



Northern Treatment  
Advisory Group

# **Alirocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia**

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## Summary

- Alirocumab (Praluent®▼, Sanofi) is a monoclonal anti-PCSK9 antibody licensed for the treatment of primary hypercholesterolaemia (familial and non-familial) and mixed dyslipidaemia in adults. It acts by reducing circulating levels of LDL-C.
- It is administered at a dose of 75 mg subcutaneously every 2 weeks, which may be increased to 150 mg every two weeks if the LDL-C response is inadequate. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg every 2 weeks. Alirocumab may be self-administered following suitable training.
- Current UK guidance recommends statins first line for most people. Ezetimibe may be considered for people who require lipid modification but have a contraindication or intolerance to statins. There are currently no further treatment options.
- Across ten phase 3 trials (n=5,296 patients) evaluating patients with HeFH and non-FH at high and moderate CV risk, alirocumab demonstrated a substantial reduction in the primary endpoint of LDL-C reduction after 24 weeks. On top of standard care (maximally tolerated statin +/- other LMTs), a reduction of 39% to 62% compared to placebo was observed. Compared with ezetimibe, a reduction of 30% was found on top of standard care, 24% to 36% on less than maximal statins, and 30% to 32% without statin background therapy. The primary endpoint analyses were supported by consistent changes in the secondary lipid profile endpoints across all studies.
- The safety profile of alirocumab was comparable to comparators (placebo and ezetimibe). The most common adverse events were nasopharyngitis, injection site reaction, upper respiratory tract infection, influenza, headache, myalgia, and arthralgia. There were no differences in the rates of serious adverse events, or events leading to discontinuation.
- None of the safety concerns commonly associated with other LMTs, such as liver disorders, renal disorders, diabetes and musculoskeletal disorders, was evident with alirocumab treatment. However, the long-term safety of alirocumab remains to be established.
- Both the alirocumab 75 mg/ml and the 150 mg/ml doses cost £168.00 for one single-use pen or syringe, and £336.00 for two, equating to £4,360 per patient per year. Ezetimibe currently costs £343.03 per patient per year. There may be additional costs incurred to either administer each dose or provide suitable training for patients to self-administer.
- Alirocumab represents an additional treatment option for adults with primary HeFH or non-FH with high CV risk who do not adequately respond to maximally tolerated statin therapy, or who cannot be given statins.
- Alirocumab will compete directly with evolocumab (Repatha®▼, Amgen) another monoclonal anti-PCSK9 antibody recently licensed for hypercholesterolaemia and mixed dyslipidaemia.

## Introduction and background

Hypercholesterolaemia is a form of dyslipidaemia characterised by abnormalities of lipoprotein transport associated with high levels of cholesterol, especially low-density lipoprotein (LDL) cholesterol in the blood. Primary hypercholesterolaemia is associated with an underlying genetic cause, which may be a specific genetic defect as in familial hypercholesterolaemia (FH), or more commonly non-familial hypercholesterolaemia (non-FH) in which a number of genes interact with dietary and other factors such as smoking and physical inactivity.<sup>1-3</sup>

In heterozygous familial hypercholesterolemia (HeFH), an individual typically inherits a defect or mutation in the LDL-C receptor gene from one parent only. Occasionally, HeFH can be caused by mutations of other genes such as proprotein convertase subtilisin/Kexin type 9 (PCSK9), or apolipoprotein B. In homozygous familial hypercholesterolemia (HoFH), an individual inherits a causal mutation in the affected gene from both parents.<sup>1,2</sup>

Primary HeFH is the most common autosomal dominant disorder with an estimated prevalence of 1 in 500 people (106,000) in England, although only around 15–17% are thought to be diagnosed. Primary non-FH affects about 4% of the adult population, equating to around 1.5 million people in England, of whom an estimated 600,000 are diagnosed and 460,000 are receiving treatment.<sup>1-3</sup>

Hypercholesterolaemia is major risk factor for the development and progression of cardiovascular disease (CVD). Long-term exposure to significantly elevated LDL-C accelerates the development of atherosclerosis which can lead to angina, myocardial infarction and stroke, particularly in patients with HeFH. Untreated, men have a greater than 50% risk of coronary heart disease (CHD) by the age of 50 years, and women at least 30% by the age of 60 years.<sup>1-3</sup>

Managing primary hypercholesterolaemia involves dietary and lifestyle changes such as smoking cessation, weight loss and increased physical activity. The decision to initiate treatment with lipid-modifying therapy (LMT) is generally based on an assessment of the person's overall cardiovascular risk rather than meeting target cholesterol levels.<sup>1-5</sup>

Statins are considered the standard of care in the UK for the management of HeFH and non-FH, but most patients with HeFH will require statin-based combination therapy. Ezetimibe is used as monotherapy when statins are contraindicated or not tolerated, and in combination with a statin in when LDL-C is not appropriately controlled with maximally tolerated statin therapy. Infrequently, other LMTs such as fibrates, nicotinic acid derivatives or anion exchange resins may also be used.<sup>1,2,4</sup>

Alirocumab (Praluent®▼, Sanofi) is a fully human monoclonal antibody which binds selectively to PCSK9 and prevents it binding to low density lipoprotein (LDL) receptors.<sup>6,7</sup> As LDL receptors are the major pathway through which LDL-cholesterol is cleared from the circulation, inhibiting the binding of PCSK9 increases the availability of these receptors to clear LDL particles, thereby lowering serum LDL-C.

Alirocumab is licensed for treatment of adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia, as an adjunct to diet:

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

This report will review the evidence for the use of alirocumab in the treatment of primary hypercholesterolaemia (heterozygous familial or non-familial) and dyslipidaemia.

