# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using alirocumab in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see the project documents) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using alirocumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

**The key dates for this appraisal are:**

Closing date for comments: 5pm on 29 February 2016

Second Appraisal Committee meeting: 9 March 2016

Details of membership of the Appraisal Committee are given in the project documents.

# 1      Recommendations

1.1     Alirocumab is not recommended within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia in adults.

1.2     People whose treatment with alirocumab 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.

# 2      The technology

2.1     Alirocumab (Praluent, Sanofi/Regeneron) is a monoclonal antibody that targets proprotein convertase subtilisin/kextin type 9 (PCSK9). It stops low-density lipoprotein receptors in the liver from degrading, helping to lower levels of low-density lipoprotein cholesterol (LDL-c) in the blood. Alirocumab has a marketing authorisation in the UK for treating 'adults with primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid modification therapies in patients unable to reach LDL-c goals with the maximal tolerated dose of statin (when used as recommended by treatment guidelines) or
- alone or in combination with other lipid modification therapies in patients who are statin intolerant or for whom a statin is contraindicated.'

Alirocumab is given by subcutaneous injection. The recommended dose is either 75 mg or 150 mg every 2 weeks.

2.2     Common reported adverse reactions include local injection site reactions, upper respiratory tract signs and symptoms, and pruritus. For full details

of adverse reactions and contraindications, see the summary of product characteristics.

2.3     Alirocumab costs £168 for a 75 mg or 150 mg single-use prefilled pen (excluding VAT; MIMS, January 2016). The annual cost of treatment per patient is £4,368 for 75 mg or 150 mg every 2 weeks. The company has agreed a patient access scheme with the Department of Health. If alirocumab had been  recommended, this scheme would provide a simple discount to the list price of alirocumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

# 3     Evidence

The Appraisal Committee considered evidence submitted by Sanofi and a review of this submission by the Evidence Review Group (ERG). See the Committee papers for full details of the evidence.

## *Clinical effectiveness*

3.1     The company presented evidence of the clinical effectiveness of alirocumab from 10 trials: ODYSSEY HIGH FH, FH I and II, LONG TERM, COMBO I and II, OPTIONS I and II, MONO and ALTERNATIVE. The trials were from the ODYSSEY programme, which evaluated alirocumab as an add-on to maximal tolerated dose statins with or without other lipid-modifying therapies (LMT) including ezetimibe.

### Clinical trials

3.2     ODYSSEY HIGH FH was a randomised, double-blind study in 107 people with heterozygous-familial hypercholesterolaemia whose LDL-c levels were not adequately controlled with a maximally tolerated, stable, daily dose of statin. Patients were randomised in a 2:1 ratio to either

alirocumab 150 mg or placebo. The difference in mean percent change from baseline in LDL-c level at 24 weeks was −39.1% (p<0.0001) with alirocumab compared with placebo.

3.3    ODYSSEY FH I was a randomised, double-blind, study in 486 people with heterozygous-familial hypercholesterolaemia whose LDL-c levels were not adequately controlled with a maximally tolerated, stable, daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) or placebo. The difference in mean percent change from baseline in LDL-c level at 24 weeks (with possible up-titration) was −57.9% (p<0.0001) with alirocumab compared with placebo.

3.4    ODYSSEY FH II was a randomised, double-blind study in 249 people with heterozygous-familial hypercholesterolaemia whose LDL-c levels were not adequately controlled with a maximally tolerated, stable, daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) or placebo. The difference in mean percent change from baseline in LDL-c level at 24 weeks (with possible up-titration) was −51.4% (p<0.0001) with alirocumab compared with placebo.

3.5    ODYSSEY COMBO I was a randomised, double-blind study in 316 people with hypercholesterolaemia and established coronary heart disease or coronary heart disease risk equivalents whose LDL-c levels were not adequately controlled with a maximally tolerated daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) or placebo. The difference in mean percent change from baseline in LDL-c level at 24 weeks was −45.9% (p<0.0001) with alirocumab compared with placebo.

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

3.7    ODYSSEY LONG TERM was a randomised, double-blind study in 2341 people with non-familial hypercholesterolaemia or established coronary heart disease/coronary heart disease risk equivalent, or people with heterozygous-familial hypercholesterolaemia with or without coronary heart disease/coronary heart disease risk equivalents whose LDL-c levels were not adequately controlled with a maximally tolerated daily dose of statin. Patients were randomised in a 2:1 ratio to either alirocumab 150 mg or placebo. The difference in mean percent change from baseline in LDL-c level at 24 weeks was −61.9% (p<0.0001) with alirocumab compared with placebo.

3.8    ODYSSEY OPTIONS I was a randomised, double-blind study in 355 people with non-familial hypercholesterolaemia or heterozygous-familial hypercholesterolaemia and a history of coronary heart disease, risk of cardiovascular disease or diabetes with target organ damage whose LDL-c levels were not adequately controlled with atorvastatin 20 mg to 40 mg. Patients on a atorvastatin 20 mg baseline regimen were randomised in a 1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) with atorvastatin 20 mg, atorvastatin 40 mg, or atorvastatin 20 mg with ezetimibe 10 mg. Patients on a atorvastatin 40 mg baseline regimen were randomised in a 1:1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at

12 weeks based on LDL-c levels) with atorvastatin 40 mg, atorvastatin 80 mg, atorvastatin 40 mg with ezetimibe 10 mg, or rosuvastatin 40 mg. For patients having atorvastatin 20 mg, the difference in mean percent change from baseline in LDL-c level at 24 weeks (with possible up-titration) was −39.1% (p<0.0001) with alirocumab and statin (atorvastatin 20 mg) compared with statin (atorvastatin 40 mg) alone. The difference in mean percent change from baseline in LDL-c level was −23.6% (p<0.0001) with alirocumab with statin (atorvastatin 20 mg) compared with ezetimibe with statin (atorvastatin 20 mg). For patients on atorvastatin 40 mg at baseline, the difference in mean percent change from baseline in LDL-c level at 24 weeks (with possible up-titration) was −39.2% (p<0.0001) with alirocumab with statin (atorvastatin 40 mg) compared with statin (atorvastatin 80 mg) alone. The difference in mean percent change from baseline in LDL-c level was −32.6% (p<0.0001) with alirocumab with statin (atorvastatin 40 mg) compared with statin alone (rosuvastatin 40 mg). The difference in mean percent change from baseline in LDL-c level was −31.4% (p<0.0001) with alirocumab with statin (atorvastatin 40 mg) compared with ezetimibe with statin (atorvastatin 40 mg).

3.9     ODYSSEY OPTIONS II was a randomised, double-blind study in 305 people with non-familial hypercholesterolaemia or heterozygous-familial hypercholesterolaemia and a history of coronary heart disease, risk of cardiovascular disease, or diabetes with target organ damage whose LDL-c levels were not adequately controlled with rosuvastatin 10 mg to 20 mg. Patients on a rosuvastatin 10 mg baseline regimen were randomised in a 1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) with rosuvastatin 10 mg, rosuvastatin 20 mg, or rosuvastatin 10 mg with ezetimibe 10 mg. Patients on a rosuvastatin 20 mg baseline regimen were randomised in a 1:1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) with rosuvastatin 20 mg, rosuvastatin 40 mg, or rosuvastatin 20 mg with ezetimibe 10 mg. For

patients having rosuvastatin 10 mg at baseline, the difference in mean percent change from baseline in LDL-c level at 24 weeks (with possible up-titration) was −34.2% (p<0.0001) with alirocumab and statin (rosuvastatin 10 mg) compared with statin (rosuvastatin 20 mg) alone. The difference in mean percent change from baseline in LDL-c level (with possible up-titration) was −36.2% (p<0.0001) with alirocumab and statin (rosuvastatin 10 mg) compared with ezetimibe and statin (rosuvastatin 10 mg). For patients on rosuvastatin 20 mg at baseline, the difference in mean percent change from baseline in LDL-c level at 24 weeks (with possible up-titration) was −20.3% (p=0.0453) with alirocumab and statin (rosuvastatin 20 mg) compared with statin (rosuvastatin 40 mg) alone. The difference in mean percent change from baseline in LDL-c level was −25.3% (p=0.0136) with alirocumab with statin (rosuvastatin 20 mg) compared with ezetimibe with statin (rosuvastatin 20 mg).

