolaemia) where conventional therapy have not managed to reduce their CVS risks. Patients who have high CVS risk but have not tolerated any of the conventional therapy. Evolocumab should be considered is as a third line therapy (after statin or ezetimibe) before decision is made for patient to undergo apheresis therapy. Evolucumab should not be continued beyond 6 months unless it could be clearly demonstrated that it has lowered LDL-cholesterol by 35% or more.	
Section 1	

(Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant in Metabolic Medicine
Other role	NHS Professional
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

I have read the appraisal document with interest and appreciate the time and effort involved in its preparation. While this document covered many areas of lipid management, I am afraid that some issues were not addressed thus making the conclusion flawed.

In the appraisal document, there has been no distinction between familial hypercholesterolaemia patients with disease and those without disease. These are two separate group of patients with different requirements in terms of cardiovascular risk reduction and this should be considered.

You have highlighted that there is no outcome data on the efficacy of evolocumab in cardiovascular risk reduction. The appraisal team have overlooked the information from the OSLER study which showed a 53% reduction in cardiovascular events. While this was a study looking at the effect of evolocumab on cholesterol and lipid parameters, it also showed reduction in cardiovascular events.

Evolocumab leads to 61% reduction in LDL cholesterol and 52% reduction in non-HDL cholesterol. We know that LDL cholesterol has been implicated in cardiovascular disease as well as LDL-cholesterol reduction reduces cardiovascular disease (CTT metaanalysis). Since LDL -cholesterol reduction is central to most management strategies in lipid clinics, this should have been considered.

Perhaps we should review which groups should be considered for evolocumab use rather than a blanket view that it is not recommended. We should consider use in familial hypercholesterolaemia with cardiovascular events, Homozygous FH, statin intolerant patients with cardiovascular events as a priority. Evolocumab and other medication in the group provide promise to a select group of patients, and this should be considered.

Section 1 (Appraisal Committee's preliminary	

recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant in Metabolic Medicine
Other role	NHS Professional
Organisation	
Location	England
Conflict	Yes: [redacted]
Notes	

Comments on individual sections of the ACD:

There is a significant unmet need for innovative lipid lowering therapies in secondary prevention of cardiovascular disease particularly in patients who have recurrent MIs despite statins. Early cardiac data for PCSK9 inhibitors looks promising. We also know that mutations in the PCSK9 gene cause the most severe phenotype in familial hypercholesterolaemia (FH) and anticipate that PCSK9 inhibition will prove effective at preventing cardiovascular events. I urge NICE to reconsider their guidance particularly for secondary prevention of cardiovascular events in patients who:

1. Have repeat MIs despite statins, and/or

2. Who fail to reach target lipid levels either because of statin intolerance or because of resistance to statins common in familial hypercholesterolaemia.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant in Clinical Biochemistry and Visiting Senior Fellow in

	Metabolic, Endocrine and Nutritoinal Medicine
Other role	NHS Professional
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

It is regrettable that the NICE draft guidelines for evolocumab do not recommend this drug. Whilst the vast majority of people with high cardiovascular risk can be adequately managed with statins and ezetimibe, it still leaves a small but significant number of patients who are not and remain at very high risk. This includes people with established atherosclerotic cardiovascular disease and / or people with Familial Hypercholesterolaemia.

This drug affects LDL receptor function, which is how statins modify cardiovascular risk. The OSLER trial confirmed that this drug reduces cardiovascular events. I firmly believe that this drug should be available for this small group of patients in whom conventional treatments have failed, since it has been shown to be effective and there is very little else that can be offered to reduce their risks.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
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Name	[redacted]
Role	Honorary Consultant Physician and Lipidologist
Other role	NHS Professional
Organisation	
Location	England
Conflict	No
Notes	I see patients both NHS and private on the [redacted] I am [redacted] which manages the FH register for the UK, and in the last 3 years has initiated the Paediatric Register, hosted by the RCP.

Comments on individual sections of the ACD:

It is disappointing that NICE has turned down PCSK9 inhibitors, as these would be an extremely useful therapy in exceptional cases as follows:

1. In patients in whom secondary prevention targets are not achieved with the maximum tolerated lipid lowering therapy available at present,[statins + ezetimibe] and in whom further cardiac interventions might be avoided with effective medication.

2. In those whom lipid levels are not effectively treated because their genetic hyperlipidaemias, [familial combined hyperlipidaemia and familial hypercholesterolaemia] are not sufficiently responsive to available therapies, statins + ezetimibe as above.

3. The NICE guidline 71 on FH, 2008 for which I was a member of the GDG, states that there is an indication for lipoprotein apheresis in patients who have symptomatic and deteriorating CHD symptoms in spite of maximum tolerated cardioprotective therapies.

In such patients the additional use of PCSK9 inhibitors would be likely to obviate the need for apheresis, which is both expensive and tough on patients, and be a less expensive option.

I have several patients attending my Lipid Clinic in category 1 above.

For example a 52 year old long haul pilot with FH who has recently had CABG and whose cholesterol is >5.5 and LDL>3mmol/l, considerably above the levels at which atherosclerosis is progressive, and for which the recommendation is LDL<1.8mmol/l. He is taking maximum statin + ezetimibe, but lipids are poorly controlled. Here we have a youngish man who is returning to work, and would benefit from a PCSK9 inhibitor to achieve secondary prevention levels and to avoid a return of CHD interventions.

With the advent of thjeeffective and well tolerated new therapies there is a real chance to treat optimally those in need of further lipid lowering therapy.

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Name	[redacted]
Role	Researcher
Other role	Patient
Organisation	

Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

As someone with FH and a scientist who has been following the development of Evolocumab since its first development I have a good understanding of its problems and the usefulness.. I tested positive for high cholesterol when I was 6, early 70s. I have used most of the treatments available to reduce my cholesterol with either extreme side effects or no real impact on cholesterol levels. I was given Atromid S as a child which gave me extreme headaches. Tried fibrates and niacin with little effect. Statins had some effect but the side effects are so disabling that I can only take 5 mgs a day for about one month and then stop until the muscle/joint pain, insomnia, irritability, stop and then take again. Hence it has limited usefulness. My way of dealing with the FH has been to stay as fit as possible. With a resting heart rate of 56 and ability to run up to ten miles - I'm fit. However, the only way I have been able to maintain this is to get a series of stents in the arteries closed by my cholesterol. So far I have six stents. Each of the surgeries I have had cost a great deal of money. To slow down the need for stents I get apheresis every other week. This costs approximately Â£1,500 each time. My cholesterol is kept down to approximately 7-8 by low levels of statins and ezetimibe between apheresis. Hence the efficacy of apheresis is fairly limited for me. So when I hear that the new drug that will get my cholesterol down to acceptable levels at a cost of approximately Â£6,000/year is not cost effective, I wonder where the people making their decisions are getting their data. It will be much more cost effective than the treatment NHS is already funding. I accept this is only in extreme cases such as mine, but we too have to be considered. If you don't provide me with this treatment I will once again have to have more stents and/or have a heart attack.

In addition, my research into pharmaceutical impact on aquatic organisms has indicated that the cost of reducing the impact on the environment will also become a factor in developing drugs. Antibodies to PCSK9 are biologicals hence break down fairly quickly and are unlikely to have an impact on the environment, so once again an advantage in treatment.

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Name	[redacted]
Role	Professor of Medicine
Other role	NHS Professional
Organisation	[redacted]

Location	Wales
Conflict	No
Notes	

Comments on individual sections of the ACD:

We have participated in the clinical trial programme of Evolocumab and have been impressed both by the reductions in LDL-cholesterol seen and the tolerability. I am sure that there will be a niche of high cardiovascular patients who are unable to tolerate statins and for whom ezetimibe is insufficient to hit the current NICE targets outlined in CG 181.

he ERG seems to doubt the premise that a rediction in LDL-C concentration is clinically important since it can be used as a surrogate for cardiovascular disease (CVD). This seems at odds with mainstream thinking, especially following on from the results of the SHARP and IMPROVE-IT studies showing that LDL-cholesterol reductions with ezetimibe benefit CVD outcomes. Indeed, the trials of all of the PCSK9 inhibitors are based on this premise, which appears to be supported by naturally occurring mutations within the PCSK9 gene. Can the ERG justify its stance on this issue?

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Name	[redacted]
Role	retail manager, retired nurse,
Other role	Patient
Organisation	
Location	
Conflict	No
Notes	[redacted]

Comments on individual sections of the ACD:

The populations covered by the committee I believe to be to generalised and therefore cost effectiveness as per QALY far to expensive. Instead it should have had specific subtypes Homogzygous and hetrozygous of those where standard statin, ezetimibe are not enough (lipoprotein a above recommended levels) and for those already on maximal current therapies including those not mentioned already on ldl-apheresis . I am from one of these patient groups and was hoping that evolucumab would prevent me from either having to increase ldl-apheresis as currently it is no longer so effective due to access issues resulting in the use of one arm. In itself a expensive treatment but remains the only way to reduce lipoprotein a or undergo more cardiac surgery.