### Guidance and related advice

NICE CG181 for lipid modification to prevent CVD and NICE CG71 for FH recommends initial treatment with statins. When a decision is made to prescribe a statin, the guideline recommends using a statin of high-intensity and low acquisition cost. Atorvastatin 20 mg is recommended for the primary prevention of CVD in people who have a 10% or greater 10-year risk of developing CVD, as defined by the QRISK2 risk assessment tool. Statin treatment for people with CVD (secondary prevention) should usually start with atorvastatin 80 mg daily. NICE CG181 does not routinely recommend the use of nicotinic acid, bile acid sequestrants or omega-3 fatty acid compounds. Additionally, it does not routinely recommend the use of fibrates, which it states are more appropriate in treating hypertriglyceridaemia.<sup>2,4</sup>

In October 2015, NICE published draft guidance recommending ezetimibe monotherapy for adults with primary HeFH and non-FH when a statin is considered inappropriate or is not tolerated, but only if: patients need lipid modification therapy for the primary prevention of cardiovascular disease and have both type II diabetes and a 20% or greater 10-year risk of developing cardiovascular disease according to the QRISK2 risk assessment tool, or they need LMT for secondary prevention of CVD.<sup>5</sup>

A NICE single technology appraisal of alirocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia (ID779) is currently in progress with an estimated publication date of June 2016.<sup>8</sup>

A NICE single technology appraisal of evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia (ID765) is currently in progress with an estimated publication date of April 2016.<sup>9</sup>

### Clinical evidence

The clinical development program for alirocumab includes 17 phase 3 studies designed to assess the efficacy and safety of alirocumab in the treatment of patients with primary hypercholesterolaemia and mixed dyslipidaemia. The evidence reviewed in this report focusses on the ten phase 3 trials that have either been completed, or are ongoing and have completed at least the 'first-step analysis' of the primary endpoint at week 24 and all key secondary endpoints up to week 52. Only six of the studies have been published (FH I, II, LONG TERM, COMBO I, II, OPTION I, and MONO)<sup>10-16</sup> with the remaining studies available as conference abstracts and media reports. However, sufficiently comprehensive data on all 10 studies are presented in the EMA and FDA appraisal reports.<sup>7,17</sup> In total, 5,296 subjects were randomized

across these trials, with 3,188 assigned to receive alirocumab, 620 assigned to ezetimibe, and 1,175 placebo, and 313 to a change in the background statin regimen.

The overall design the ten phase 3 studies were very similar, and considered appropriate for this therapeutic setting. All the trials were randomized, double-blind, parallel-group, placebo- or active-controlled trials. The studies enrolled patients with primary HeFH (diagnosed by either genotype or clinical criteria) and non-FH, including mixed dyslipidaemia. In most trials, the entry criterion for LDL-C was either  $\geq 70$  mg/dL and/or  $\geq 100$  mg/dL depending on the individual patient's CV risk at entry. Each trial consisted of a screening and injection training period of 2 to 6 weeks duration, a double-blind treatment period of 6 to 24 months, and an 8-week follow-up period for those not entering into an open-label extension period. Two different alirocumab dosing regimens were studied. Eight trials evaluated alirocumab 75 mg Q2W with up-titration to 150 mg Q2W at week 12 if the predefined LDL-C target was not achieved by week 8. Two trials investigated alirocumab 150 mg Q2W for the entire study duration. In six of the studies patients were required to be on maximally tolerated doses of statins, defined as: rosuvastatin 20 mg; atorvastatin 40 mg or 80 mg daily, or simvastatin 80 mg daily, but only if the patient was already on this dose for more than one year. All concomitant LMTs were to be at stable dose for at least four weeks before the screening visit and throughout the study period.

Five trials (FH I, FH II, HIGH FH, COMBO I, and LONG TERM) compared alirocumab to placebo when added to a background dose of maximally tolerated statin, with or without other LMTs, if previously received. The FH and HIGH FH studies exclusively enrolled patients with HeFH, and LONG TERM enrolled patients with either HeFH or non-FH but high CV risk. The other five trials compared alirocumab to ezetimibe 10 mg daily. COMBO II enrolled patients with high CV risk who were taking a maximally tolerated statin without other LMTs. OPTIONS I and II enrolled patients with HeFH or non-FH but high CV risk on a less than maximal dose of statin with or without other LMTs. Both studies also included statin up-titration arms (or a switch from one statin to another) as additional active control groups. ALTERNATIVE enrolled patients intolerant of statins with or without other LMTs. This study also included an atorvastatin re-challenge arm to validate the definition of statin intolerance used for patient eligibility. The MONO study enrolled patients at moderate CV risk not receiving a statin or any other LMT.

In all studies the primary endpoint in all 10 studies was the percent change in calculated LDL-C from baseline to week 24 in the intention-to-treat (ITT) population. Secondary endpoints included the percent change from baseline in Total-C, Apo B, non-HDL-C, Lp (a), fasting TG, HDL-C, and Apo-A1.

Across trials differences in patient demographic and baseline characteristics were reflective of the different patient populations studied. The LDL-C levels at baseline were comparable between the alirocumab and the control group in the different groups of studies. Overall, 31% of patients had type 2 diabetes mellitus, and 64% of patients had a history of coronary heart disease, with 34% having a prior myocardial infarction.

In all studies, at week 24, alirocumab demonstrated a substantial reduction in the primary endpoint of percent change in mean LDL-C compared to placebo or ezetimibe, regardless of background statin therapy (Table 1 and Appendix 1). This

result was consistent across studies evaluating patients with HeFH and non-FH at high risk and at moderate CV risk. On top of standard care (maximally tolerated statin +/- other LMTs), a reduction of 39% to 62% compared to placebo was observed. The reduction in LDL-C was well maintained from week 24 out to week 52 in the FH I, II, HIGH-FH, COMBO I and II studies, and to week 78 in the LONG-TERM study. Compared with ezetimibe, a reduction of 30% was found on top of standard care, 24% to 36% on less than maximal statins, and 30% to 32% without statin background therapy. The primary endpoint analyses were supported by consistent changes in the secondary lipid profile endpoints across all studies, including significant reductions Apo B, Total-C, non-HDL-C, Lp(a) and fasting TG and increases in HDL-C and Apo A-I, with the exception of no significant reductions in fasting TG versus ezetimibe.