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

3.11    ODYSSEY MONO was a randomised, ezetimibe-controlled, double-blind study in 103 people with hypercholesterolaemia with a moderate cardiovascular risk. Patients were randomised in a 1:1 ratio to either alirocumab 75 mg (with up-titration to alirocumab 150 mg at 12 weeks based on LDL-c levels) or ezetimibe 10 mg. The difference in mean percent change from baseline in LDL-c level at week 24 (with possible up-

titration) was −31.6% (p<0.0001) with alirocumab compared with ezetimibe.

**Meta-analyses**

3.12    The company undertook meta-analyses of individual patient data for the mean percent change from baseline in calculated LDL-c levels (on-treatment) using a fixed-effects model. In these analyses, alirocumab (with or without statins) was compared with a statin or ezetimibe (with or without statin). The meta-analyses showed:

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

3.13    The company also provided information from an independent meta-analysis of PCSK9 inhibitors (Navarese et al.). This showed a difference in mean percent change from baseline in LDL-c level of −47.49% (95% confidence interval [CI] −69.64 to −25.35) and reduced all-cause mortality

and cardiovascular mortality with PCSK9 antibodies compared with control. The company stated that a large randomised controlled trial exploring the occurrence of cardiovascular events of alirocumab compared with placebo is expected to report in 2018.

## Adverse effects of treatment

3.14    The company provided safety information based on combined phase II and phase III studies. The company stated that the rate of treatment-emergent adverse events (including serious adverse events) − was similar between the alirocumab and control arms. It stated that there was no difference in the safety profile observed between alirocumab 75 mg and 150 mg. It also stated that discontinuation due to general allergic adverse events was infrequent but occurred in a higher percentage of the people having alirocumab.

3.15    The company estimated the risk of major adverse cardiovascular events (death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation) by pooling phase III ODYSSEY trial data. The analysis showed a lower risk of a major adverse cardiovascular event with alirocumab compared with control (hazard ratio [HR] 0.81; 95% CI 0.52 to 1.25, although this was not statistically significant). A post-hoc analysis from LONG TERM also showed a lower risk of major adverse cardiac events with alirocumab compared with placebo (HR 0.52; 95% CI 0.31 to 0.90).

## ERG's comments

3.16    The ERG noted that evolocumab was not considered as a relevant comparator by the company because it was still under assessment by NICE. It noted that there were no head-to-head trials of alirocumab compared with evolocumab.

3.17 The ERG stated that although it had identified missing terms in the company's search strategy which may have affected its overall sensitivity, it generally considered the company's searches to be fit for purpose.

3.18 The ERG noted that the LDL-c reduction with alirocumab compared with control was rapid and persistent throughout follow-up.

## *Cost effectiveness*

3.19 The company presented base-case cost-effectiveness analyses for alirocumab, either as an adjunct to statin with ezetimibe or with ezetimibe alone, in 4 populations:

- people with heterozygous-familial hypercholesterolaemia for primary prevention (referred to as the primary prevention [heterozygous-familial] population)
- people with heterozygous-familial hypercholesterolaemia for secondary prevention (referred to as the secondary prevention [heterozygous-familial] population)
- people with non-familial hypercholesterolaemia with existing high-risk cardiovascular disease (CVD), coronary revascularisation or other arterial revascularisation procedures (referred to as the high-risk CVD [non-familial] population)
- people with non-familial hypercholesterolemia with recurrent cardiovascular events or polyvascular disease (referred to as the recurrent events/polyvascular disease [non-familial] population).

**Model structure**

3.20 The company submitted a Markov model based on the modelling approaches developed for NICE guidelines on lipid modification and familial hypercholesterolaemia, and technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia, ticagrelor for the treatment of acute

coronary syndromes and rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome. The cycle length was 1 year and a half cycle correction was applied. An annual discount rate of 3.5% was applied to costs and health effects. The model had a lifetime time horizon and was conducted from a NHS and personal social services perspective.

3.21    The company's model consisted of 12 mutually exclusive health states:

- 3 initial health states: stable, 0–1 years following an acute coronary syndrome event, 1–2 years following an acute coronary syndrome event
- 3 types of events: non-fatal acute coronary syndrome including myocardial infarction and unstable angina, non-fatal ischaemic stroke, and elective revascularisation)
- 7 post-event health states: post non-fatal acute coronary syndrome (0–1 years, 1–2 years and stable chronic heart disease; that is, more than 2 years after an acute coronary syndrome event), post non-fatal ischaemic stroke (0–1 years, 1–2 years and stable ischaemic stroke; that is, more than 2 years following ischaemic stroke) and stable elective revascularisation.

The model also consisted of health states for cardiovascular death and non-cardiovascular death. Costs and outcomes were compared between identical cohorts of people on alirocumab and comparators.

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

- For heterozygous-familial hypercholesterolaemia, the starting age was 50 years for primary prevention and 60 years for secondary prevention. The baseline LDL-c level was 2.59 mmol/L, 50% of the cohort were men and 7% had diabetes.

- For high-risk cardiovascular disease, the starting age was 65 years and the baseline LDL-c level was 3.36 mmol/L. Around 60% of the cohort were men and 23% had diabetes.

- For recurrent events/polyvascular disease, the starting age was 65 years and the baseline LDL-c level was 2.59 mmol/L/ Around 60% of the cohort were men and 30% had diabetes.

3.23    The baseline probabilities of cardiovascular death in all post-acute coronary syndrome and post-ischaemic stroke health states were adjusted to account for the higher risk of future events associated with recurrence of cardiovascular events.

**Treatment, clinical variables and parameters**

3.24    Alirocumab was given in line with its marketing authorisation. The patient population was modelled according to severity of hypercholesterolaemia (bybaseline LDL-c levels) before starting treatment. Baseline cardiovascular risk (calculated using THIN data) was adjusted by LDL-c level using a log-linear relationship between the absolute LDL-c observed in statin studies and cardiovascular events using the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of statins. The company used the difference in mean percent change of alirocumab compared with alternatives based on estimates from specific clinical trials and meta-analyses. The modelassumed that the relative reduction in LDL-c for alirocumab was constant across all subgroups.

3.25    In the absence of cardiovascular events data from the clinical trials for alirocumab, the company used LDL-c reduction as a surrogate to link to cardiovascular events. In its base-case analysis, the company chose the

Navarese meta-analysis of 24 randomised controlled trials (n=10,159) to provide the rate at which the risk of a cardiovascular event declines with a reduction in LDL-c levels. This was because it preferred estimates from PCSK9 inhibitor studies rather than estimates from statin studies (such as CTTC), because they better reflected the population who will have alirocumab. By assuming a log-linear relationship between LDL-c levels and cardiovascular events, the company estimated the risk reduction for cardiovascular mortality as rate ratios (RRs): 0.64 per 1.0 mmol/L reduction in LDL-c rate (95% CI 0.40 to 1.04) and 0.64 for myocardial infarction (95% CI 0.43 to 0.96). The risk reduction for coronary revascularisation and ischaemic stroke was assumed to be the same as other non-fatal cardiovascular events.