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Name	[redacted]
Role	Consultant Chemical Pathologist, Professor of Metabolic Medicine
Other role	NHS Professional
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

Use of PCSK9 inhibitors

The question for NICE to ponder upon is which patients are entitled to be treated with these agents. Obviously in view of evidence and cost statins and ezetimibe must be used prior to PCSK9 inhibitors. Benefit in line with LDL-cholesterol (LDL-c) reduction in the SHARP and IMPROVE-IT studies may suggest a role for LDL-c more than that of a surrogate marker. This was the basis that led to the approval by the regulatory bodies. So what should the criteria be for use? As a practising clinician my belief is that it should be restricted to secondary prevention and familial hypercholestrolaemia, but at what TC/LDL-c levels. Risks and benefits have to be calculated at each TC and LDL-c level.

I would suggest visiting the 4S data from 1994. The inclusion criteria was TC > 5.5mmol/l; mean baseline TC was 6.75mmol/l (placebo), 6.74mmol/l (simvastatin) and LDL-c was 4.87mmol/l (placebo and simvastatin groups). Interestingly one of the tertiary end-points suggested that the probability of escaping either death or any atherosclerotic cardiovascular event after 6 years was 53% in the placebo group and 62.9% in the simvastatin group. Although this was a tertiary analysis the figures are stark; nearly half the patients recruited (mean LDL-c of 4.87mmol/l) would be subjected to CVD or death over a 6 year period. Going by the LDL-c hypothesis one would expect greater benefit with a PCSK9 inhibitor than simvastatin in view of efficacy**.**

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Name	[redacted]
Role	Consultant Chemical Pathologist
Other role	NHS Professional
Organisation	[redacted]
Location	Wales
Conflict	No
Notes	

Comments on individual sections of the ACD:

1. It is acknowledged that Evolocumab should be reserved primarily for patients established as being at high risk of CVD, which would include patients with genetically confirmed Heterozygous Familial Hypercholesterolaemia and those patients who are unable to tolerate statin therapies and in whom Ezetimibe is ineffective in controlling the LDL-C levels. It is disappointing, therefore that NICE has chosen not to recommend the use of Evolocumab, particularly as I have a significant number of patients within my geographical area of clinical practice responsibility within Wales who would fall into this cohort of patients and would therefore, potentially benefit from PCSK9-therapy, especially as this therapeutic product has proven LDL-C lowering capacity.
2. LDL-C lowering is associated with reducing CVD Risk and the number of CVD Events. It is well established that lowering LDL-C is associated with reducing CVD Risk and Events via statin therapies and other lipid-modifying approaches. It is noted that some statin therapies were approved for therapeutic use prior to confirmimg clinically proven outcome efficacy. PCSK9 Inhibitors have been shown to have significant LDL-C lowering capacity via a mechanism that is similar to that of statins, notably by increasing the number of cell surface LDL receptors and hence increasing the efficacy of LDL-C clearance from the circulation. Whilst it is acknowledged that there is currently no completed clinical outcome data re PCSK9 Inhibitors there seems little reason to question the use of LDL-C lowering capacity as a surrogate marker for CVD risk and event reduction.
3. Unmet Clinical Need in Cwm Taf University Health Board

   (i) I have a well establsihed FH Genetic Testing and Family Cascade Screening and Lipid Clinic Service in Cwm Taf University Health Board which forms part of the All Wales Familial Hypercholesterolaemia and Family Cascade Screening Service across Wales. The FH Clinics are run and lead primarily by Consultant Chemical Pathologists across Wales supported by and working in collaboration with the Cardiff based FH Genetic Testing Service and the FH Specialist Nursing Network, which is part funded via the BHF. Consequently, over the last 5-6 years I have identified an increasing number of genetically comfirmed patients and families with FH. Whilst these patients are initially treated with optimal statin therapy, a significant proportion of these patients are either not reaching satisfactory targets or are intolerant of all available statins and hence remain at increased risk of developing

premature CVD nad or exacerbating further CVD events if left unsatisfactorily controlled.

(ii) I have a very well established Lipid and Metabolic Clinic Service across Cwn Taf University Health Board which runs in parallel with my FH Clinical Services. I have three clinics : 1. Prince Charles Hospital, Merthyr Tydfil, 2. Ysbyty Cwm Cynon, Mountain Ash/Aberdare and 3. Ysbyty Cwm Rhondda, Pontypridd, Rhondda and Vale of Glamorgan covering a catchment population of approximately 220,000 with an inherent high prevalence and incidence of CVD. These clinics as well as being responsible for managing patients and families with genetically confirmed FH also see a very large number of patients with CVD and or Diabetes mellitus with concomitant dyslipidaemia whom also require optimisation of their lipid profiles. As with the FH patients there are significant numbers of patients within these patient groups who are unable to tolerate statin therapies or hose lipid profile is inadequately managed by Ezetimibe alone.

(iii) Both these types of patients are therefore, likely to benefit from PCSK9 Inhibition and its proven LDL-C lowering capacity and without adequate treatment remain at sustained risk of CVD and CVD events.

4. Given the evident biochemical efficacy of Evolocumab treatment with a reassuring tolerability profile and given the significant current unmet need in the geographical area of Wales for which I have responsibily for managing i.e patients with FH and CVD/DM with dyslipidaemias I would strongly urge NICE to reconsider its recommendations in the draft appraisal with a view to recommending using this product in as wide a population as is cost effectively feasible under the careful guidance and auspices of the Specialist Lipid Clinics.

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Name	[redacted]
Role	Consultant Chemical Pathology & Metabolic Medicine
Other role	
Organisation	[redacted]
Location	England

Conflict	No
Notes	

Comments on individual sections of the ACD:
I don't agree with NICE as there are definite groups of patients who stand to benefit from this treatment. They include:

1. FH patients who meet the NICE CG71 criteria for apheresis but do not have access locally. For patients in most parts of Cumbria, the nearest LDL apheresis centre is Leeds which is practically inaccessible.

2. Patients with progressive CVD who are intolerant of multiple statins.

3. Definite FH patients whose treated LDL on maximal therapy remains significantly increased e.g. >5.1mmol/L.

4. Patients with GOF PCSK9 mutations who respond poorly to statins.

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Name	[redacted]
Role	Consultant Chemical Pathologist
Other role	
Organisation	[redacted]
Location	Wales
Conflict	No
Notes	Sponsorship by Amgen of one recent meeting of Welsh Chemical Pathologists. Sponsorship rotated around different companies with interest in lipid-lowering therapies. Promotional literature available but talk was given by non-promotional medical arm of Amgen, Dr Simon Williams, Cardiovascular Therapy Area Head.

Comments on individual sections of the ACD:
Response to Appraisal Consultation - Hypercholesterolaemia (primary), dyslipidaemia (mixed) - evolocumab [ID765]

1. It is acknowledged that Evolocumab should be reserved primarily for patients established as being at high risk of CVD, which would include patients with genetically confirmed Heterozygous Familial Hypercholesterolaemia and those patients who are unable to tolerate statin therapies and in whom Ezetimibe is ineffective in controlling the LDL-C levels. It is disappointing, therefore that NICE has

chosen not to recommend the use of Evolucumab, particularly as we have a significant number of patients in Wales who would fall into this cohort of patients and would therefore, potentially benefit from PCSK9 therapy, especially as this therapeutic product has proven LDL-C lowering capacity.

2. LDL-C Lowering is associated with reducing CVD Risk and the number of CVD Events. It is well established that lowering LDL-C is associated with reducing CVD Risk and events via statin therapies and other lipid modifying approaches. It is noted that some statin therapies and ezetimibe were approved for therapeutic use prior to confirming clinically proven outcome efficacy. The PCSK9 Inhibitors have been shown to have a significant LDL-C lowering capacity via a mechanism that is similar to that of Statin therapies, notably by increasing the number of cell surface LDL receptors. Whilst it is acknowledged that there is currently no completed clinical outcome data re PCSK9 inhibitors there seems little reason to question the use of LDL-C lowering capacity as a surrogate marker for CVD risk and event reduction.

3. Unmet Clinical Need in Wales:

(i) We have a well established Genetic Testing service in Wales which is identifying an increasing number of genetically confirmed FH and whilst these patients are initially treated with optimal statin therapy, a significant proportion of these patients are either not reaching satisfactory targets or are intolerant of all available statins and hence remain at increased risk of developing premature CVD and/or exacerbating further CVD events if left unsatisfactorily controlled.