**Table 1. Summary of primary outcome at week 24 for placebo and ezetimibe comparisons.**

Control group / background therapy	Study	Alirocumab vs. control (95% CI)
<b>Placebo</b>		
Maximally tolerated dose of statin +/- other LMTs	FH I	-58% (-63 to -53)
	FH II	-51% (-58 to -45)
	HIGH FH	-39% (-51 to -27)
	COMBO I	-46% (-52 to -39)
	LONG TERM	-62% (-64 to -59)
<b>Ezetimibe</b>		
Maximally tolerated statin without other LMTs	COMBO II	-30% (-34 to -25)
Less than maximal does of statin	OPTIONS I: atorva 20 mg	-24% (-41 to -7)
	OPTIONS I: atorva 40 mg	-31% (-48 to -16)
	OPTIONS II: rosuva 10 mg	-36% (-52 to -21)
	OPTIONS II: rosuva 20 mg	-25% (-51 to 0.3)
LMT (no statin)	ALTERNATIVE	-30% (-37 to -24)
None	MONO	-32% (-40 to -23)

The proportion of subjects randomized to alirocumab who required a dose up-titration to alirocumab 150 mg Q2W varied considerably across trials, from 14% to 50%. As expected, the proportion of patients who required an up-titration was higher in the studies with higher baseline LDL-C. After up-titration, an additional reduction in calculated LDL-C was observed from week 12 to week 24 demonstrating the added benefit of this higher dose. The additional reduction in LDL-C was more pronounced in patients on a background of statin therapy (-14.2%), compared with that in patients not using statin as background therapy (-3.1%). This modest increase in benefit observed with the higher dose in patients not on background statins could indicate that the near-maximal PCSK9-inhibiting effect is already reached with the 75 mg dose for most of these patients not receiving statins. However, 25% of these patients achieved at least an additional 10% LDL-C lowering after up-titration, which is considered clinically significant.

The safety and efficacy of alirocumab in children and adolescents under 18 years of age have not been established. No data are available.

## Safety

The integrated safety database includes the aforementioned ten phase 3 trials, and an additional four phase 2 studies encompassing a total of 3,340 patients exposed to alirocumab, with 2,856 subjects for at least 24 weeks, 2,408 Subjects for  $\geq 52$  weeks and 638 alirocumab exposed subjects for at least 76 weeks. The other ongoing studies are not included in the integrated safety dataset, as the data for these studies is not yet unblinded. The safety database is divided into two main safety pools based on the control group used, placebo or ezetimibe.

The placebo-controlled pool comprises of nine studies (four phase 2 and five phase 3 studies; FHI, II, HIGH-FH, COMBI I, and LONG-TERM). Within this pool, the mean duration of exposure was 58 weeks, with most of the patients (81% in the alirocumab group; 79% in the placebo group) exposed for at least 52 weeks. The ezetimibe-controlled pool comprises of five phase 3 studies (COMBO II, OPTIONS I, II, ALTERNATIVE and MONO). Within this pool, the mean duration of exposure was 42 weeks in the alirocumab group and 35.5 weeks in the ezetimibe group, with 47% and 34% respectively, exposed for at least 52 weeks. A third global pool including all the placebo- and ezetimibe-controlled studies was used to evaluate selected safety topics including, anti-drug antibodies, deaths, and injection site reactions.

The placebo- and ezetimibe-controlled groups were well matched for demographic and baseline characteristics. The alirocumab population included patients with HeFH and non-FH, representing approximately 27% and 73% of the safety population, respectively. The majority of patients in both the main safety pools had a history of CHD (60 to 70%), with a third of patients reporting a history of a MI, approximately 70% a history of hypertension and an estimated 30% a history of diabetes mellitus.

Overall, the proportion of patients who experienced any treatment emergent adverse event (TEAE), serious treatment emergent adverse event (STEAE fatal and non-fatal combined), or TEAE leading to discontinuation were similar between the alirocumab and control groups. Table 2 below summarises the treatment emergent adverse events (TEAE) within the safety population of placebo-controlled studies (phase 2/3) and ezetimibe-controlled studies (phase 3).

**Table 2. Overview of adverse event profile - Treatment-emergent adverse events.**

Patients with - n (%)	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (N=1,276)	Alirocumab (N=2,476)	Ezetimibe (N=618)	Alirocumab (N=864)
Any TEAE	975 (76.4%)	1,876 (75.8%)	421 (68.1%)	607 (70.3%)
Any treatment-emergent SAE	182 (14.3%)	340 (13.7%)	69 (11.2%)	113 (13.1%)
Any TEAE leading to death	11 (0.9%)	13 (0.5%)	7 (1.1%)	2 (0.2%)
Any TEAE leading to permanent treatment discontinuation	65 (5.1%)	131 (5.3%)	60 (9.7%)	76 (8.8%)

### Common TEAEs

In the placebo-controlled pool, the most common TEAEs ( $\geq 5\%$  of patients in any group) were in order of decreasing frequency in the alirocumab group; nasopharyngitis (11.3% in the alirocumab group vs. 11.1% in the placebo group), injection site reaction

(6.7% vs. 4.8%), upper respiratory tract infection (6.1% vs.7.0%), influenza (5.7% vs. 4.6%), headache (4.8% vs. 5.2%), and arthralgia (4.0% vs. 5.5%). TEAEs that occurred in  $\geq 2.0$  of patients in the alirocumab group and with a higher incidence (difference  $\geq 0.5\%$ ) than in placebo group were injection site reactions, influenza, myalgia, muscle spasms, contusion, and musculoskeletal pain. In contrast, TEAEs that occurred with higher incidence in the placebo group were arthralgia, dizziness, pain in extremity, fall and depression. The most frequently reported TEAEs that led to treatment discontinuation were injection site reactions, nausea, myalgia, fatigue, increased ALT, anaemia, vertigo, diarrhoea, and pruritus.

In the ezetimibe-controlled pool, the most common TEAEs ( $\geq 5\%$ ) were; myalgia (6.7% in the alirocumab group vs 7.6% in the ezetimibe group), upper respiratory tract infection (5.9% vs 6.0%), and nasopharyngitis (5.4% vs. 5.7%). TEAEs ( $\geq 2.0\%$ ) occurring with higher incidence in the alirocumab group versus ezetimibe group (difference  $\geq 0.5\%$ ) were accidental overdose, headache, influenza, injection site reaction, fatigue, and constipation. In contrast, TEAEs that occurred with higher incidence in the placebo group were myalgia, dizziness, back pain, urinary tract infection, nausea, and sinusitis. The most frequently reported TEAEs that led to treatment discontinuation were headache and injection site reaction.