**Transition probabilities**

3.26    Transition probabilities were based on Kaplan–Meier analyses from an observational retrospective cohort analysis using the THIN database of people with established cardiovascular disease, diabetes, familial hypercholesterolaemia or chronic kidney disease. This was used to calculate 1-year cardiovascular risk probabilities. Transition probabilities for the primary prevention population were based on the Dutch lipid criteria for people with heterozygous-familial hypercholesterolaemia, because the patient characteristics from THIN were not representative of this population. For the secondary prevention (heterozygous-familial) population (see section 3.19), some patient characteristics (such as rate of diabetes and age) were different from known prevalence. To address this, the company used data from Mohrschladt (2003) in its base-case analysis for this population.

3.27    Non-cardiovascular death probabilities in the model increased in accordance with age and sex using UK life tables. Probability of cardiovascular events also increased with age, in line with published data.

**Utility values**

3.28    Age-adjusted utility values for the primary prevention (heterozygous-familial) population were calculated using Health Survey for England (HSE) data for people with no history of cardiovascular disease, multiplied by the disutility associated with cardiovascular events taken from on Ara and Brazier 2010. Baseline utilities in the model were as follows: non-fatal myocardial infarction 0.765, unstable angina 0.765, acute coronary syndrome 0.765, ischaemic stroke 0.775.

3.29    Age-adjusted utility values for the secondary prevention (heterozygous-familial), high-risk cardiovascular disease and recurrent events/polyvascular disease (non-familial) populations were calculated using HSE data for people with no history of cardiovascular disease, multiplied by the disutility values associated with a chronic cardiovascular health state (cardiovascular event more than 1 year ago) taken from Ara and Brazier 2010. Utility multipliers in the model were as follows: primary prevention of heterozygous-familial hypercholesterolaemia 1 (assumed), secondary prevention of heterozygous-familial hypercholesterolaemia 0.924, acute coronary syndrome (0 to 12 months) 0.765, history of ischaemic stroke 0.822, acute coronary syndrome (13 to 24 months) 0.924, chronic heart disease 0.924, peripheral arterial disease 0.924, and polyvascular 0.854. Disutilities for further cardiovascular events in the model were applied to the secondary prevention population baseline utilities.

**Costs**

3.30    Initial costs of treatment for hypercholesterolaemia and cardiovascular events were based on the cost of hospitalisation, follow-up care and medication. Drug acquisition costs from January 2015 for the comparators were taken from the British national formulary. The cost of the background therapy was weighted by the proportion of the cohort using the statin

sources from market research data. The cost of alirocumab incorporated the patient access scheme.

3.31 Health state costs were based on the NICE guideline on lipid modification and costs for the first 3 years after a cardiovascular event were taken from the British national formulary, the NHS Drug Tariff, NHS reference costs, PSSRU unit costs, and the NICE guideline on stroke rehabilitation in adults. The costs for each health state were as follows:

- non-fatal myocardial infarction: £3337 (incremental cost years 2 and 3: £788)
- unstable angina: £3313 (incremental cost years 2 and 3: £385)
- acute coronary syndrome: £3329 (incremental cost years 2 and 3: £654
- revascularisation: £3802
- ischaemic stroke: £4092 (incremental cost years 2 and 3: £155)
- cardiovascular death: £1174
- non-cardiovascular death: £0.

## ERG comments

3.32 The ERG stated that in terms of face validity, the company's model structure and transition probabilities were plausible. However, the ERG noted that the company's model omitted the transient ischaemic attack and stable angina health states and that it had limited capacity to capture multiple cardiovascular event histories. It also stated that the company omitted treatment-emergent adverse events from the model. The ERG also noted that the secondary prevention (heterozygous-familial) population (see section 3.19) using Mohrschladt had a higher cardiovascular risk compared with data from THIN. It was unable to verify the most appropriate risk without another external data source. The ERG believed that the company's use of THIN for cardiovascular event and transition probabilities was appropriate because QRISK2 risk estimates were not valid for the high cardiovascular risk population.

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

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

- It was satisfied with the company's approach to estimate the LDL-c reduction with alirocumab compared with placebo.
- The ERG noted that the company assumed there is a linear/log-linear relationship is between LDL-c and cardiovascular events as demonstrated by CTTC. It noted that the estimated relative reduction in cardiovascular events from Navarese was greater than estimates from CTTC. The ERG also noted that the estimates from Navarese were based on a smaller number of events reported in shorter trials with fewer patients compared with CTTC.
- The ERG noted that the company used all the trials used to estimate the mean reduction with LDL-c from the Navarese analysis, instead of only the trials used to estimate the HRs for specific cardiovascular events. In its response to clarification, the company provided estimates of LDL-c reduction using trials only informing the HRs for myocardial infarction and cardiovascular death; an LDL-c reduction of 1 mmol/L resulted in HRs of 0.58 for cardiovascular death and 0.68 for myocardial infarction. The ERG considered these values to be more relevant.

- The ERG noted that the company's estimated HR for myocardial infarction events was used for ischaemic stroke and coronary revascularisation events. The ERG stated this was a controversial assumption, because other studies (such as CTTC) show that a reduction in LDL-c levels may have less of an effect on ischaemic stroke risk than on acute coronary syndrome risk.

3.35    The ERG stated that the company assumed 100% treatment continuation and compliance over the entire time horizon. It noted that the high compliance was in line with ODYSSEY (approximately 98%) and that the assumption was consistent with the NICE guideline on lipid modification and the technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia.

3.36    The ERG stated that the company's health state utility values were calculated and implemented appropriately. However, it had had several comments on the costs used in the model:

- The company's model only captured costs for the first 6 months after a cardiovascular event in the first year, and so did not capture follow-up for the second half of the first year.
- Follow-up costs for cardiovascular events were incurred for up to 3 years after the event. The ERG considered this to be conservative and possibly unrealistic, considering the need for ongoing social care and medical attention.
- The costs for the stroke and post-stroke health states were low and inconsistent with costs applied in previous technology appraisals.
- The ERG was unclear how the cost of revascularisation was estimated.
- The company's submission mentioned that alirocumab will be continued in secondary care via a sponsored homecare service.

## Company's results and sensitivity analysis

3.37    The company's incremental cost-effectiveness ratios (ICERs) for all comparisons, populations and sensitivity analyses incorporated the patient access scheme for alirocumab, as do all ICERs in this document (see tables 1 to 4).

3.38    In the primary prevention (heterozygous-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER was £36,793 per quality-adjusted life year (QALY) gained (incremental costs £52,256; incremental QALYs 1.42). For alirocumab and a statin compared with ezetimibe and a statin, the ICER was £16,896 per QALY gained (incremental costs £39,306; incremental QALYs 2.33).

3.39    In the secondary prevention (heterozygous-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER was £16,896 per QALY gained (incremental costs £39,306; incremental QALYs 2.33). For alirocumab and a statin compared with ezetimibe and a statin, the ICER was £20,352 per QALY gained (incremental costs £34,632; incremental QALYs 1.70). Using baseline risk data from THIN instead of Mohrschladt (2003) the ICER was £19,060 per QALY gained (incremental costs £40,733; incremental QALYs 2.14) for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe.

3.40    In the high-risk cardiovascular disease (non-familial) population, for alirocumab and a statin compared with a statin alone, the ICER was £19,751 per QALY gained (incremental costs £34,684; incremental QALYs 1.76). For alirocumab and a statin compared with ezetimibe and a statin, the ICER was £24,175 per QALY gained (incremental costs £31,195; incremental QALYs 1.29). In the high-risk cardiovascular disease (non-familial) population who cannot have statins, the ICER for

alirocumab and ezetimibe compared with ezetimibe alone was £17,256 per QALY gained (incremental costs £35,146; incremental QALYs 2.04). For alirocumab alone compared with ezetimibe alone the ICER was £17,295 per QALY gained (incremental costs £30,829; incremental QALYs 1.78).