(ii) We have a well established Lipid Clinic Service across Wales which is managed by members of the Welsh Chemical Pathologists across each of the Health Boards across the Principality. These clinics as well as being responsible for managing patients with genetically proven FH also see a very large number of patients with CVD and/or Diabetes mellitus with concomitant dyslipidaemia whom also require optimisation of their lipid profiles. As with the FH patients there are a significant number of patients within these groups of patients who are unable to tolerate statin therapies and whose lipid profile is not adequately managed by Ezetimibe alone.

(iii) Both these types of patients are therefore, likely to benefit from PCSK9 Inhibition and its proven LDL-C lowering capacity and without adequate treatment remain at sustained risk of CVD and CVD events.

4. Given the evident biochemical efficacy of Evolocumab treatment with a reassuring tolerability profile and given the significant current unmet clinical need in Wales we would strongly urge NICE to reconsider its recommendations in the draft appraisal with a view to recommending using this product in as wide a population as

is cost effectively feasible.

5. Although this Appraisal concerns Evolocumab our comments given above would apply to any PCSK9 inhibitors that come to market.

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Name	[redacted]
Role	[redacted]
Other role	
Organisation	The consultant body at the Lipid Clinic, OUH NHS Foundation Trust, Oxford
Location	
Conflict	No
Notes	None of the signatories of this response have received payment or honoraria for consulting, attending meetings or acted on speakers bureau for Amgen

Comments on individual sections of the ACD:

We fully agree with the NICE position that the evidence does not support the use of evolocumab in routine clinical care. However, we strongly disagree that it should not be used in any clinical circumstance.

As specialists working in a tertiary specialist Lipid clinic managing patients with complex or severe lipid disorders, we would like NICE to reconsider the non-recommendation of evolocumab and allow its use in a limited set of circumstances. These circumstances would include the following:

â€¢ Patients with homozygous or heterozygous familial hypercholesterolaemia who have LDL cholesterol above 5 mmol/l despite maximally tolerated statin plus ezetimibe therapy progressive coronary heart disease despite some years of maximally tolerated statin based LDL lowering treatment in combination with ezetimibe (in line with NICE TA132). Alternative therapies for these patients would include plasmapheresis (which is a very costly).

â€¢ Patients at high vascular risk unable to take a statins or other adequate lipid lowering medication because of well documented unacceptable side effects with all available agents.

We propose that any recommendation for evolocumab would need to be made by a specialist consultant in a Lipid clinic and the lipid-lowering effectiveness carefully

monitored. The number of eligible patients is very small and for these people treatment with PCSK9 inhibitors is likely to prove cost-effective given that they are at very high risk of cardiovascular complications. Applying strict criteria, we currently estimate there to be less than 10 among our clinic population based on a catchment population of over 1 million.

Since the numbers of such patients under these circumstances is so small, we would propose that the appropriate route for the implementation of such guidance of a high cost drug would be through national commissioning at NHS England rather than by local CCGs. Such commissioning arrangements are analogous to the use of high cost/low use drugs in endocrinology, such as pegvisomont.

For this selected group of vulnerable patients, PCSK9 inhibitors may be life-saving. Consequently we request that NICE reconsider its decision and allow Lipid specialists to flexibility prescribe these drugs in these limited conditions. We would be happy to work with NICE to help provide further information in support of this case.

Yours sincerely,

[redacted]

on behalf of the Oxford University Hospital Trust Lipid Clinic

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Name	[redacted]
Role	Professor of Medicine
Other role	
Organisation	Lipid Clinic, Hammersmith Hospital
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

Comments on NICE Appraisal consultation document

Comments on NICE Appraisal consultation document

Evolocumab and similar drugs for treating primary hypercholesterolaemia and mixed dyslipidaemia

General Impression

Although half a dozen members of the Appraisal Committee are medically qualified only a minority are practicing clinicians and none has any obvious expertise in cardiology or lipidology. The majority work in the arenas of public health and health economics and therefore never see patients. Their area of expertise presumably explains why the emphasis of this document is more on the cost of evolocumab rather than on its efficacy. The case history appended below illustrates the type of patient in whom this novel compound could, by reducing LDL cholesterol by 50 - 60% when added to maximal conventional therapy, be literally life saving. In addition the committee should consider for treatment patients with FH, who cannot tolerate statins.

Comments on specific sections of the document

3.14: The ERG view that the data from Osler 1 & 2 are inadmissible because they contain data from trials other than those submitted to NICE for systematic review is questionable. The trials that were not included contributed only 25% of the patients in the analysis of Osler 1 & 2 and it most unlikely that their omission would have affected the main conclusion, namely that there was a 53% reduction in CV events after 1 year treatment with evolocumab [1].

3.22: Why should patients with FH who do or do not have CVD be modelled separately? Its presence or absence does not make the slightest difference to the relative reduction in LDL cholesterol achieved by lipid-lowering drug therapy.

3.30: The assertion that the risk of CVD in heterozygous FH is markedly increased is supported by the data of Versmissen et al [2]. These authors showed that the hazard ratio in untreated Dutch patients was 8.69 (4.77 to 15.82, P< 0.001) compared with the population at large.

3.33 and 3.35: The recently published data of Sabatine et al [1] clearly support the well established correlation between reductions in LDL cholesterol and CV events and the use of the former as a surrogate marker of the latter.

4.13: In clinical practice most patients with heterozygous FH get treated with maximally tolerated doses of statins and ezetimibe, irrespective of whether they do or do not have CVD. This strategy is based on NICE recommendations that LDL

cholesterol should be reduced by 50% in all FH patients [3].

4.17: Which clinical experts• stated that there is no evidence that the risk of CVD is increased in FH? See refs [4-8] and [2].

4.24: The Committee decision not to recommend the use of evolocumab in patients with heterozygous FH should be reconsidered. At the very least it should sanction its use in those categories of patient currently recommended for treatment with lipoprotein apheresis by HEART UK, namely those whose coronary disease progresses and whose LDL cholesterol remains > 5 mmol/l or decreases by <40% despite maximally tolerated doses of combination drug therapy [9].

4.27: The authors of the QRisk2 equation specifically state that it should not be used in patients with FH [10].

References

1. Sabatine MS et al Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Eng J Med 2015; 372: 1500-9.

2 Versmissen J et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ 2008; 337:a2423.

3. NICE clinical guideline 71. Identification and management of familial hypercholesterolaemia. August 2008.

4. Slack J. Risks of ischaemic heart-disease in familial hperlipoproteinaemic states. Lancet 1969; 2: 1380-2.

5. Stone NJ et al. Coronary artery disease in 118 kindred with familial type II hyperlipoproteinemia. Circulation 1974; 49: 476-88.

6. Heiberg A. The risk of atherosclerotic vascular disease in subjects with xanthomatosis. Acta Med Scand 1978; 198: 249-61.

Continuation comment one

7. Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. BMJ 1991; 303: 893-6.

8. Benn M et al. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab 2012; 97: 3956-64.

9. Thompson GR et al. Recommendations for the use of LDL apheresis. Atherosclerosis 2008; 198: 247-55.

10. Hippisley-Cox J et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008; 336:1475-82.

Case history

[redacted]

Diagnosis: Heterozygous FH.

Pre-treatment serum cholesterol 10.9 mmol/l (422 mg/dl), Lp(a) 1200 mg/l.

Family history: Father died MI age 57. Mother serum cholesterol 18 mmol/l.

Past history: 1985 FH diagnosed at age 25 after sudden death of father.

Asymptomatic but positive exercise test. Treated with simvastatin and cholesteyramine.

1988: Coronary angiogram, LAD 90% stenosis, RCA complete occlusion.

1989: Angioplasty of LAD, VF during procedure.

1991: Angioplasty of re-stenosed LAD.

1991-1998: Cholesterol reasonably well controlled on simvastatin, cholestyramine and nicotinic acid.

1998: Angina on exertion. LAD 80% stenosis, aortic gradient 80-90 mm Hg, funnelling of aortic root.

1999; Tendon xanthomas both hands, pre-tibial tuberosities, Achilles tendons. Aortic systolic murmur, L carotid bruit.

Serum total cholesterol 5.3, TG 1.3, HDLC 0.78, LDLC 3.9 mmol/l. bilirubin 50 umol/l (Gilbert syndrome) while on atorvastatin 80 mg, cholestyramine 32 g daily.

2000: Asymptomatic, tendon Xs regressing.

2001: Mild angina on exertion.

2003: LDLR mutation detected. Single base pair substitution in exon 9 in EGF precursor-like domain.

2012: Aortic valve replacement and CABG.

Current status:

2014: Referred back to HH Lipid Clinic. Reasonably well but TC 6, TG 1.1, HDLC 1.2, LDLC 4.3 mmol/l (232, 97, 46, 166 mg/dl) despite rosuvastatin 40 mg, ezetimibe 10 mg, colesevalam 4-5 tabs daily plus aspirin 75 mg and clopidigrel 75 mg daily.