Overall, there were no clinically meaningful differences observed in the frequency of TEAEs between the alirocumab and control groups in patients at high CV risk vs moderate CV risk, diabetic vs. non-diabetic patients, statin intolerant vs statin tolerant, and monotherapy vs. maximally tolerated statin therapy. Only slight differences were observed between HeFH and non-FH patients.

### **Serous TEAEs**

The overall incidence of treatment-emergent SAEs was similar in the alirocumab and control groups (Table 3). No significant difference between the treatment groups was observed for any individual system organ class (SOC). The most common SAEs were related to cardiac disorders, however no pattern could be observed for the combined incidence of cardiac disorders, with similar incidence in the placebo-controlled pool and higher incidence for alirocumab in the ezetimibe-controlled pool.

### **Cardiovascular events and mortality**

The effect of alirocumab on cardiovascular morbidity and mortality has not yet been fully established. None of the trials completed to date had mortality associated with cardiovascular events as a pre-specified primary efficacy outcome.

### **Major Adverse Cardiac Events (MACE)**

In the global phase 3 pool, the composite endpoint of adjudicated MACE events (CHD death, nonfatal MI, fatal or nonfatal ischaemic stroke, and unstable angina requiring hospitalisation) occurred in 52 (1.6%) patients in the alirocumab group and 33 (1.8%) patients in the control group. The incidence rate (per 100 patient-years) was 1.5 and 1.8 in the alirocumab and control groups, respectively, with HR (95% CI): 0.81 (0.52 to 1.25). The majority of events came from LONG TERM trial in which MACE confirmed by adjudication (pre-specified *post hoc* analysis) were reported in 27 of 1550 (1.7%) patients in the alirocumab group and 26 of 788 (3.3%) patients in the placebo group, HR=0.52 (95% CI, 0.31 to 0.90, p=0.02).

When the definition of MACE in the global phase 3 pool was expanded to include endpoints of CHF hospitalisation or revascularisation, the HR for alirocumab versus control increased to 1.08 (95% CI 0.78, 1.50), primarily driven by a greater incidence of revascularisations in the alirocumab group (2.3% vs. 1.7%).

**Table 3. Serious TEAEs reported in ≥0.5% of patients in any treatment group.**

Serious TEAEs - n (%)	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (N=1,276)	Alirocumab (N=2,476)	Ezetimibe (N=618)	Alirocumab (N=864)
Any class	182 (14.3%)	340 (13.7%)	69 (11.2%)	113 (13.1%)
Cardiac disorders	58 (4.5)	109 (4.4%)	25 (4.0%)	48 (5.6%)
Unstable angina	9 (0.7%)	25 (1.0%)	2 (0.3%)	12 (1.4%)
Angina pectoris	7 (0.5%)	16 (0.6%)	6 (1.0%)	8 (0.9%)
Coronary artery disease	3 (0.2%)	15 (0.6%)	2 (0.3%)	12 (1.4%)
Acute MI	11 (0.9%)	7 (0.3%)	3 (0.5%)	11 (1.3%)
Atrial fibrillation	9 (0.7%)	9 (0.4%)	3 (0.5%)	5 (0.6%)
MI	6 (0.5%)	7 (0.3%)	0	3 (0.3%)
Infections and infestations	26 (2.0%)	44 (1.8%)	7 (1.1%)	23 (2.7%)
Pneumonia	6 (0.5%)	6 (0.2%)	2 (0.3%)	7 (0.8%)
Nervous system disorders	19 (1.5%)	47 (1.9%)	10 (1.6%)	15 (1.7%)
Syncope	7 (0.5%)	11 (0.4%)	3 (0.5%)	3 (0.3%)
Respiratory, thoracic and mediastinal disorders	15 (1.2%)	23 (0.9%)	3 (0.5%)	5 (0.6%)
Chronic obstructive pulmonary	7 (0.5%)	5 (0.2%)	0	3 (0.3%)
General disorders and administration site conditions	15 (1.2%)	19 (0.8%)	8 (1.3%)	5 (0.6%)
Non-cardiac chest pain	6 (0.5%)	14 (0.6%)	5 (0.8%)	2 (0.2%)
Gastrointestinal disorders	18 (1.4%)	22 (0.9%)	4 (0.6%)	13 (1.5%)
Ulcer haemorrhage	0	1 (<0.1%)	0	3 (0.3%)
Vomiting	1 (<0.1%)	0	0	2 (0.2%)
Haemorrhoids	0	1 (<0.1%)	0	2 (0.2%)

### All-cause mortality

In the global pool, all-cause mortality was 0.6% (20 of 3182 patients) in the alirocumab group and 0.9% (17 of 1792 patients) in the control group. The majority of these deaths were CV related - 11 occurring in the control group and 15 occurring in the alirocumab group, which is not unexpected given the high CV risk profile of the population studied. An analysis on the incidences of TEAEs leading to death found an exact odds ratio (OR) versus control, stratified by study, of 0.44 (95% CI: 0.21 to 0.93).<sup>7</sup>

However, the data are limited and there were too few events to evaluate the effect of alirocumab on reduction of CV events and mortality with any certainty. The ongoing phase 3 OUTCOMES trial is comparing the effect of alirocumab with placebo on the occurrence of MACE (CHD death, MI, ischemic stroke and unstable angina requiring hospitalization) in approximately 18,000 patients who have experienced an ACS event. The results of this study are unlikely to be available before 2018.<sup>18</sup>