3.41     In the recurrent events/polyvascular disease (non-familial) population, for alirocumab and a statin compared with a statin alone, the ICER was £19,447 per QALY gained (incremental costs £31,953; incremental QALYs 1.64). For alirocumab and a statin compared with ezetimibe and a statin, the ICER was £23,078 per QALY gained (incremental costs £28,781; incremental QALYs 1.25). For the recurrent events/polyvascular disease (non-familial) population who cannot have statins, the ICER for alirocumab and ezetimibe compared with ezetimibe alone was £13,669 per QALY gained (incremental costs £32,798; incremental QALYs 2.40). For alirocumab alone compared with ezetimibe alone, the ICER was 13,469 per QALY gained (incremental costs £28,820; incremental QALYs 2.14)

**Sensitivity analyses**

3.42     The company undertook a number of probabilistic sensitivity analyses, stating that the uncertainty in the results reflected the wide confidence intervals from preliminary PCSK9 inhibitor outcomes data.

- For the primary prevention (heterozygous-familial) population, the probability of cost-effectiveness for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe was between 15% and 36% (for a maximum ICER of £20,000 to £30,000 per QALY gained).
- For the secondary prevention (heterozygous-familial) population, the probability of cost-effectiveness for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe was between 56% and 79% (for a maximum ICER of £20,000 to £30,000 per QALY gained).

- For the high-risk cardiovascular disease (non-familial) population, the probability of cost-effectiveness for alirocumab and a statin compared with a statin alone was between 46% and 78% (for a maximum ICER of £20,000 to £30,000 per QALY gained).

- For the recurrent events/polyvascular disease (non-familial) population, the probability of cost-effectiveness for alirocumab and a statin compared with a statin alone was between 49% and 80% (for a maximum ICER of £20,000 to £30,000 per QALY gained).

3.43    The company also undertook  deterministic sensitivity analyses to explore the upper and lower bounds of the confidence interval or by varying selected inputs by an arbitrary ±20%. The ICERs for all populations were most sensitive to changes in the relationship of LDL-c level to cardiovascular events and annual cardiovascular risk.

**Subgroup and scenario analyses**

3.44    The company conducted subgroup analyses by LDL-c level:

- In the primary prevention (heterozygous-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER decreased from £36,793 per QALY gained at a threshold of 2.59 mmol/L to £28,923 per QALY gained at a threshold of 4.13 mmol/L.

- In the secondary prevention (heterozygous-familial) population, for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe, the ICER decreased from £16,896 per QALY gained at a threshold of 2.59 mmol/L to £14,242 per QALY gained at a threshold of 4.13 mmol/L.

- In the high-risk cardiovascular disease (non-familial) population, for alirocumab and a statin compared with a statin alone, the ICER decreased from £25,287 per QALY gained at a threshold of 2.59 mmol/L to £16,043 per QALY gained at a threshold of 4.13 mmol/L.

- In the recurrent events/polyvascular (non-familial) disease population, for alirocumab and a statin compared with a statin alone, the ICER decreased from £19,447 per QALY gained at a threshold of 2.59 mmol/L to £12,606 per QALY gained at a threshold of 4.13 mmol/L.

3.45    The company conducted a range of scenario analyses:

- Increasing the discontinuation rate from 0% to 3% and 8% led to a modest increase in the ICERs for all populations.
- Changing the cost and benefit discount rates from 3.5% to 0 or 5% substantially changed the ICERs in all populations.
- Reducing the treatment duration from lifetime to 1 to 5 years had a modest impact on the ICERs in all populations.
- Decreasing the time horizon from lifetime to 5 or 10 years substantially increased the ICERs in all populations.
- Using a different source to link LDL-c reduction to cardiovascular relative risk instead of Navarese changed the ICERs in all populations:
  - using relative risks from CTTC instead of Navarese increased the ICERs by approximately £16,000 to £24,700 per QALY gained
  - using relative risks from pooled phase III trials instead of Navarese increased the ICERs by approximately £8,800 to £15,700 per QALY gained
  - using relative risks from LONG-TERM instead of Navarese increased the ICERs by approximately £2,400 to £4,100 per QALY gained.
- Using a different adjustment to baseline cardiovascular risk had a modest impact on the ICERs in all populations.
- Using utility values from ODYSSEY instead of Ara 2010 significantly decreased ICERs in all populations.

- Changing the treatment strategy from up-titration to 100% use of alirocumab 75 mg or 150 mg had a modest impact on the ICERs in all populations

## *ERG's exploratory analyses*

3.46    The ERG undertook exploratory analyses for all comparators and populations, making 7 changes to the company's model. It presented ICERs for both Navarese and CTTC meta-analyses to show the uncertainty in the relationship between LDL-c reduction and cardiovascular events. In summary, the ERG's exploratory analyses:

- applied annual post-cardiovascular event costs (such as care for stroke) over the entire modelled time horizon (lifetime) instead of 3 years
- applied follow-up costs to the second half of first year costs following a cardiovascular event
- applied an updated cost of £8618 for stroke and an annual care cost for stroke of £1769
- used only trials informing the hazard ratios in Navarese instead of all trials, applying rate ratios of 0.67 per 1 mmol/L reduction for myocardial infarction and 0.58 per 1 mmol/L reduction in cardiovascular death
- applied a rate ratio of 0.79 per 1 mmol/L reduction in LDL-c for ischaemic stroke based on results from CTTC, instead of assuming the same rate ratio of 0.64 per 1 mmol/L reduction
- applied an annual discontinuation rate of 8% instead of 0% so that it is consistent with discontinuation observed in ODYSSEY and LONG-TERM
- applied the effects of ezetimibe on LDL-c reduction using rate ratios from CTTC.

3.47    In summary, the ERG's exploratory analyses showed only modest changes to the base-case ICERs for all comparisons in all populations

using Navarese to estimate the relationship between LDL-c and cardiovascular events. Using CTTC to estimate the relationship between LDL-c and cardiovascular events substantially increased the ICERs for all comparisons in all populations. All these ICERs were in excess of £20,000 per QALY gained.

**Table 1 ERG exploratory analyses: deterministic base-case and additional comparison ICERs for the primary prevention (heterozygous-familial) population (cost per QALY), including PAS**

| | Company's base case with rate ratios from Navarese | Company's scenario analysis with ratios from CTTC | ERG scenario with rate ratios from Navarese | ERG scenario with rate ratios from CTTC |
|---|---|---|---|---|
| Alirocumab + statins + ezetimibe vs statins + ezetimibe | £36,793 | £60,736 | £41,243 | £67,215 |
| <u>People who cannot tolerate statins</u> Alirocumab +ezetimibe vs ezetimibe | - | - | - | £45,786 |
| <u>Comparison with ezetimibe</u> Alirocumab + statins vs ezetimibe + statins | £48,193 | - | £52,363 | £119,161 |

**Table 2 ERG exploratory analyses: deterministic base-case and additional comparison ICERs for the secondary prevention (heterozygous-familial) population (cost per QALY) including PAS**

| | Company's base case with rate ratios from Navarese | Company's scenario analysis with ratios from CTTC | ERG scenario with rate ratios from Navarese | ERG scenario with rate ratios from CTTC |
|---|---|---|---|---|
| Alirocumab + statins + ezetimibe vs statins + ezetimibe | £16,896 | £32,937 | £16,933 | £33,339 |
| <u>People who cannot tolerate statins</u> Alirocumab +ezetimibe vs ezetimibe | - | - | - | £22,042 |
| <u>Comparison with ezetimibe</u> Alirocumab + statins vs ezetimibe + statins | £20,352 | - | £19,437 | £56,968 |