[redacted]

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Name	[redacted]
Role	
Other role	NHS Professional
Organisation	Queen Elizabeth Hospital, Gatsehead
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

Repatha is important therapy for patients not achieving 50% reduction in NHD-c or LDLc as suggested by NICE guidelines . This means patients with homozygous FH, heterozygous including intolerant of therapy. Also this therapy offers therapeutic option for patients with secondary prevention not achieving 40% reduction in LDLc and NHDL-c as suggested by NICE. 25% of my patients attending lipid clinic are intolerant of statins.

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Name	[redacted]
Role	[redacted], Irish Atherosclerosis Society - a society of clinicians in Northern Ireland and RoI with an interest in hyperlipidaemia

Other role	
Organisation	Irish Atherosclerosis Society
Location	N. Ireland
Conflict	No
Notes	PCSK9 manufacturers have previously given educational grants to the Irish Cardiac Society (of which Irish Atherosclerosis Society is a subgroup) . Individuals within the society have taken part as investigators/sub-investigators in PCSK9 clinical trials.

Comments on individual sections of the ACD:
here are a small but important number of patients with familial hyperlipidaemia for whom current NICE approved therapy options do not achieve optimal control of lipids. Several clinical trials of PCSK9 inhibitors including evolocumab have demonstrated additive benefit to standard therapies.

While ongoing endpoint trials are required to evaluate the benefit of evolocumab in wider patient populations such as acute coronary syndrome, based on clinical trials to date, the Irish Atherosclerosis Society sees a clinical role for PCSK9 inhibitors for some patients with familial hyperlipidaemia.

We would be grateful if the committee would consider supporting use at this time in the limited numbers of patients with familial hyperlipidaemia for whom current NICE approved therapy options do not achieve optimal control of lipids.

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Name	[redacted]
Role	Professor of Medicine, Head of Lipid Clinic
Other role	
Organisation	Hammersmith Hospital Lipid Clinic
Location	
Conflict	No
Notes	

Comments on individual sections of the ACD:
This gives our qualifications in relation to our prior comments.

[redacted] is one of the UKs foremost lipidologists. [redacted] ,DSc, FRCP, [redacted] Hammersmith Hospital, Imperial College London

[redacted] FMedSci and FRS, and one of the UKs foremost medical scientists. He was formly [redacted] Chief of Medicine, head of the NHS Medical directorate, and Chief of Cardiology. He is head of the [redacted].

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Name	[redacted]
Role	Senior Lecturer and Consultant in Medical Biochemistry
Other role	
Organisation	[redacted]
Location	Wales
Conflict	No
Notes	I was a member of the NICE Guideline Development Group for [redacted]

Comments on individual sections of the ACD:
Response from Wales FH Professional Advisory Group

This response is written on behalf of the Wales FH professional advisory group, which has professional oversight of the All Wales Familial Hypercholesterolaemia (FH) service. This group has extensive clinical experience of assessing and treating patients with inherited hyperlipidaemia, particularly FH.

On clinical grounds we consider that PCSK9 inhibitors should have a specific indication for treating

Patients with FH who are intolerant of statins

Treating patients with FH who have progressive cardiovascular disease with persistently elevated LDL cholesterol concentrations despite optimum treatment by all other approaches.

We note that the NICE assessment committee felt that it had insufficient evidence to fully assess these indications. We have summarised our views under 5 headings as below.

1) FH is an inborn error of metabolism

We consider that FH is a special case and should be regarded as an inborn error of

LDL cholesterol metabolism that requires specific and targeted treatment to lower LDL cholesterol.

2) PCSK9 genetic variants cause/protect from heart disease

One of the genetic mutations that cause FH is a gain of function mutation in the PCSK9 gene which leads to increased PCSK9 protein expression. This in turn causes the LDL receptors to be degraded in the cell so that they are available for further clearance of LDL cholesterol from the blood stream.

Conversely there is now clear evidence that individuals with genetically lower PCSK9 concentrations have lower LDL cholesterol concentrations and significantly lower rates of coronary heart disease. Also some individuals with genetically absent PCSK9 have been described with no adverse clinical features which is very reassuring from a safety perspective.

3) The clinical argument for statin therapy in FH also applies to PCSK9 inhibitors

It should be noted that the clinical evidence for statin benefit in FH is not based on randomised clinical trials in FH but rather the pharmacological evidence that it targets LDL cholesterol metabolism, combined with general safety and efficacy data. Randomised placebo controlled trials of statin therapy on cardiovascular events, have not been carried out in FH because it would be regarded as unethical to withhold statin therapy in FH patients. (NICE FH guideline GC 71 2008). Similarly, we would regard it as clinically unethical to withhold treatment with PCSK9 inhibitors from patients with FH in situations where other therapy is not tolerated (ie statins) or is not effective.

4) PCSK9 inhibitors are a form of personalised medicine to be used as a 3rd line agent

In the era of personalised medicine, we would regard PCSK9 inhibitors as an agent that specifically targets the metabolic defect that is FH. This should be regarded as genetically targeted 3rd line therapy (after statins and ezetimibe) for patients who are not suitable for these first and second line agents.

5) The number of patients appropriate for PCSK9 inhibitors will be small

We estimate that the proportion of FH patients who cannot tolerate statins is less than 5% of the patients with a diagnosis of FH. Therefore we think that the number of patients requiring PCSK9 inhibitors would be relatively small.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
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Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	

Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Policy manager at medical research charity
Other role	
Organisation	British Heart Foundation
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: The British Heart Foundation supports the proposed recommendation by NICE not to advocate evolocumab for all patients with high cholesterol. However, we would urge NICE to consider making it available for a well defined group of individuals with exceptionally high cholesterol levels, who are unable to take statins because of the severe side effects that they have experienced.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
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Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant Metabolic Physician & Chemical Pathologist
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: We, the undersigned, are extremely disappointed by the initial position taken by NICE regards the benefits of evolocumab in patients with dyslipidaemia. Please see our comments in response to the consultation document. NICE Statement: The Committee acknowledged that evolocumab was a first-in-class therapy with a novel mechanism of action, which consistently reduced LDL-C concentrations compared with placebo and ezetimibe, while also being well-tolerated by patients. However, the Committee recalled its previous conclusion that the extent to which evolocumab could reduce CVD was a key area of uncertainty.• (overall conclusion	

4.26, pg 53)

Comment

We are encouraged to note that the case for the effectiveness of LDL lowering by evolocumab has accepted by NICE but we have to disagree with the second statement quoted above. Since the publication of the Improve- IT trial results(1) and the CTT meta-analysis(2) of data from 27 major statin outcome trials- the argument for the lower is better hypothesis has become stronger and very likely irrefutable. We agree with the opinion of the clinical experts that presented to the Committee and as summarised in the consultation document:

NICE Statement
The Committee noted that the clinical experts generally considered LDL-C to be a reasonable surrogate for future CV events, although this relationship was uncertain when the LDL-C concentration at baseline is low (below 2.0 mmol/litre). It also heard from them that evolocumab should have a beneficial effect on CV outcomes because it has the same ultimate mechanism for LDL-C reduction as statins.• (pg 40)

This view has also been accepted by the European Society of Cardiology as seen by the statement based on the results of the trial (Improve-IT), further LDL cholesterol lowering with a non-statin agent should be considered in patients with LDL cholesterol â‰¥70 mg/dL (â‰¥1.8 mmol/L) after NSTE-ACS despite a maximally tolerated dose of statin. At the time of finalizing the guidelines, this recommendation applies only to ezetimibe.• (3)

Therefore to await outcome data for evolocumab is a delay that needs to be avoided.
NICE Statement

although evolocumab might be cost effective in specific subgroups with CVD, the analyses presented by the company had several limitations, which made it (the committee) unsure about the reliability of the results.• (overall conclusion 4.26, pg 54)

Comment

We are encouraged by the above statement and we would urge NICE to approve the availability of evolocumab for the sub group of patients with:

Established coronary artery disease with LDL> 2mmol/L despite optimally tolerated therapy.

Patients with Heterozygous Familial Hypercholesterolemia who cannot tolerate the currently available optimal lipid lowering therapy as defined by the NICE CG 71 document.(4)

General comment

The impact of the delay in approving the medication for NHS use is already having a negative impact to our clinical practice. We have patients who can pay for the medication privately and other who cannot. Unfortunately this is creating a two tier health care system which goes against the very ethos of the NHS.

We hope that NICE will reconsider its position and make evolocumab available to the

NHS.