### **Adverse events of special interest**

Specific attention was given to musculoskeletal and connective tissue disorders, hepatic disorders, renal disorders, and diabetes, as these are known to be associated with several lipid lowering agents. No muscle-related safety signal has been identified. In the placebo-controlled pool, on a background of statin therapy, the incidence in skeletal muscle-related TEAEs was comparable between patients in the alirocumab group (15.1%) versus patients in the placebo group (15.4%). Hepatic disorder TEAEs were reported slightly more common with alirocumab (2.5%) than with (1.8%) placebo, but were slightly lower in the alirocumab group (1.9%) compared to the ezetimibe group (2.3%). In general, the incidences of renal adverse events do not indicate any adverse effect of alirocumab on the kidney. A similar number renal and urinary TEAEs were reported in the alirocumab and placebo group (3.9% vs. 4.7%, respectively), and the alirocumab and ezetimibe group (3.7% vs. 3.9% respectively). No effect on incidence of diabetes or incidences of abnormalities in fasting glucose or HbA1C was found for alirocumab

### **Injection site reactions**

In the global pool, a higher incidence of local injection site reactions were reported in patients receiving alirocumab, 6.1% compared with 4.1% in the pooled control groups. Most injection site reactions were transient and of mild intensity and few patients discontinued treatment due to an injection site reaction. Symptoms associated with local injection site reactions included erythema/redness (2.9%), swelling (2.3%), pain (1.9%), and hematoma (0.3%).

### **Immunogenicity**

As would be expected the incidence of anti-alirocumab antibodies (ADA) was higher in the pooled alirocumab group (4.8%) versus the pooled control group (0.6%, placebo or ezetimibe), but were still relatively infrequent. Development of ADA did not appear to affect the incidence of overall TEAEs among alirocumab-treated patients (75.9% without a positive ADA response vs. 76.2% with a positive ADA response). However, there was a higher incidence rate of injection site reactions among those who developed ADAs.

### **LDL-C values <25 mg/dL (0.65 mmol/L)**

In total, 23.8% of patients treated with alirocumab had two consecutive values of LDL-C <25 mg/dL (0.65 mmol/L), including 8.6% with two consecutive values <5 mg/dL (0.39 mmol/L). These mostly occurred in patients initiated and maintained on the 150 mg Q2W dose of alirocumab. For those patients achieving very low LDL-C levels (<25 mg/dL) specific TEAEs of interest including neurocognitive and neurologic events did not indicate meaningful safety risks.

### **Safety by individual alirocumab dose**

There are no head-to-head safety data comparing the safety of the two alirocumab doses. In an analysis of the 75 mg QW2 dose up to week 12, a total of 165 (47.0%) patients in the alirocumab group versus 338 (48.6%) in the placebo group, and 402 (46.5%) patients in the alirocumab group and 288 (46.6%) patients in the ezetimibe group reported at least one TEAE. Overall, there were no significant differences in the incidences of TEAEs, SAEs, mortality and discontinuations due to TEAEs between

alirocumab and respective control groups. The nature and severity of TEAEs were consistent with that reported for the primary safety analyses pools in which the safety data of the two regimens were combined.

### **Up-titration**

An exploratory analysis was conducted to evaluate the safety of alirocumab in patients remaining on 75 mg QW2 versus patients who had their dose increased to 150 mg QW2 at week 12. Overall, there were no significant differences in the incidences of TEAEs, SAEs, mortality and discontinuations due to TEAEs by up-titration status at after week 12. There was no difference in the incidence of injection site reactions between the two groups.

### **Dosage and administration**

Prior initiating alirocumab secondary causes of hyperlipidaemia or dyslipidaemia should be excluded. Alirocumab is not recommended for children and adolescents under 18 years of age.

Alirocumab solution for injection is available as 75 mg/ml and 150mg/ml doses, each available in a 1ml pre-filled pen, or a 1ml pre-filled syringe. Each pre-filled pen or pre-filled syringe is for single-use only. The usual starting dose of alirocumab is 75 mg administered subcutaneously once every 2 weeks. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. Alternatively, patients requiring larger LDL-C reduction (>60%) may be started on 150 mg administered subcutaneously once every 2 weeks. Patients should be treated with the lowest necessary dose to achieve the desired LDL-C reduction. Lipid levels can be measured within 4 to 8 weeks of initiating or titrating alirocumab to assess response and dose adjusted accordingly. No dose adjustment is needed for elderly patients, those with mild or moderate hepatic or renal impairment.

Praluent should be allowed to warm to room temperature prior to use, and should be used as soon as possible after it has warmed up. Alirocumab should be administered as a subcutaneous injection into the thigh, abdomen or upper arm. It is recommended to rotate the injection site with each injection. It must not be co-administered with other injectable medicinal products at the same injection site.

The patient may either self-inject alirocumab, or a caregiver may administer alirocumab after guidance has been provided by a healthcare professional on proper subcutaneous injection technique.

An alternative dosing regimen of once monthly alirocumab is currently being evaluated in the ongoing CHOICE I (300 mg Q4W, n=803) and CHOICE II (150 mg Q4W, n=233) trials.<sup>19,20</sup>

## Cost analysis

No published economic analyses on the use of alirocumab were identified.

Both the alirocumab 75 mg/ml and the 150 mg/ml doses cost £168.00 for one single-use pen or syringe, and £336.00 for two ((all prices exclude VAT).<sup>21</sup>

Alirocumab will be an additional treatment option for adults with primary HeFH or non-FH, either alone or in combination with other LMTs including ezetimibe when statins are contraindicated or not tolerated, or in combination with a statin in patients whose condition is not appropriately controlled with maximally tolerated statin therapy.

Accurately estimating the numbers of patients who might be eligible for treatment with alirocumab is difficult. NICE estimates that primary non-FH affects around 4 in 100 of the adult population, and primary HeFH affects around 1 in 500 people. Based on an adult population (≥18 years) of 2.61 million, this equates to approximately 104,400 adults with non-FH, and 5,220 adults with HeFH in the NTAG area.

The costing statement for ezetimibe in the treatment of primary HeFH and non-FH states that almost all of the people with HeFH are likely to require treatment with an LMT, although only around 75% of people with non-FH are likely to require treatment (approximately 78,300 people).<sup>22</sup> Therefore, a total of approximately 83,520 adults could be eligible for treatment with a statin in the NTAG area.