**Table 3 ERG exploratory analyses: deterministic base-case and additional comparison ICERs for the high-risk CVD (non-familial) population (cost per QALY), including PAS**

| | Company's base case with rate ratios from Navarese | Company's scenario analysis with ratios from CTTC | ERG scenario with rate ratios from Navarese | ERG scenario with rate ratios from CTTC |
|---|---|---|---|---|
| Alirocumab + statins vs statins | £19,751 | £41,431 | £19,432 | £42,131 |
| People who cannot tolerate statins Alirocumab +ezetimibe vs ezetimibe | £17,256 | - | £17,130 | £34,600 |
| Comparison with ezetimibe Alirocumab + statins vs ezetimibe + statins | £24,175 | - | £21,932 | £70,081 |
| People who cannot tolerate statins comparison with ezetimibe Alirocumab vs ezetimibe | £17,295 | - | £16,487 | £41,412 |

**Table 4 ERG exploratory analyses: deterministic base-case and additional comparison ICERs for the recurrent events/polyvascular disease (non-familial) population (cost per QALY), including PAS**

| | Company's base case with rate ratios from Navarese | Company's scenario analysis with ratios from CTTC | ERG scenario with rate ratios from Navarese | ERG scenario with rate ratios from CTTC |
|---|---|---|---|---|
| Alirocumab + statins vs statins | 19,447 | 44,154 | 19,021 | 44,759 |
| People who cannot tolerate statins Alirocumab + ezetimibe vs ezetimibe | 13,669 | - | 15,791 | 33,519 |
| Comparison with ezetimibe Alirocumab + statins vs ezetimibe + statins | 23,078 | - | 20,891 | 73,941 |
| People who cannot tolerate statins comparison with ezetimibe alirocumab vs ezetimibe | 13,469 | - | 13,342 | 32,742 |

3.48    The ERG provided subgroup analyses by LDL-c level, showing that the ICERs for each population decreased as the baseline LDL-c level increased from 2.59 mmol/L to 4.13 mmol/L.

3.49    The ERG also explored parameter uncertainty in the same way as the company (see section 3.43). The ICERs for all populations were most sensitive to changes in the baseline LDL-c, the relationship of LDL-c level to cardiovascular events and annual cardiovascular risk. The changes to the ICERs followed a similar pattern to the company's deterministic sensitivity analyses.

# 4    Committee discussion

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of alirocumab, having considered evidence on the nature of primary hypercholesterolaemia and mixed dyslipidaemia and the value placed on the benefits of alirocumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1    The Committee heard from the patient experts about the nature of the condition and their experience with treatment. It heard that people with familial hypercholesterolaemia have a lifetime risk of cardiovascular events and their quality of life is adversely affected by the need to be on treatment throughout their life. The Committee noted that some people taking statins for hypercholesterolaemia can experience side effects such as muscle and joint pain that can disrupt daily activities and reduce quality of life. It heard from the clinical and patient experts that although low-density lipoprotein (LDL) apheresis is an alternative treatment option for people with hypercholesterolaemia, it is not available in all areas and is not a sustainable therapy because it requires lengthy attendance at a clinic every 2 weeks and time to recover from the procedure. The Committee concluded that the current treatment options for

hypercholesterolaemia can negatively affect the quality of life of patients, particularly those with familial hypercholesterolaemia who need lifelong treatment; and that alternative treatment options are desirable.

4.2    The Committee discussed whether the populations as defined in the company's submission correspond to clinically relevant subgroups of people with hypercholesterolaemia and the marketing authorisation for alirocumab. . It understood that the company's submission presented the evidence separately for 4 distinct clinical groups:

- a primary prevention heterozygous-familial hypercholesterolaemia group (the primary prevention [heterozygous-familial] population)
- a secondary prevention heterozygous-familial hypercholesterolaemia group (the secondary prevention [heterozygous-familial] population)
- a secondary prevention non-familial group of people with established cardiovascular disease who have previously had a cardiovascular event (the high-risk cardiovascular disease [non-familial] population)
- a subgroup of people from the high-risk group who have had more than 1 previous cardiovascular event or who have polyvascular disease (referred to as the recurrent events / polyvascular disease [non-familial] population).

The Committee was aware that alirocumab has a marketing authorisation for treating adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia (see section 2.1). The Committee noted that the 4 groups defined by the company were within the marketing authorisation. It was also aware that the homozygous-familial hypercholesterolaemia population is not within the marketing authorisation for alirocumab and that the company did not present any evidence for people with mixed dyslipidaemia. The Committee then heard from the clinical expert that the people with the highest unmet need are those with familial hypercholesterolaemia and

those in whom cardiovascular risk remains high despite having maximally tolerated lipid-modifying therapies, and for people who cannot take statins because of intolerance or contraindication. It considered that these groups broadly correspond to those defined in the company submission. The Committee was aware of the low-density lipoprotein cholesterol (LDL-c) levels at which treatment had been initiated in the groups as defined by the company; that is, an LDL-c level of at least 2.59 mmol/L for the primary and secondary (heterozygous-familial) prevention populations and recurrent events / polyvascular disease population, and at least 3.36 mmol/L for the high-risk cardiovascular disease (non-familial) population. However, the Committee understood that these were not the only defining clinical characteristic for a population, particularly for the non-familial populations whose disease is treated according to overall risk of a cardiovascular event. Nevertheless the Committee was conscious that the company's definitions of the populations were intended to focus on those patients who have the greatest unmet need despite current treatment and that this was in line with where clinicians and patients would use alirocumab. Therefore, the Committee concluded that the company's subgroups were appropriately defined and relevant for their decision making.

4.3    The Committee considered the current treatment options for people with hypercholesterolaemia. The Committee heard from the clinical experts that statins are the main treatment option for familial and non-familial hypercholesterolaemia (as described in NICE's guidelines on familial hypercholesterolaemia and on lipid modification), andthat statins are not appropriate for some people. It understood that common side effects such as fibromyalgia and headache contribute to intolerance and discontinuation of statin therapy. The Committee accepted that there is no universally accepted definition of intolerance to statins, but was aware of the definition of intolerance used in NICE's guideline on familial hypercholesterolaemia. The Committee was also aware that NICE's

technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia recommends ezetimibe monotherapy as an option to treat primary hypercholesterolaemia when a statin is considered inappropriate or is not tolerated. Ezetimibe with a statin is also recommended as an option when cholesterol levels are not low enough, even when the statin dose is increased, or if a person cannot tolerate higher doses of the statin. The Committee concluded that statins and ezetimibe are the main options for treating hypercholesterolaemia (heterozygous-familial and non-familial), and that ezetimibe is used as an option to treat hypercholesterolaemia in adults who are unable to tolerate a statin at an appropriately high dose.

4.4      The Committee considered the most appropriate comparators for alirocumab. It noted that the company considered ezetimibe with a statin to be an appropriate comparator for the heterozygous-familial hypercholesterolaemia population, but not for the non-familial hypercholesterolaemia population because of the variation in the use of ezetimibe in clinical practice in England. The Committee heard from the clinical expert that adding ezetimibe to a statin offers a modest benefit in reducing the risk of cardiovascular events, and consequently may not always be used for people with non-familial hypercholesterolaemia. However, the Committee was aware that ezetimibe is recommended as an option in combination with a statin in NICE's technology appraisal guidance on ezetimibe and recalled its earlier conclusion regarding the main options for treating hypercholesterolaemia (see section 4.3). It noted that adding ezetimibe to a statin is the main treatment option for a person whose LDL-c level is not appropriately controlled after treatment with a statin. It therefore considered that ezetimibe would be used in these circumstances. It was also mindful of draft NICE technology appraisal guidance for a drug with the same mechanism of action and marketing authorisation (evolocumab), in which the technology was compared with ezetimibe and a statin in people with hypercholesterolaemia. This

strengthened the Committee's view that ezetimibe with a statin was an appropriate comparator in both the heterozygous-familial and non-familial populations who can tolerate statins. The Committee concluded that alirocumab should be compared with ezetimibe and a statin for people who can tolerate statins, and with ezetimibe alone in people who are unable to take statins for hypercholesterolaemia.