Signed By:

[redacted], Consultant Metabolic Physician & Chemical Pathologist, [redacted]

[redacted], Consultant Metabolic Medicine and Chemical Pathology, Lead Lipid Clinic [redacted]

[redacted], Consultant Physician, Diabetes & Endocrinology Clinical Director, Medicine & A&E, [redacted]

[redacted], Consultant Physician Diabetes and Endocrinology & Director, Emergency and Speciality Medicine, [redacted]

[redacted], Consultant Chemical Pathologist, [redacted]

[redacted], Consultant Physician, Diabetes and Endocrinology,x[redacted]

[redacted], Consultant Metabolic Medicine & HOD Chemical Pathology, [redacted] Lipid Guideline Group

[redacted], , Consultant Physician, Diabetes and Endocrinology, [redacted]

[redacted], Consultant Metabolic Physician & Chemical Pathologist, [redacted]

[redacted]Consultant Chemical Pathologist, [redacted], Dept of Clinical Biochemistry

Section 1 (Appraisal Committee's preliminary recommendations)	
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(The manufacturer's submission)	
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Section 5 (Implementation)	
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Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant Chemical Pathologist
Other role	
Organisation	
Location	England
Conflict	No
Notes	As a consultant, I have received payment for lecturing from a range of pharmaceutical companies and have attended education events / conferences sponsored by the industry.

Comments on individual sections of the ACD:

It is interesting that nicotinic acid is claimed to be a treatment used for patients who cannot tolerate statins. Since the completion of the Oxford-run THRIVE trial of niacin/laropiprant which demonstrated no benefit and a higher incidence of side effects, niacin has effectively been removed from the armory. This has reduced the options available for patients who are statin intolerant.

The committee notes that primary prevention should only be started in patients once their risk exceeds 10%. It should be noted that this is not considered appropriate for patients with familial hypercholesterolaemia, for whom no risk threshold is advocated

The committee should also perhaps consider a further group who may benefit from treatment. There is a very significant incidence of heart disease in patients with mental illness; and many of these are at high risk but are unreliable at taking medication. The use of a long-acting lipid-lowering agent that could be used in conjunction with depot anti-psychotic therapy could be a significant benefit in this group.

Whilst the committee considers QRISK might be better, it should be aware that many sources are used to calculate risk and the Framingham risk calculator is used extremely frequently [because it is included in the British National Formulary]. Until QRISK calculators are in routine use in clinical practice, it may be more reasonable to use the calculator that most specialists have access to [Framingham]. It is important to note [as above] that risk calculation is not appropriate in patients with familial hypercholesterolaemia.

The biggest need is for patients with FH and significantly elevated LDL who cannot tolerate alternative treatments. It would be very helpful if the committee could suggest a level of LDL above which patients should be entitled to receive PCSK-9 inhibitors as a NICE recommended drug when they have been tested with all other alternatives and been found to be intolerant

Section 1 (Appraisal Committee's preliminary	

recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant Cardiologist
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:

I am surprised by the decision to reject use of PCSK9 inhibitors in the treatment of uncontrolled hyperlipidaemia. I understand the committee's reservations regarding the cost benefit analysis and the relative absence of outcome data relating to cardiovascular endpoints. However, this new class of agents quite clearly provides an opportunity to achieve lipid control in the highest risk individuals (familial hypercholseterolaemia & high risk cardiac patients resistant/intolerant of statins). The numbers of patients appropriate for treatment are likely to be small and the arrival of this new drug class will hopefully result in a reappraisal of current measures to control/modify 'at risk' individual's lipid profiles.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Received by email

I write prior to the second round of consultation on evolocumab due to take place on Tuesday December 8th 2015. I believe the recommendation is to be that the PCSK9 inhibitors are not going to be recommended for use in the NHS, and that the reason for this is lack of outcome data. The association between improved cardiovascular outcome and lowering of LDL cholesterol is undisputed, and has been shown in numerous clinical trials across the range of concentrations of LDL cholesterol. Agents which lower LDL cholesterol to the degree that the PSCK9 inhibitors do are virtually inevitably going to show improved CV outcomes with time. The side effect profiles prior to clinical use are good. I work in a lipid clinic and have a group of patients unable to be successfully treated with statins, often for reasons of intolerance whose cardiovascular risks are very high. For them treatment with PCSK9 inhibitors would be the effective treatment they have so far been unable to access. This treatment would be of course less of a burden to the health economy than LDL apheresis.

I would be grateful if this could be brought to the attention of the committee prior to making a final decision

Best wishes

[redacted]
Consultant Chemical Pathologist
[redacted]

Sent by email:

Single Technology Appraisal

Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia [ID765]

Dear [redacted],

Further to your additional analyses in response to the ACD consultation, the NICE technical team kindly requests that you provide the estimate of the rate ratio for any CV event between HeFH and non-HeFH in primary and secondary prevention using the CPRD database, as this is believed to inform the Committee in its deliberations?

Please, could you provide your response by 12pm Friday 8 January 2015.

I would be grateful if you could cc. tacommc@nice.org.uk to your response.

Many thanks,

Stephanie

Stephanie Yates
Project Manager, Technology Appraisals – Committee C
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
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Single Technology Appraisal: Evolocumab for treating primary hyperlipidaemia and mixed dyslipidaemia [ID765]

Request – 6th January 2016:

Further to your additional analyses in response to the ACD consultation, the NICE technical team kindly requests that you provide the estimate of the rate ratio for any CV event between HeFH and non-HeFH in primary and secondary prevention using the CPRD database, as this is believed to inform the Committee in its deliberations?

Thank you for your request for additional information. We have provided this additional information to support the Committee in its deliberations.

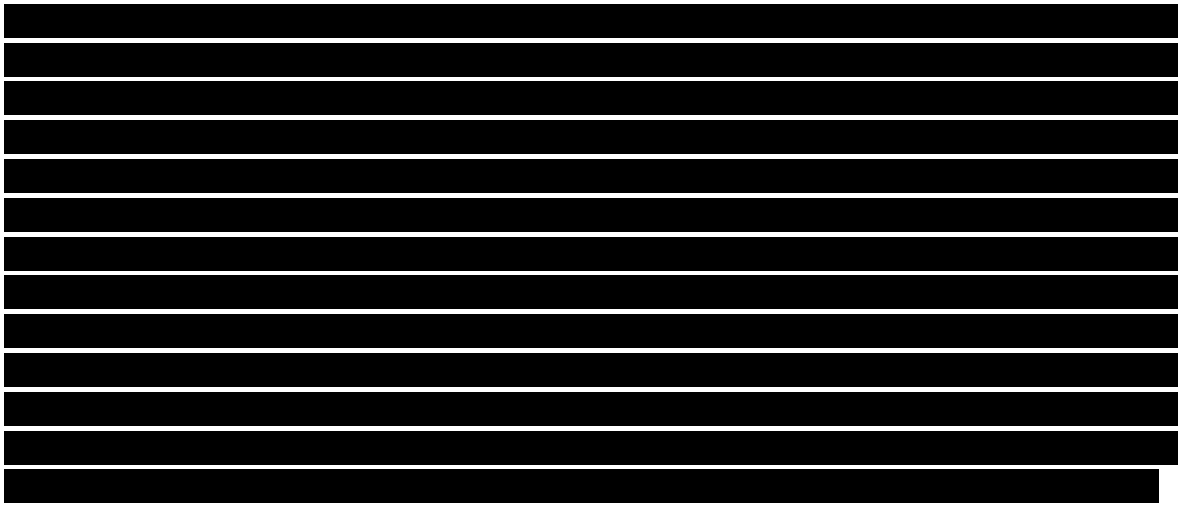
We conducted a study in CPRD titled Prevalence and clinical management of familial hypercholesterolaemia: a retrospective UK database pilot study (Amgen Study Number 20140465, ISAC protocol number 12_247A2, ISAC approval 07/8/2015). The primary objective of this study was to estimate the prevalence and incidence of familial hypercholesterolaemia (FH) in the UK. The secondary objective was to describe parameters related to clinical management of diagnosed FH, including patient demographics and characteristics, LDL-C concentrations, use of lipid modifying therapies, and outcomes over time. An exploratory objective was to estimate the incidence of cardiovascular (CV) events in diagnosed FH patients.

FH diagnoses registered in CPRD between 1st August 2008 and 31st July 2013, for patients with a minimum of 12 months follow-up post-diagnosis, were included. This period was defined following initial assessment of CPRD which indicated a notable change in incidence (Figure 1) of FH diagnosis corresponding with the publication of NICE Clinical Guideline 71 (familial hypercholesterolaemia: identification and management) in August 2008 which included defined FH diagnostic criteria.