NICE estimate that only around 2% of eligible patients are unable to take statins because of contraindications or intolerance. Therefore approximately 1,670 patients (64 per 100,000 population) could be eligible for treatment with alirocumab or ezetimibe.

Of those patients who are able to tolerate statins, around 30% would be considered for an alternative statin, or alirocumab or ezetimibe. Thus, approximately 24,555 patients (941 per 100,000 population) could be eligible for treatment with a statin in combination with alirocumab.

In January 2014 to 2015, 38% of the patients receiving ezetimibe in the UK were on monotherapy and 62% were co-prescribed with a statin.<sup>23</sup> In the NTAG area in the first quarter of 2015/16 a total of 27,900 items of ezetimibe were prescribed at a cost of around £742,000.

Alirocumab costs £4,360 per patient per year compared to £342.03 for ezetimibe. It is likely that ezetimibe will be the preferred second-line option for the majority of patients in whom a statin is ineffective, not tolerated or contraindicated. However, if patients were to receive alirocumab instead of ezetimibe this would result in an approximate incremental cost of £4,018 per patient per year. In some patients alirocumab may be used in addition to ezetimibe plus statins, and therefore the costs would be additive. There may be additional costs incurred with alirocumab to either administer each dose or provide suitable training for patients to self-administer.

Alirocumab will compete directly with the other recently launched PCSK9 antibody evolocumab (Repatha<sup>®</sup>▼, Amgen).<sup>24</sup> The incremental cost of prescribing evolocumab second-line instead of ezetimibe would be between £4,081 (140 mg QW2) and £5,782 (420 mg QW4) per patient per year.

## Points to consider

Alirocumab, a monoclonal antibody, is one of a new class of LMTs that inhibit the selectively inhibits PCSK9. It is intended for the long-term treatment of adults with primary hypercholesterolaemia (HeFH or non-FH) or mixed dyslipidaemia.

Across ten phase 3 trials (n=5,296 patients) evaluating patients with HeFH and non-FH at high and moderate CV risk, alirocumab demonstrated a substantial reduction in the primary endpoint of LDL-C reduction after 24 weeks. On top of standard care (maximally tolerated statin +/- other LMTs), a reduction of 39% to 62% compared to placebo was observed. Compared with ezetimibe, a reduction of 30% was found on top of standard care, 24% to 36% on less than maximal statins, and 30% to 32% without statin background therapy. The primary endpoint analyses were supported by consistent changes in the secondary lipid profile endpoints across all studies.

The safety profile of alirocumab was comparable to that of the control groups (placebo or ezetimibe). The most common TEAEs were nasopharyngitis, injection site reaction, upper respiratory tract infection, influenza, headache, myalgia, and arthralgia. The number of patients discontinuing treatment or experiencing SAEs was low. None of the safety concerns commonly associated with other LMTs, such as liver disorders, renal disorders, diabetes and musculoskeletal disorders, was evident with alirocumab treatment. However, the long-term safety of alirocumab remains to be established.

The effect of alirocumab on cardiovascular morbidity and mortality has not been established. None of the trials completed to date had mortality associated with CV events as a pre-specified primary outcome. From the limited data available, no clear signs of a detrimental effect on CV morbidity or mortality could be identified, although there were too few events to evaluate this outcome with any certainty. The ongoing OUTCOMES trial is evaluating the effect of alirocumab on the occurrence of MACE in ~18,000 patients with ACS, but the results are unlikely to be available before 2018.

Alirocumab is relatively expensive at £4,360 per patient per year compared to £342 for ezetimibe. If alirocumab was used instead of ezetimibe the incremental cost would be £4,018 per patient per year. In some patients alirocumab may be used in addition to ezetimibe, and therefore the costs would be additive. The incremental cost of prescribing the other available PCSK9 inhibitor evolocumab instead of ezetimibe would be between £4,081 and £5,782 per patient per year.

Alirocumab represents an additional treatment option for adults with primary HeFH or non-FH with high CV risk who do not adequately respond to maximally tolerated statin therapy, or who cannot be given statins. Unlike statins or ezetimibe, alirocumab must be administered subcutaneously once every two weeks, which may limited it use, but it may be suitable for self-administration.

Alirocumab will compete directly with evolocumab. There are no direct head-to-head data comparing the two drugs. However, the evidence base suggests that both drugs lead to superior reductions in LDL-C levels compared to placebo or ezetimibe. Evolocumab appears to result in slightly greater LDL-C reductions than alirocumab, but variances in the underlying populations studied may explain these relatively small differences. The overall safety profile of the two drugs appears to be comparable. Unlike evolocumab, up-titration with alirocumab provides the ability to tailor therapy to suit individual patient needs.

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## Appendix 1. Summary of completed or ongoing Phase 3 trials with primary (first-step analysis) double-blind treatment period completed.