4.5     The Committee considered evolocumab and whether it should be considered a comparator for alirocumab. It was aware that evolocumab had been specified as a comparator in the scope for this appraisal, subject to NICE technology appraisal guidance, and that draft guidance had been issued.. It was further aware that evolocumab, as a PCSK9 inhibitor, has the same mechanism of action and marketing authorisation as alirocumab. The Committee was aware that the company had not compared alirocumab with evolocumab  because it considered that evolocumab was not established clinical practice in the NHS in England. However, the Committee was mindful of its duty to provide the best advice to patients and the NHS, and considered that because of the exceptional circumstances created by the convergence of the regulatory timelines for the two treatments, evolocumab should not be dismissed as a possible comparator. The Committee heard from the clinical expert that both treatments appear to have similar efficacy in terms of LDL-c reduction. This further strengthened the Committee's view that it would be in the interests of the NHS and patients to understand the relative cost-effectiveness of alirocumab compared with evolocumab. The Committee therefore concluded that evolocumab was a relevant comparator and important in the context of its decision regarding the cost-effectiveness of alirocumab.

### Clinical effectiveness

4.6     The Committee considered the clinical effectiveness evidence for alirocumab. It agreed that the trials included people whose characteristics

reflected those with hypercholesterolaemia seen in clinical practice in England and could be generalised to clinical practice.It noted that in people with hypercholesterolaemia, alirocumab significantly reduced LDL-c levels from baseline at 24 weeks by 39% to 62% compared with placebo, 24% to 36% compared with ezetimibe, and 20% to 49% compared with a statin. The Committee heard from the clinical expert that PCSK9 inhibitors could reduce LDL-c by up to 60% compared with placebo and that the treatment would have a sustained benefit especially for people with familial hypercholesterolaemia. It also noted the Evidence Review Group's (ERG's) comments that alirocumab was shown to have a similar safety profile to control groups. The Committee concluded that alirocumab is clinically effective in reducing LDL-c levels when compared with placebo, ezetimibe or statins in people with hypercholesterolaemia.

4.7     The Committee discussed the effect of alirocumab on cardiovascular events in people with hypercholesterolaemia. It noted that the trials mainly reported surrogate end points (such as LDL-c) and were not powered to measure cardiovascular outcomes, which the Committee considered to be an important limitation of the evidence base. The Committee noted that the company provided information about the relationship between LDL-c and cardiovascular events from the Navarese meta-analyses of PCSK9 inhibitor trials. The Committee heard from the clinical expert that the currently accepted relationship between LDL-c and cardiovascular events is based on a Cholesterol Treatment Trialist' Collaboration (CTTC) meta-analysis of statin trials. It understood that the CTTC meta-analysis included trials that had long follow-up periods, were designed to measure cardiovascular outcomes, had a large number of patients and many observed events. In contrast, the Navarese meta-analysis of PCSK9 inhibitors included trials with shorter follow-up periods, fewer patients and fewer events. It also heard that the IMPROVE-IT trial for ezetimibe also supported the relationship between LDL-c level and cardiovascular outcomes as estimated by the CTTC meta-analysis. The Committee

considered whether the relationship between LDL-c and cardiovascular outcomes from the CTTC meta-analysis of statin trials was relevant to alirocumab (a PCSK9 inhibitor). It heard from the clinical expert that although there could be clinically plausible reasons why the relationship established in the CTTC meta-analysis would be different for PCSK9 inhibitors (such as a different mechanism of action), there were no long-term cardiovascular outcome data to support such a conclusion. The Committee further heard from the ERG that the estimates of the relationship between LDL-c and cardiovascular outcomes were more precise in the CTTC meta-analysis, and that it estimated the relationship between LDL-c to a greater number of cardiovascular outcomes (such as revascularisation and ischaemic stroke) compared with the Navarese meta-analysis. Therefore, the Committee considered that the relationship between LDL-c and cardiovascular outcomes estimated by the CTTC meta-analysis are based on more mature data and clinically acceptable compared with the Navarse meta-analysis. The Committee concluded that, although it was reasonable to infer that alirocumab would reduce cardiovascular events, the extent of this reduction was an area of uncertainty. It further concluded that on balance, the best available evidence to assess this relationship was from the CTTC meta-analysis, which showed that a reduction in LDL-c was associated with fewer cardiovascular events.

## *Cost effectiveness*

4.8    The Committee considered the approach and structure of the company's model. It noted that the model was consistent with the approaches for hypercholesterolaemia developed for related NICE guidance. Although the structure omitted the transient ischaemic attack and stable angina health states, the ERG considered these limitations to be conservative assumptions and considered the model to be of good quality with an appropriate structure. The Committee concluded that the company's

approach to modelling and the model structure was acceptable for its decision-making.

4.9    The Committee considered the baseline characteristics, risks and the transition probabilities used by the company. The Committee understood that they were based on relevant real-world data from the Health Improvement Network [THIN] database, and noted the ERG's comment that there was good agreement with medium-term survival for the high-risk cardiovascular disease and recurrent events / polyvascular disease (non-familial) populations. The Committee therefore agreed that using data from THIN for these populations was appropriate. The Committee understood that the company checked the face validity of baseline characteristics with known prevalence. It was aware that the company acknowledged that the baseline characteristics based on THIN were different from the known prevalence for the primary and secondary prevention (heterozygous-familial) populations. Therefore, the Committee accepted the company's approach using the Dutch lipid criteria with THIN instead of THIN alone, to identify people for the primary prevention (heterozygous-familial) population because the baseline characteristics were considered more realistic. The Committee noted the company believed that the patient characteristics for the secondary prevention (heterozygous-familial) population using the Dutch lipid criteria with THIN still lacked face validity because the patient characteristics were still different from known prevalence. It noted that the company used an alternative source (Mohrschladt) for this population and that this resulted in a composite annual baseline cardiovascular risk twice as high when compared with data from THIN. Although the ERG was unable to verify whether this alternative source was appropriate, the Committee agreed that on balance, given that the patient characteristics from real-world dataset (THIN) were different from known prevalence, it was appropriate to use Mohrschladt for the secondary prevention population. The

Committee concluded that the baseline characteristics, risks and transition probabilities had been appropriately specified in the company's model.

4.10    The Committee discussed whether the company's model accurately captured the costs and health benefits associated with treating hypercholesterolaemia. The Committee accepted the ERG's opinion that the company's health state utility values were calculated and implemented appropriately. The Committee agreed with the ERG that the full costs of cardiovascular health states (such as stroke and post-stroke health states) should be applied beyond 3 years in the model, and that the approach to should be consistent with previous NICE guidance on [ezetimibe](#) and [lipid modification](#). Because the company's costs for each health state did not reflect the true cost associated with care following a cardiovascular event, the Committee preferred the more up-to-date follow-up costs used in the ERG's exploratory analyses. The Committee concluded that the utility values in the company's model were acceptable and accepted the costs applied in the ERG's exploratory analyses.

4.11    The Committee discussed the company's assumptions used for the treatment effect in the model:

- It considered the company's approach to link LDL-c levels to cardiovascular events. The Committee noted that the company's base-case analyses used the Navarese meta-analysis to link LDL-c levels to the cardiovascular outcomes. It also noted that using a different source (the CTTC meta-analysis) to link LDL-c reduction to cardiovascular relative risk instead of Navarese increased the ICERs in all the analyses (see section 3.45). The Committee recalled its conclusion (see section 4.7) that the best available evidence to assess the relationship between LDL-c and cardiovascular was from the CTTC meta-analysis. The Committee was aware that using the CTTC meta-analysis instead of the Navarese meta-analysis also resolved some of the ERG's concerns about the trials used to inform the hazard ratios for

cardiovascular events and the effect of LDL-c on ischaemic stroke rates. The Committee concluded that it preferred analyses in which the CTTC meta-analysis (see section 3.46) had been used to provide the source for the link between a reduction in LDL-c levels and the risk of cardiovascular events.