Unfortunately, we have not been able to estimate a rate ratio for any CV event between HeFH and non-HeFH in primary and secondary prevention using CPRD. This was due to the following three reasons; firstly, during assessment of the exploratory objective there was a reduction in the patient numbers with HES-linked data for CV events (CV events identified using the same ICD-10-CM codes in the studies, Evidence Submission, Appendix 11) compared to the overall study cohorts, particularly for FH secondary prevention cohort (n=83). Secondly, there was a shorter mean follow-up compared to the high-risk CVD CPRD study as a consequence of the time period of the study for identifying diagnosed FH patients. For example, a mean follow-up of 7.03 years and 2.79 years for primary prevention patients in high-risk CVD CPRD study and the FH CPRD study, respectively. An overview of the two CPRD studies is provided in Table 1. Thirdly, estimation of a rate ratio for HeFH vs. non-FH in primary and secondary prevention would require control of risk factors. For example, Benn et al. (2012), risk of coronary artery disease for individuals with a diagnosis of definite/probable and possible FH relative to those with unlikely FH was

estimated by multivariable logistic regression, adjusting for gender, age, body mass index, hypertension, metabolic syndrome, diabetes mellitus, and smoking. As such, estimation of a rate ratio for any CV event between HeFH and non-HeFH would require the design of a specific study with review by the CPRD Independent Scientific Advisory Committee (ISAC).

Figure 1 [redacted]



We have estimated an annualised CV event rate and calculated a 10-year risk of a CV event for the different populations (Table 1). This indicates a 10-year CVD risk of 7% and 73% in FH primary and secondary prevention for ACS, IS, HF and CV death, respectively. We suggest that the estimates for the CPRD study are interpreted with caution given the limitations described above. Furthermore, there are notable differences in age between the populations (and potentially other risk factors) in the two CPRD studies.

Table 1 CPRD studies – high-risk CVD and familial hypercholesterolaemia

	High-risk cardiovascular disease					Familial Hypercholesterolaemia	
	PP (DM)	SP (ECVD)	SP (ACS)	SP (IS)	SP (HF)	PP	SP
Sample size	7627	9411	1539	414	1170	2208	83
Mean age	63	69	69	72	73	52	63
Mean LDL-C (mmol/L)	2.69	2.77	2.70	2.60	2.37	4.77	3.71
Mean follow-up (years)	7.03	6.79	4.63	4.40	3.92	2.79	2.00
Total CV events[†]	893 (1525)	2137	566	129	561	44 (NR)	22
Rate per patient-year	0.02 (0.03)	0.03	0.08	0.07	0.12	0.01 (NR)	0.13
10-year CVD risk	15% (25%)	28%	55%	51%	71%	7% (NR)	73%

Note: The estimates in parentheses are based on including ECVD. Where, ECVD was defined as stable angina, revascularisation (percutaneous coronary intervention or coronary artery bypass grafting), transient ischemic attack, carotid stenosis, abdominal aortic aneurysm, or peripheral vascular disease. Primary prevention and secondary prevention also includes ACS, IS, HF and CV death as CV events.

ACS, acute coronary syndrome; CPRD, clinical practice research datalink; CVD, cardiovascular disease; DM; diabetes mellitus; ECVD, established cardiovascular disease; FH, familial hypercholesterolaemia; IS, ischaemic stroke; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; NR, not reported; PP, primary prevention; SP, secondary prevention

Additionally, we have estimated rate ratios for HeFH and non-HeFH primary and secondary prevention from the economic model based on lifetime modelled CV events to provide further context if they are deemed appropriate for the Committee in its deliberations. These are summarised in Table 2.

Table 2 HeFH: Lifetime modelled number of CV events and rate ratios

	RUTHERFORD-2		CPRD	
	Primary prevention	**Secondary prevention**	**Primary prevention**	**Secondary prevention**
Lifetime modelled number of CV events predicted using risk equations alone [A]	0.46	0.68	0.67	0.73
Lifetime modelled number of CV events after adjustment based on Benn, et al. (2012) [B]	2.52	2.53	3.00	2.90
Lifetime modelled number of events using high-risk CVD calibration based on CPRD study [C]	0.79	1.67	1.16	1.79
Rate ratio: FH (adjustment) vs. FH (risk equations alone) [B/A]	5.46	3.71	4.47	3.95
Rate ratio: FH (adjustment) vs. non-FH (high-risk CVD calibration) [B/C]	**3.19**	**1.51**	**2.58**	**1.62**

CPRD, clinical practice research datalink; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolaemia

Notes:
- [A] derived by amending FH rate ratio to 1 (*Main* worksheet, cell I10)
- [B] derived by amending FH rate ratio to 6.1(*Main* worksheet, cell I10)
- [C] derived by amending FH indicator to 0 (*Populations* worksheet, row 35), thereby assuming the population is high-risk non-HeFH

This indicates that we predict a HeFH patient to experience between approximately 2 to 3 CV events during their lifetime compared to approximately 1 to 2 for a non-HeFH patient with identical patient characteristics. The numbers of CV events (based on risk equations alone and also after Benn, et al. adjustment) are similar for both HeFH primary prevention and secondary prevention. The rate ratio of the lifetime modelled CV events for a HeFH population compared to a non-HeFH population (with identical patient characteristics using RUTHERFORD-2) is 3.19 and 1.51 in primary prevention and secondary prevention, respectively. Based on the patient-level characteristics derived from the CPRD study, the rate ratio for a HeFH population compared to a non-HeFH population is 2.58 and 1.62 in primary prevention and secondary prevention, respectively.

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

Critique of company's response to the ACD

Mr Rachid Rafia, Research Fellow, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Dr Paul Tappenden, Reader in Health Economic Modelling, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Dr Christopher Carroll, Reader in Health Technology Assessment, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

21st December 2015

1. Introduction

As part of the NICE appraisal of evolocumab, the company submitted a dossier of evidence[1] relating to the clinical effectiveness and cost effectiveness of the product in people with mixed dyslipidaemia and hypercholesterolemia. The economic analysis considered at the first committee meeting included a Patient Access Scheme[2] (PAS) as well as other amendments to address problems in the model identified by the Evidence Review Group (ERG).[3] A report detailing the ERG's critique of the company's original submission is available on the NICE website.[4]

NICE's Appraisal Consultation Document[5] (ACD) for evolocumab makes the following recommendations:

"1.1 Evolocumab, alone or in combination with lipid-lowering therapies, is not recommended within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia in adults.

1.2 Adults whose treatment with evolocumab was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop." (NICE ACD,[5] page 3).

Following the publication of the ACD,[5] the company submitted a revised economic model together with an 84-page response describing changes made to the model and further clarification points relating to the issues raised in the ACD.[6]

Given time and resource constraints, this document presents a brief critique of the changes made to the company's revised economic model, focussing particularly on those populations/subgroups in which the company suggests that the ICER for evolocumab will fall below a threshold of £30,000 per QALY gained.

2. Summary of ICERs reported by the company following revision of the economic model

The company's ACD response reports the results of a number of analyses: in people with familial and non-familial hypercholesterolemia; and in people with and without a history of cardiovascular disease (CVD), who are able to take statins or for whom statins are contraindicated or not tolerated. These analyses are further divided into a number of subgroups examining people with an individual risk factor, or combinations of risk factors, including: the presence of diabetes; history of Acute Coronary Syndrome (ACS); baseline LDL-C level; age and gender. Table 3 of the company's ACD response[6] (reproduced in Table 1 of this critique) summarises the populations in which, on the basis of the company's revised model, the ICER for evolocumab versus ezetimibe (in combination with statins

when tolerated/not contraindicated) is expected to fall below £30,000 per QALY gained. As shown in Table 1, the company's analyses suggest that the ICER for evolocumab versus ezetimibe is below £30,000 per QALY gained in the following populations:

- Secondary prevention (non-familial) patients who are statin tolerant, with a minimum LDL-C and additional risk factors;
- Secondary prevention (non-familial) patients who are statin intolerant/contraindicated, with a minimum LDL-C, with or without additional risk factors;
- Patients with Heterozygous Familial Hypercholesterolaemia (HeFH).

Table 1: Summary of populations where evolocumab demonstrates cost-effectiveness versus ezetimibe (reproduced from company's ACD response,[6] Table 3)

Population	Modelled subgroup	Minimum LDL-C (mmol/L)	Cohort ICER (£ per QALY gained)
Secondary prevention (non-familial) statin tolerant[a]	Diabetes mellitus	4.5 mmol/L	£28,859
	Atrial fibrillation	4.5 mmol/L	£27,669
	Two vascular beds affected	4.5 mmol/L	£28,573
	History of ACS	4.5 mmol/L	£27,036
	Three vascular beds affected	3.5 mmol/L	£24,899
	Two or more of the following risk factors: • Diabetes mellitus • Atrial fibrillation • Two or more vascular beds affected • History of ACS	3.0 mmol/L	£21,111 to £30,524 depending on combination of risk factors
Secondary prevention (non-familial) statin intolerant	None	5.5 mmol/L	£28,916
	Diabetes mellitus	4.0 mmol/L	£27,409
	History of ACS	4.0 mmol/L	£28,690
HeFH[b]	None	None	£21,733 to £27,220

[a]Secondary prevention (non-familial) modelled results based on patient-level characteristics from CPRD.
[b]HeFH (primary and secondary prevention) results based on HeFH primary prevention and HeFH secondary prevention analyses in RUTHERFORD-2 and CPRD and subsequently derived using a weighted cost-effectiveness analysis (Table 3-2 and Table 3-4)

It is noteworthy that the ICERs for evolocumab versus ezetimibe for primary prevention (non-familial) patients who are statin tolerant or intolerant were above £30,000 per QALY gained irrespective of minimum LDL-C and/or additional risk factors.