Trial	Study design	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Duration of study	Outcome measures and effect size (ITT population)	Additional comments
<b>FH I</b>  <b>(completed)<sup>10</sup></b>  <a href="#">NCT01623115</a>	Randomised, double-blind, placebo-controlled, parallel group study.	<p><b>Inclusion</b></p> <p>Adults aged &gt; ≥18 years with HeFH not adequately controlled on stable maximally-tolerated daily dose of statin for ≥4 weeks prior to screening, with or without other LMT.</p> <p>(LDL-C ≥70 mg/dL (1.81 mmol/L) with CVD, or LDL-C ≥100 mg/dL (2.59 mmol/L) without CVD)</p> <p><b>Exclusion</b></p> <p>History of HoFH, fasting serum triglycerides ≥400 mg/dL (4.52 mmol/L), currently taking statins other than atorvastatin (max 80 mg), rosuvastatin (40 mg) or simvastatin (40 mg), except for patients on 80 mg for &gt;1 year, who are eligible).</p>	<p>n=486</p> <p>HeFH; 100%</p> <p>Non-FH: 0%</p> <p>Male: 56%</p> <p>Mean age: 52 years</p> <p>Weight (Kg): 85</p> <p>BMI (Kg/m<sup>2</sup>): 29</p> <p>Any CV history/risk factors: 51%</p> <p>CHD: 46%</p> <p>CHD risk equivalents: 16%</p> <p>Categorisation of CV risk per protocol:</p> <p>Very high 51%</p> <p>High 49%</p> <p>Moderate 0%</p> <p>Hypertension: 43%</p> <p>T1DM: 0%</p> <p>T2DM: 12%</p> <p>Family history of premature CHD: 45%</p> <p>Current smoker: 12%</p> <p>Statin use at baseline 83%</p> <p>Calculated mean LDL-C: 145 mg/dL (3.7 mmol/L)</p>	<p>Alirocumab 75 mg SC Q2W with possible up-titration at week 12 to 150 mg SC Q2W (n=322)</p> <p>Placebo SC Q2W (n=163)</p>	78 week randomized treatment period, and 8 week follow-up period, or entry in to open-label extension study.	<p><b>Primary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 24 (± SE)</b></p> <p>Alirocumab: -48.8% (± 1.6)</p> <p>Placebo: 9.1% (± 2.2)</p> <p>Difference alirocumab vs. placebo -57.9% (± 2.7 [95% CI -63.3 to -52.6]); p&lt;0.0001</p> <p><b>Secondary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 52</b></p> <p>Difference vs. placebo -56%; p&lt;0.0001</p> <p><b>Mean change from baseline vs placebo at week 24;</b></p> <p><b>Measured LDL-C:</b> -50%, p&lt;0.0001</p> <p><b>Total-C:</b> -39%, p&lt;0.0001</p> <p><b>Apo B:</b> -46%, p&lt;0.0001</p> <p><b>Non-HDL-C:</b> -52%, p&lt;0.0001</p> <p><b>Lp (a):</b> -18%, p&lt;0.0001</p> <p><b>Fasting TG:</b> -16%, p&lt;0.0001</p> <p><b>HDL-C:</b> 8.0%, p&lt;0.0001</p> <p><b>Apo-A1:</b> 4.7%, p=0.0002</p>	During the study, two sites were found to have good clinical practice (GCP) issues, and a sensitivity analysis was performed excluding patients from these sites. Excluding these patients the difference vs. placebo of -58.6 (95% CI -63.7, -53.5).

Trial	Study design	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Duration of study	Outcome measures and effect size (ITT population)	Additional comments
<b>FH II</b> <b>(completed)<sup>10</sup></b> <a href="#">NCT01709500</a>	Randomised, double-blind, placebo-controlled, parallel group study.	<p><b>Inclusion</b></p> <p>Adults aged ≥18 years with HeFH not adequately controlled on stable maximally-tolerated daily dose of statin for ≥4 weeks prior to screening, with or without other LMT.</p> <p>(LDL-C ≥70 mg/dL (1.81 mmol/L) with CVD, or LDL-C ≥100 mg/dL (2.59 mmol/L) without CVD)</p> <p><b>Exclusion</b></p> <p>History of HoFH, fasting serum triglycerides ≥400 mg/dL (4.52 mmol/L), currently taking statins other than atorvastatin (max 80 mg), rosuvastatin (40 mg) or simvastatin (40 mg), except for patients on 80 mg for &gt;1 year, who are eligible).</p>	<p>n=249</p> <p>HeFH; 100%</p> <p>Non-FH: 0%</p> <p>Male: 53%</p> <p>Mean age: 52 years</p> <p>Weight (Kg): 85</p> <p>BMI (Kg/m<sup>2</sup>): 28</p> <p>Any CV history/risk factors: 39%</p> <p>CHD: 35%</p> <p>CHD risk equivalents: 8%</p> <p>Categorisation of CV risk per protocol:</p> <p>Very high 39%</p> <p>High 61%</p> <p>Moderate 0%</p> <p>Hypertension: 33%</p> <p>T1DM: 0.4%</p> <p>T2DM: 4%</p> <p>Family history of premature CHD: 49%</p> <p>Current smoker: 20%</p> <p>Statin use at baseline 88%</p> <p>Calculated mean LDL-C: 134 mg/dL (3.5 mmol/L)</p>	<p>Alirocumab 75 mg SC Q2W with possible up-titration at week 12 to 150 mg SC Q2W (n=167)</p> <p>Placebo SC Q2W (n=82)</p>	78 week randomized treatment period, and 8 week follow-up period, or entry in to open-label extension study.	<p><b>Primary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 24 (± SE)</b></p> <p>Alirocumab: -48.7% (± 1.9)</p> <p>Placebo: 2.8% (± 2.8)</p> <p>Difference alirocumab vs. placebo -51.4% (± 3.4 [95% CI -58.1 to -44.8]); p&lt;0.0001</p> <p><b>Secondary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 52</b></p> <p>Difference vs. placebo -50%; p&lt;0.0001</p> <p><b>Mean change from baseline vs placebo at week 24;</b></p> <p><b>Measured LDL-C:</b> -50%, p&lt;0.0001</p> <p><b>Total-C:</b> -33%, p&lt;0.0001</p> <p><b>Apo B:</b> -39%, p&lt;0.0001</p> <p><b>Non-HDL-C:</b> -46%, p&lt;0.0001</p> <p><b>Lp (a):</b> -20%, p&lt;0.0001</p> <p><b>Fasting TG:</b> -11%, p=0.0012</p> <p><b>HDL-C:</b> 6.8%, p=0.0009</p> <p><b>Apo-A1:</b> 4.4%, p=0.0062</p>	FH II had the same HeFH population and study design as FH I.