- It considered the ERG's concern that the company's assumption of a 0% discontinuation rate with alirocumab was unrealistic. The Committee noted that evidence from LONG-TERM suggested a discontinuation rate of 8% with alirocumab, and agreed that it was important to incorporate the discontinuation rate associated with treatment. The Committee agreed with the approach taken in the ERG's exploratory analyses.

4.12     The Committee considered the incremental cost-effectiveness ratios (ICERs) per quality-adjusted life year (QALY) for the 4 groups separately. It considered that the ICERs from the ERG's exploratory analyses were the most appropriate for consideration because they were the only analyses using both the updated cost data (see section 4.10) and the CTTC meta-analysis (see section 4.11). The Committee agreed that the ICERs to be considered for each population were:

- For the primary prevention (heterozygous-familial) population:
  - £67,200 per QALY gained for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe
  - £45,800 per QALY gained for alirocumab and ezetimibe compared with ezetimibe alone in people who are unable to take statins.
- For the secondary prevention (heterozygous-familial) population:
  - £33,300 per QALY gained for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe
  - £22,000 per QALY gained for alirocumab and ezetimibe compared with ezetimibe alone for people who are unable to take statins.
- For the high-risk cardiovascular (non-familial) population:

- − £42,100 per QALY gained for alirocumab and a statin compared with a statin alone

  - − £34,600 per QALY gained for alirocumab and ezetimibe compared with ezetimibe alone for people who are unable to take statins.

- For the recurrent events/polyvascular disease (non-familial) population:

  - − £44,759 per QALY gained for alirocumab and a statin compared with a statin alone.

  - − £33,519 per QALY gained for alirocumab and ezetimibe compared with ezetimibe alone for people who are unable to take statins.

4.13    The Committee discussed these ICERs for all the populations:

- The Committee noted that there was a large difference in the ICERs for the primary and secondary (heterozygous-familial) prevention populations (see section 4.12). The Committee understood from the clinical expert that this would not necessarily be expected, given that the lifetime risk of an event is high for these populations regardless of whether a previous event has already been experienced. It therefore considered there to be uncertainty regarding these estimates of the ICER. The Committee also recognised that, with the exception of the ICER for secondary prevention of heterozygous-familial hypercholesterolaemia in people unable to take statins, the ICERs exceeded the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained) and therefore alirocumab was not a cost-effective use of NHS resources. In addition, it was concerned that evolocumab had not been included as a comparator within an incremental cost-effectiveness analysis for any of the populations. Given these concerns, the Committee decided not to recommend alirocumab for treating heterozygous-familial hypercholesterolaemia.

- The Committee considered the ICERs for the non-familial hypercholesterolaemia populations (that is, the high-risk cardiovascular disease and the recurrent events / polyvascular disease [non-familial] populations). For those populations in which a statin is an appropriate treatment, the Committee was concerned that the comparator had been modelled as a statin alone, and not a statin in combination with ezetimibe (see section 4.4). In addition, for all the populations, it was concerned that evolocumab had not been included as a comparator in an incremental analysis (see section 4.5). The Committee noted that all of the ICERs (including those for people who are unable to take statins) were in excess of £30,000 per QALY gained and therefore exceeded the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained). Therefore, the Committee concluded that alirocumab was not a cost-effective use of NHS resources and did not recommend alirocumab for the non-familial hypercholesterolaemia populations.

4.14    In summary, the Committee considered that the ICERs presented for its consideration contained several uncertainties. In particular, the Committee was concerned by the absence of ezetimibe plus a statin as a comparator in the analyses for the non-familial hypercholesterolaemia populations, and evolocumab as a comparator for all the populations. The Committee recalled its earlier conclusion that both alirocumab and evolocumab appeared to have similar efficacy in terms of LDL-c reduction and, therefore, their relative drug acquisition costs would be a likely key driver of their cost-effectiveness. Therefore, the Committee concluded that both the high ICERs and key uncertainties meant that alirocumab was not a cost-effective use of NHS resources and therefore did not recommend alirocumab for treating hypercholesterolaemia (heterozygous-familial and non-familial).

4.15    The Committee discussed whether alirocumab was considered innovative, and noted that clinical and patient experts thought it to be an innovative drug. The Committee acknowledged that alirocumab was one of the first in a new class of drugs with a novel mechanism of action. However, it concluded that even though alirocumab was one of the first in a new class of drugs for hypercholesterolaemia, there was no evidence of additional gains in health-related quality of life over those already included in the QALY calculations, and that there was no need to change its conclusions on that basis.

4.16    The Committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

## *Summary of Appraisal Committee's key conclusions*

| TAXXX | **Appraisal title:** alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia | **Section** |
|---|---|---|
| **Key conclusion** | | |
| Alirocumab is not recommended within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia in adults. The Committee concluded that both the high ICERs and key | | 1.1, 4.14 |

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| uncertainties meant that alirocumab was could not be considered a cost-effective use of NHS resources and therefore did not recommend alirocumab for treating hypercholesterolaemia (heterozygous-familial and non-familial). | | |
| **Current practice** | | |
| Clinical need of patients, including the availability of alternative treatments | The Committee heard from the clinical expert that the people with the highest unmet need are those with familial hypercholesterolaemia and those in whom cardiovascular risk remains high despite having maximally tolerated lipid-modifying therapies, and for people who are cannot take statins because of intolerance or contraindication. | 4.2 |
| **The technology** | | |
| Proposed benefits of the technology  How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | The Committee acknowledged that alirocumab was one of the first in a new class of drugs with a novel mechanism of action. The Committee concluded that alirocumab is clinically effective in reducing LDL-c levels when compared with placebo, ezetimibe or statins in people with hypercholesterolaemia.  There were no evidence of additional gains in health related quality of life over those already included in the QALY calculations. | 4.6, 4.16 |

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| What is the position of the treatment in the pathway of care for the condition? | The Committee concluded that statins and ezetimibe are the main options for treating hypercholesterolaemia (heterozygous-familial and non-familial), and that ezetimibe is used as an option to treat hypercholesterolaemia in adults who are unable to tolerate a statin at an appropriately high dose. | 4.1 |
| Adverse reactions | The Committee concluded that safety profile of alirocumab was similar to that of the comparators. | 4.6 |
| **Evidence for clinical effectiveness** | | |
| Availability, nature and quality of evidence | The Committee noted that the trials mainly reported surrogate end points (such as LDL-c) and were not powered to measure cardiovascular outcomes. | 4.7 |
| Relevance to general clinical practice in the NHS | Committee concluded that the current treatment options for hypercholesterolaemia can negatively affect the quality of life of patients, particularly those with familial hypercholesterolaemia who need lifelong treatment; and that alternative treatment options are desirable. | 4.1 |
| Uncertainties generated by the evidence | The Committee concluded that, although it was reasonable to infer that alirocumab would reduce cardiovascular events, the extent of this reduction was an area of uncertainty. | 4.7 |

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| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | The Committee heard from the clinical expert that PCSK9 inhibitors could reduce LDL-c by up to 60% compared with placebo and that the treatment would have a sustained benefit especially for people with familial hypercholesterolaemia. | 4.6 |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The Committee noted that in people with hypercholesterolaemia, alirocumab significantly reduced LDL-c levels from baseline at 24 weeks by 39% to 62% compared with placebo, 24% to 36% compared with ezetimibe, and 20% to 49% compared with a statin. | 4.6 |
| **Evidence for cost effectiveness** | | |
| Availability and nature of evidence | The Committee concluded that the company's approach to modelling and the model structure was acceptable for its decision-making. | 4.8 |
| Uncertainties around and plausibility of assumptions and inputs in the economic model | The Committee concluded that, although it was reasonable to infer that alirocumab would reduce cardiovascular events, the extent of this reduction was an area of uncertainty.<br><br>Committee preferred the more up-to-date follow-up costs used in the ERG's exploratory analyses because the company's costs for each health state did not reflect the true cost associated with care following a | 4.7, 4.10, 4.11, 4.13 |

cardiovascular event.