The ICERs for secondary prevention (non-familial) patients who are able to take statins were below £30,000 per QALY gained only when considering a combination of a minimum LDL-C level and additional risk factors. The ICER for secondary prevention (non-familial) patients for whom statins

are not tolerated or contraindicated were below £30,000 per QALY gained only when considering a minimum LDL-C level, with the minimum LDL-C level also required when combined with additional risk factors.

The company's analysis suggests that the ICERs for evolocumab versus ezetimibe for the HeFH primary prevention and secondary prevention populations are below £30,000 per QALY gained irrespective of minimum LDL-C, the presence of additional risk factors or statin tolerance.

3. Description and critique of model amendments outlined within the company's ACD response

Table 2 summarises the amendments to the model together with additional points of clarification made by the company in response to the ACD.[6]

Table 2: Appraisal Committee preferences for cost-effectiveness evidence (reproduced from company's ACD response,[6] Table 1-1)

Element	Committee Preference	Comments
Long-term treatment effects with evolocumab	Considering alternative scenarios to reflect different assumptions about future treatment effects. These should include assuming that evolocumab does not give further benefit after a certain duration of treatment, or that its treatment effect tapers in the long term.	Refer to Section 1.1. We have provided additional information regarding this preference.
Baseline CVD risk – statin intolerant population	Using the baseline characteristics of the population in GAUSS-2 to model patients who cannot tolerate statins.	Amended as per the Committee's preference. Refer to Section 1.2– baseline characteristics from GAUSS-2 used to model non-FH patients who cannot tolerate statins.
Baseline CVD risk – HeFH and CVD history	Modelling the HeFH population with or without CVD separately.	Amended as per the Committee's preference. Refer to Section 1.3 – HeFH population modelled separately based on CVD history.
CVD risk equation - QRISK2 versus Framingham	Using the QRISK2 assessment tool to estimate the level of CVD risk in people without CVD (non-familial or HeFH). For the variables for which data were not collected, the average value for the specific UK population that reflects this variable could be used.	Amended as per the Committee's preference. Refer to Section 1.1 – QRISK2 has been used to estimate the level of CVD risk people without CVD (non-familial or HeFH).
Baseline CVD risk – HeFH and risk of CVD	Adjusting the risk of CVD in people with HeFH, with sensitivity analyses, based on a well-conducted systematic review of the literature, and taking into account the studies identified by the ERG about the natural history of HeFH.	Amended as per the Committee's preference. Refer to Section 1.5 – CVD risk for patients with HeFH assessed in further detail based on a literature review. CVD risk adjusted and further sensitivity analyses provided.

Element	Committee Preference	Comments
Background health-related quality of life	Using the equation from the Health Survey for England to inform the relationship between age and background health-related quality of life.	Amended as per the Committee's preference. Refer to Section 1.6 – background health-related quality of life adjusted using Ara et al 2010 equation based on the Health Survey for England.
Subgroup analyses	Modelling subgroups reflecting all the characteristics of the actual subgroup in clinical trials.	Amended as per the Committee's preference. Refer to Section 1.7.
Drug acquisition	Taking into account FP10 prescribing of evolocumab in primary care to reflect the true cost of evolocumab to the NHS.	Refer to Section 1.8. We have provided additional information regarding this preference.
CV, cardiovascular; ERG, Evidence Review Group; HeFH, heterozygous familial hypercholesterolaemia; NHS, National Health Service		

The amendments and points of clarification are briefly described and critiqued by the ERG below.

3.1 Baseline CVD risk – statin intolerant population

In response to the ACD, the company made two amendments to the baseline CVD risk in patients for whom statins are contraindicated or not tolerated:

(i) Baseline characteristics from the GAUSS-2 trial are used to model non-familial patients who are unable to take statins. As per the company's original submission, baseline characteristics from RUTHERFORD-2 are used to model HeFH patients who are unable to tolerate statins.

(ii) The statin indicator variable from the REACH registry equation is set to 'no' to model patients who cannot take statins.

ERG comments

The ERG believes the amendments made by the company to be appropriate.

3.2 CVD risk equation – use of QRISK2 instead of Framingham

In response to the ACD, the company amended the model to use the QRISK2 risk equation (instead of Framingham) to estimate the level of CVD risk in people without CVD (non-familial or HeFH). This involved the following:

- Re-estimating the calibration factors within the CPRD data to reflect the difference between observed CVD events and predicted CVD events using the QRISK2 risk equations;
- Imputing average values in the economic model when variables were not available,
- Estimating the effect of age and gender on the risk of CV events.

ERG comments

Given time constraints and the limited details provided, the ERG is not able to provide an in-depth verification of the economic model and assumptions made by the company, but notes that the use of QRISK2 in the economic model appears to have been implemented appropriately. The ERG agrees with the company in that this amendment is likely to have a limited impact given that estimates from QRISK2 (or Framingham) are subsequently adjusted against data from the CPRD.

However, the ERG remains concerned regarding the validity of the approach used by the company. Whilst calibration factors are estimated by the company, a series of assumptions are required within the model, notably removing the effect of age and sex, and as well as other assumptions regarding missing variables. It is also noteworthy that the calibration factors for the primary prevention population are estimated using patients with diabetes within the CPRD dataset; it is unclear whether the calibration factors would have been the same if patients without diabetes had been used in the calibration process. As discussed within the original ERG report[4] (see Section 5.3.1, pages 115-116), the approach used by the company is circular, overly-complicated and counter-intuitive, as it requires a number of assumptions and adjustments in the estimation and application of the calibration factors. In effect, the company's approach involves estimating CV risk using risk equations and then adjusting these to reflect 'real-world' CPRD/HES data. The ERG considers that it would have been more appropriate, and considerably simpler, to estimate baseline CVD risk using the CPRD/HES data directly.

3.3 Baseline CVD risk – HeFH and CVD history

In response to the ACD, the HeFH population is modelled separately based on CVD history (primary and secondary prevention).

ERG comments

This amendment is in line with the recommendations set out in the original ERG report.[4]

3.4 Estimate of the risk of CVD in HeFH patients

The company reports results from a literature review. The company states that the objective of the review was to *"determine the CVD risk associated with familial hypercholesterolaemia."*[6] The company identified 14 publications which met their inclusion criteria. Of these, the Benn *et al* study[7] was deemed to be at the lowest risk of bias.

Benn *et al*[7] examined the prevalence of familial hypercholesterolaemia (FH) and the risk of Coronary Artery Disease (CAD) for FH patients in a population of 69,016 individuals from the Danish general population. The authors used a general sample of the adult Danish population and applied diagnostic criteria for the determination of FH (using a modification of the Dutch Lipid Network Criteria). The

authors do not report the risk of CVD, but instead report the odd ratios for CAD for patients with possible FH and definite/probable FH CAD versus a reference group of patients with unlikely FH (not on statins). Separate odds ratios are presented for each group according to whether they are receiving statins or not. [redacted]

Within their response to the ACD,[6] the company derive a rate ratio from Benn *et al*[7] which is further adjusted to reflect, according to the company, the fact that some patients were not on statins. This rate ratio, which represents the increased risk of CAD in HeFH patients versus non-familial patients, is then applied in the health economic model by adjusting (increasing) the risk of CVD estimated using risk equations applied to the baseline characteristics in the RUTHERFORD-2 trial (which recruited HeFH patients).

On pages 22 and 48 of the company's ACD response,[6] the company briefly discusses the results from an analysis conducted using data from the CPRD (Amgen Study: Prevalence and clinical management of familial hypercholesterolaemia: a retrospective UK database pilot study; Study 20140465). The company's ACD response states that this study was based on an FH dataset of 8,646 patients diagnosed with FH between 1st August 2008 and 31st July 2013. FH patients were identified via the CPRD READ diagnostic codes for FH. In Table 6-8 of their ACD response,[6] the company reports the baseline characteristics and predicted 10-year and 20-month risks of CVD using the published QRISK2 and REACH risk equations in patients identified with HeFH in the CPRD. An analysis is also presented whereby the risk of CVD is estimated by using risk equations applied to baseline characteristics from the CPRD and the adjusted rate ratio.

Figures 1-5 and 1-6 of the company's ACD response[6] reports results from threshold analyses based on the revised model to determine the ICER for evolocumab against ezetimibe (each in combination with statins) according to different levels of CVD risk whilst on ezetimibe and minimum LDL-C.

ERG comments

Overall, the ERG does not consider the approach used by the company to be appropriate and believes that it would have been more appropriate to directly calculate the risk of CVD in HeFH patients from the CPRD/HES or alternative routine data. It is unclear to the ERG whether the risk used in the model for the HeFH population is appropriate. The ERG re-iterates their concerns regarding the current approach used by the company:

a. Prior to submission of the ERG report, clinical advisors to the ERG commented that risk equations (for example, QRISK2, Framingham and REACH) are not appropriate for calculating the risk of CVD in HeFH patients, hence the baseline risk of CVD calculated using QRISK2 or REACH (prior to adjustment) is likely to be biased. The extent of this bias is unclear.
b. In the company's model, the baseline characteristics of patients in the RUTHERFORD-2 trial (or baseline characteristics from CPRD for the scenario analysis) are used to estimate the baseline risk of CVD in patients without HeFH. However, this population has HeFH, therefore the risk estimated using the risk equations already represents the predicted risk of CVD in patients with HeFH (notwithstanding the previous point regarding the appropriateness of using risk equations within this population).
c. The company uses data from the Benn *et al* study[7] to adjust the risk estimated using risk equations applied to the RUTHERFORD-2 trial (or CPRD for the scenario analysis). However, the Benn *et al* study provides an estimate of the rate ratio for the increased risk of CVD between FH (diagnosed and undiagnosed) patients and non-familial patients. However, the CVD risks for which this calibration factor are applied to in the model do not reflect a non-familial population. This approach therefore results in a mismatch between the parameter derived from the Benn study and the baseline risk it is applied to in the company's model. Applying this rate ratio to patients included in the RUTHERFORD-2 trial (who already have an increased risk due to their diagnosis of HeFH) will therefore lead to an overestimate of the risk of CVD.
d. The ERG notes that the adjustment of the data reported in Benn, i.e. the derivation of the rate-ratio of 6.1, is likely to be inappropriate. The company's ACD response states that the adjustment was undertaken *"to estimate a revised rate ratio based on simulating the CV event reduction if all patients from Benn et al. (2012) were actually receiving LMT"* (company's ACD response,[6] page 38). However, the Benn *et al* study specifically reports on CAD events for each group of patients who were receiving statins and for those who were not. Therefore, it is unclear why the company's analysis does not specifically include those patients who were on statins, as reported in the paper.

Given time constraints, the ERG is unable to provide an in-depth assessment of the review conducted by the company. The ERG would suggest caution regarding the relevance of any rate ratio (or similar measure) identified in the review as this is subsequently applied in the model to the baseline CVD risk in the HeFH population estimated using risk equations (but the rate ratios/increased risks are estimated against non-familial patients in the studies included in the review). The ERG also notes that:

- The objective of the review is unclear. Whilst the company's ACD response states that the review was undertaken to determine the CVD risk associated with familial hypercholesterolaemia, only outcomes relating to the increased risk of CVD in HeFH patients versus non familial patients are considered. It is unclear to the ERG if studies reporting the risk of CVD in HeFH (without a control group) were excluded;
- The company's review excluded RCTs. The ERG believes that specifying this exclusion criterion *a priori* is inappropriate and unjustified, irrespective of whether such trials exist or not.
- It is unclear how the company's review fits with the inputs used in the model (and vice versa). Notably, [redacted] The ERG believes that this argument needs to be interpreted in relation to the parameter that is required by the model, rather than simply the likely biases associated with the study design. [redacted] However, the rate ratio from this study is applied to a population with diagnosed HeFH.

The ERG also notes that the company reported the results of their re-analysis using a threshold analysis approach. The ERG highlights that these figures are based on the level of risk in patients who are already receiving ezetimibe and have therefore already experienced a reduction in CV events compared with patients on statins.

3.5 Background health-related quality of life

The company's amended economic model uses background utility values using the equation derived using data from the Health Survey for England (HSE).[8]

ERG comments

The ERG believes this amendment to be appropriate.

3.6 Subgroup analyses

The company reports ICERs for evolocumab within a number of subgroups, in patients with a single or combination of risk factors, including minimum LDL-C level, presence of diabetes, presence of ACS, age and gender. The company reports analyses using patients characteristics for the subgroup of interest from the LAPLACE-2 trial, the GAUSS-2 trial and the CPRD. For analyses which assume differing levels of minimum baseline LDL-C, the company manually amended the cohort minimum LDL-C levels. The company justifies this approach by noting the difficulties of robustly estimating

patient-level risk for patients for each minimum LDL-C interval assessed. The company further states that *"Since we are manually increasing baseline LDL-C, it is plausible that the approach is conservative given no adjustment of other variables that could be correlated. This approach is also consistent with a previous NICE technology appraisal (NICE TA132)[27] and a clinical guideline (NICE CG181)[3]"* (Company's ACD response,[6] page 47).

ERG comments.

The ERG believes the analyses to be broadly reasonable but highlights the following with respect to their interpretation:

- As with the analyses of the full cohort, the use of direct data (in terms of event rates) which reflect the characteristics of the subgroup under consideration would be more appropriate. Notably, the company uses calibration factors that have been estimated from the broader secondary prevention population, rather than within each individual subgroup assessed. It is unclear whether the calibration factors would vary between the different subgroups; this would affect the ICERs generated by the company's model;
- The treatment effect from the full trial population is used and is assumed to be reflective of the treatment effect in the subgroup of interest;
- It is unclear whether the relative reduction in CV events associated with a reduction in LDL-C would differ according to the baseline LDL-C, the presence of diabetes or the presence of other risk factors.

3.7 Additional points made in the company's ACD response

In addition to the changes to the economic model detailed above, the company's ACD response offered three additional points of clarification. These relate to:

(a) Long-term treatment effects
(b) Drug acquisition cost based on FP10 prescribing
(c) Use of composite health states.

These are briefly detailed below.

(a) Long-term treatment effects,

The Appraisal Committee took the view that that the effect of evolocumab over time remains unknown. The Committee suggested that analyses that included assumptions that the effect of evolocumab ceases after certain duration of treatment, or tapers over time, would be desirable. The company argues that this is inappropriate and did not conduct exploratory analyses to address the impact of a diminishing effect of evolocumab within the model. The company stated that *"doubts*

regarding the long-term effects of evolocumab are unfounded and are a misinterpretation of the clinical expert comments from which they were derived."

The company states that *"two key issues raised here by the Committee represent a misinterpretation of the clinical expert comments in both cases"*

(i) **Gradual lessening of treatment effect in people with low LDL-C.** The company believes that the comment was from a mathematical rather than a clinical point of view. The company further states that given that evolocumab is aimed at patients with a high LDL-C, uncertainties around the lack of data for the benefits at the lowest end of the spectrum are not relevant.

(ii) **Gradual lessening of treatment effect due to neutralising antibodies**. In brief, the company states that *"the clinical experts comment does not represent a specific concern related to evolocumab (a fully human monoclonal antibody) but is a general point that there is a theoretical potential for neutralising antibodies to occur with monoclonal antibody therapy."* The company further notes that this was not identified as a risk by the Committee for Medicinal Products for Human Use (CHMP) and that *"a statistically significant tapering of effect has not been seen in the evolocumab trial programme, the trial programmes of other monoclonal antibodies to PCSK9 or in the extensive statin data accumulated (apart from due to patient adherence)."*

(b) Drug acquisition cost based on FP10 prescribing,

The Committee suggested that the modelling should take into account FP10 prescribing of evolocumab in primary care to reflect the true cost of evolocumab to the NHS.

This was considered to be inappropriate by the company. The company's ACD response[6] states that *"basing the cost of evolocumab on list price via FP10 does not reflect the true cost to the NHS since, A) we do not plan to operate differential pricing based on care setting, B) NHS commissioners will not proactively pay list price where the technology is only recommended in conjunction with a PAS within NICE guidance, and, C) we plan to replicate a primary care rebate model to prevent CCGs from paying the list price"* (Company's ACD response,[6] page 49).

The company has not undertaken any further analyses around this issue.

(c) Use of composite health states

The company's ACD response[6] provides additional information regarding the use of composite health states and states the *"assumptions underpinning costs, utilities and risks have been supported by clinical and economic advisors as reasonable and conservative in the absence of data."*

Whilst the ERG recognises the logical justification for including composite states, empirical evidence is not available to populate these elements of the model, thereby increasing the uncertainty in results.

Regarding the MSD ACD response:

MSD noted, under point 5, that "*Under section 3.6 of the ACD, it is noted that none of the trials studied evolocumab in combination with ezetimibe in any population. The DESCARTES study*[5] *included an arm where patients were administered evolocumab with a statin and ezetimibe*" (MSD ACD response,[9] page 1).

The ERG suggests replacing that wording with the following wording, which better qualifies the statement: *"there is no evidence on the efficacy of evolocumab in combination with ezetimibe, in comparison with placebo, in any population."*

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