The Committee considered the ERG's concern that the company's assumption of a 0% discontinuation rate with alirocumab was unrealistic and agreed that it was important to incorporate the discontinuation rate associated with treatment.

The Committee noted that there was a large difference in the ICERs for the primary and secondary (heterozygous-familial) prevention populations. The Committee understood from the clinical expert that this would not necessarily be expected, given that the lifetime risk of an event is high for these populations regardless of whether a previous event has already been experienced.

For those populations in which a statin is an appropriate treatment, the Committee was concerned that the comparator had been modelled as a statin alone, and not a statin in combination with ezetimibe. In addition, for all the populations, it was concerned that evolocumab had not been included as a comparator in an incremental analysis.

| | | |
|---|---|---|
| Incorporation of health-related quality-of-life benefits and utility values<br><br>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered? | The Committee accepted the ERG's opinion that the company's health state utility values were calculated and implemented appropriately. | 4.10 |
| Are there specific groups of people for whom the technology is particularly cost effective? | The Committee recognised that, with the exception of the ICER for secondary prevention of heterozygous-familial hypercholesterolaemia in people unable to take statins, the ICERs exceeded the range normally considered to be a cost‑effective use of NHS resources (up to £20,000–30,000 per QALY gained) and therefore alirocumab was not a cost-effective use of NHS resources. | 4.13 |

| What are the key drivers of cost effectiveness? | The Committee noted that using a different source to link LDL-c reduction to cardiovascular relative risk instead of Navarese increased the ICERs in all the analyses.<br><br>The Committee noted that there was a large difference in the ICERs for the primary and secondary (heterozygous-familial) prevention populations. The Committee understood from the clinical expert that this would not necessarily be expected, given that the lifetime risk of an event is high for these populations regardless of whether a previous event has already been experienced. It therefore considered there to be uncertainty regarding these estimates of the ICER.<br><br>For those populations in which a statin is an appropriate treatment, the Committee was concerned that the comparator had been modelled as a statin alone, and not a statin in combination with ezetimibe. In addition, for all the populations, it was concerned that evolocumab had not been included as a comparator in an incremental analysis. | 4.11, 4.13 |
| Most likely cost-effectiveness estimate (given as an ICER) | For the primary prevention (heterozygous-familial) population:<br><br>• £67,200 per QALY gained for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe | 4.12 |

- £45,800 per QALY gained for alirocumab and ezetimibe compared with ezetimibe alone in people who are unable to take statins.

For the secondary prevention (heterozygous-familial) population:

- £33,300 per QALY gained for alirocumab and a statin plus ezetimibe compared with a statin and ezetimibe
- £22,000 per QALY gained for alirocumab and ezetimibe compared with ezetimibe alone for people who are unable to take statins.

For the high-risk cardiovascular (non-familial) population:

- £42,100 per QALY gained for alirocumab and a statin compared with a statin alone
- £34,600 per QALY gained for alirocumab and ezetimibe compared with ezetimibe alone for people who are unable to take statins.

For the recurrent events / polyvascular disease (non-familial) population:

- £44,759 per QALY gained for alirocumab and a statin compared with a statin alone.
- £33,519 per QALY gained for alirocumab and ezetimibe compared with ezetimibe alone for people who are unable to take

| | statins. | |
|---|---|---|
| **Additional factors taken into account** | | |
| Patient access schemes (PPRS) | The company has agreed a patient access scheme with the Department of Health.<br><br>The Committee concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of alirocumab. | 2.3, 4.16 |
| End-of-life considerations | Not applicable. | - |
| Equalities considerations and social value judgements | The following potential equality issues were identified during the scoping process:<br><br>• Inequality of access to LDL-apheresis due to high set up costs for treatment and few established centres with appropriate expertise<br>• Injection only treatment which will exclude people who will not accept injection based therapies, including many from ethnic minority groups.<br><br>The potential equality issues identified during the scoping process have been noted by the Committee. None of these issues related to protected characteristics, as defined by the Equalities Act, and so were not considered equality issues. | - |

# 5 Recommendations for research

5.1 The Committee was aware that an ongoing randomised controlled trial exploring the occurrence of cardiovascular events of alirocumab compared with placebo are available is expected in 2018. The Committee agreed that this trial would give useful data on the direct effect of alirocumab on cardiovascular disease.

# 6 Related NICE guidance

Further information is available on the [NICE website](#).

**Published**

- [Cardiovascular disease prevention (2015)](#) NICE pathway
- [Familial hypercholesterolaemia](#) (2015) NICE pathway
- [Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease](#) (2014) NICE guideline CG181.
- [Identification and management of familial hypercholesterolaemia](#) (2008) NICE guideline CG71.
- [Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (2007)](#) NICE technology appraisal guidance TA132

**Under development**

- [Ezetimibe for treating primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132)](#) NICE technology appraisal guidance (publication expected February 2016)
- [Hypercholesterolaemia (primary), dyslipidaemia (mixed) – evolocumab.](#) NICE technology appraisal guidance (publication expected April 2016)
- [Familial hypercholesterolaemia (standing committee update)](#). NICE guideline (publication expected January 2017)

# 7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive when the results from a large randomised controlled trial exploring the occurrence of cardiovascular events of alirocumab compared with placebo are available (expected 2018). NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens

Chair, Appraisal Committee

January 2016

ISBN: [to be added at publication]

# 8    Appraisal Committee members, guideline representatives and NICE project team

## *Appraisal Committee members*

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

**Professor Andrew Stevens**

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

**Professor Eugene Milne**

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

**Professor Kathryn Abel**

Institute of Brain and Behaviour mental Health, University of Manchester

**Mr David Chandler**

Lay Member

**Professor Peter Crome**

Honorary Professor, Dept of Primary Care and Population Health, University College London

**Professor Rachel A Elliott**

Lord Trent Professor of Medicines and Health, University of Nottingham

**Dr Nigel Langford**

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

**Dr Andrea Manca**

Health Economist and Senior Research Fellow, University of York

**Dr Patrick McKiernan**

Consultant Pediatrician, Birmingham Children's Hospital

**Dr Iain Miller**

Founder & CEO, Health Strategies Group

**Dr Paul Miller**

Director, Payer Evidence, Astrazeneca UK Ltd

**Professor Stephen O'Brien**

Professor of Haematology, Newcastle University

**Professor Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

**Professor Matt Stevenson**

Technical Director, School of Health and Related Research, University of Sheffield

**Dr Judith Wardle**

Lay Member

## *NICE project team*

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Jasdeep Hayre**

Technical Lead

**Joanne Holden**

Technical Adviser

**Stephanie Yates**

Project Manager

# 9       Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen HTA Group:

Scotland G, Neilson A, Javanbakht M, Fielding S, Cruickshank M, Sharma P, Fraser C, Simpson W, Brazzelli M. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Aberdeen HTA Group, 2015.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Sanofi

II. Professional/expert and patient/carer groups:

- HEART UK
- British Cardiovascular Society
- British Heart Foundation
- Royal College of Pathologists
  Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS Birmingham South Central CCG
- NHS East Leicestershire and Rutland CCG
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety - Northern Ireland
- Healthcare Improvement Scotland
- Merck Sharp and Dohme UK
- Novartis Pharmaceuticals
- Pfizer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on alirocumab by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Professor Robin Choudhury, Professor of Cardiovascular Medicine and Consultant Cardiologist, nominated by British Cardiovascular Society – clinical expert
- Dr Alan Rees, Consultant Physician, nominated by Sanofi – clinical expert
- Karen Hasid, Patient Representative, nominated by HEART UK – patient expert

- Simon Williams, Head of Communications and Policy nominated by HEART UK

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Sanofi