Trial	Study design	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Duration of study	Outcome measures and effect size (ITT population)	Additional comments
<p><b>HIGH-FH</b></p> <p><b>(completed)</b></p> <p><a href="#">NCT01617655</a></p>	Randomised, double-blind, placebo-controlled, parallel group study.	<p><b>Inclusion</b></p> <p>Adults aged <math>\geq 18</math> years with HeFH and LDL-C level of <math>\geq 160</math> mg/dL (4.14 mmol/L) despite stable maximally-tolerated daily dose of statin for <math>\geq 4</math> weeks prior to screening, with or without other LMT.</p> <p><b>Exclusion</b></p> <p>History of HoFH, fasting serum triglycerides <math>\geq 400</math> mg/dL (4.52 mmol/L), currently taking statins other than atorvastatin (max 80 mg), rosuvastatin (40 mg) or simvastatin (40 mg), except for patients on 80 mg for <math>&gt;1</math> year, who are eligible).</p>	<p>n=107</p> <p>HeFH; 100%</p> <p>Non-FH: 0%</p> <p>Male: 55%</p> <p>Mean age: 51 years</p> <p>Weight (Kg): 83</p> <p>BMI (Kg/m<sup>2</sup>): 29</p> <p>Any CV history/risk factors: 57%</p> <p>CHD: 50%</p> <p>CHD risk equivalents: 17%</p> <p>Categorisation of CV risk per protocol:</p> <p>Very high 57%</p> <p>High 43%</p> <p>Moderate 0%</p> <p>Hypertension: 57%</p> <p>T1DM: 0%</p> <p>T2DM: 14%</p> <p>Family history of premature CHD: 57%</p> <p>Current smoker: 20%</p> <p>Statin use at baseline 79%</p> <p>Calculated mean LDL-C: 198 mg/dL (5.1 mmol/L)</p>	<p>Alirocumab 150 mg SC Q2W (n=72)</p> <p>Placebo SC Q2W (n=35)</p>	78 week randomized treatment period, and 8 week follow-up period, or entry in to open-label extension study.	<p><b>Primary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 24 (<math>\pm</math> SE)</b></p> <p>Alirocumab: -45.7% (<math>\pm</math> 3.5)</p> <p>Placebo: -6.6% (<math>\pm</math> 4.9)</p> <p>Difference alirocumab vs. placebo -39.1% (<math>\pm</math> 6.0 [95% CI -51.1 to -27.1]); p&lt;0.0001</p> <p><b>Secondary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 52</b></p> <p>Difference vs. placebo -39%; p&lt;0.0001</p> <p><b>Mean change from baseline vs placebo at week 24;</b></p> <p><b>Measured LDL-C:</b> n/a</p> <p><b>Total-C:</b> -28%, p&lt;0.0001</p> <p><b>Apo B:</b> -30%, p&lt;0.0001</p> <p><b>Non-HDL-C:</b> -36%, p&lt;0.0001</p> <p><b>Lp (a):</b> -15%, p=0.0164</p> <p><b>Fasting TG:</b> -9%, p=0.1386</p> <p><b>HDL-C:</b> 3.6%, p=0.2745</p> <p><b>Apo-A1:</b> 3.6%, p=0.1715</p>	<p>Patients were continued on 150 mg alirocumab dose for the duration of the study</p> <p>Note that the percent LDL-C change from baseline was similar in this trial as compared to FH I and FH II, despite initiating therapy with a higher dose.</p> <p>During the study, two sites were found to have good clinical practice (GCP) issues, and a sensitivity analysis was performed excluding patients from these sites. Excluding these patients the difference vs. placebo was -48.0% (<math>\pm</math> 5.0); p&lt;0.0001</p>

Trial	Study design	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Duration of study	Outcome measures and effect size (ITT population)	Additional comments
<p><b>LONG-TERM (completed)</b><sup>11</sup></p> <p><a href="https://www.clinicaltrials.gov/ct2/show/study/NCT01507831">NCT01507831</a></p>	<p>Randomised, double-blind, placebo-controlled study.</p>	<p><b>Inclusion</b></p> <p>Adults aged ≥18 years with HeFH with or without established CHD or CHD risk equivalents, <u>or</u> with hypercholesterolaemia and established CHD or CHD risk equivalents - not adequately controlled on stable maximally-tolerated daily dose of statin for ≥4 weeks prior to screening, with or without other LMT. (LDL-C ≥70 mg/dL (1.81 mmol/L))</p> <p><b>Exclusion</b></p> <p>History of HoFH, fasting serum triglycerides ≥400 mg/dL (4.52 mmol/L), currently taking statins other than atorvastatin (max 80 mg), rosuvastatin (40 mg) or simvastatin (40 mg), except for patients on 80 mg for &gt;1 year, who are eligible).</p>	<p>n=2,341</p> <p>HeFH; 18%</p> <p>Non-FH: 82%</p> <p>Male: 62%</p> <p>Mean age: 61 years</p> <p>Weight (Kg): 87</p> <p>BMI (Kg/m<sup>2</sup>): 30</p> <p>Any CV history/risk factors: 91%</p> <p>CHD: 69%</p> <p>CHD risk equivalents: 41%</p> <p>Categorisation of CV risk per protocol:</p> <p>Very high 92%</p> <p>High 9%</p> <p>Moderate 0%</p> <p>Hypertension: 75%</p> <p>T1DM: 1%</p> <p>T2DM: 35%</p> <p>Family history of premature CHD: 33%</p> <p>Current smoker: 21%</p> <p>Statin use at baseline 47%</p> <p>Calculated mean LDL-C: 122 mg/dL (3.2 mmol/L)</p>	<p>Alirocumab 150 mg SC Q2W (n=1,553)</p> <p>Placebo SC Q2W (n=788)</p>	<p>78 week randomized treatment period, and 8 week follow-up period, or entry in to open-label extension study.</p>	<p><b>Primary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 24 (± SE)</b></p> <p>Alirocumab: -61.0% (± 0.7)</p> <p>Placebo: 0.8% (± 1.0)</p> <p>Difference alicrocumab vs. placebo -61.9% (± 1.3 [95% CI -64.3 to -59.4]); p&lt;0.001</p> <p><b>Secondary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 52</b></p> <p>Difference vs. placebo -61%; p&lt;0.0001</p> <p><b>Change in calculated LDL-C from baseline to week 78</b></p> <p>Difference vs. placebo -62%; p&lt;0.0001</p> <p><b>Mean change from baseline vs placebo at week 24;</b></p> <p><b>Measured LDL-C:</b> -61%, p&lt;0.0001</p> <p><b>Total-C:</b> -38%, p&lt;0.0001</p> <p><b>Apo B:</b> -54%, p&lt;0.0001</p> <p><b>Non-HDL-C:</b> -52%, p&lt;0.0001</p> <p><b>Lp (a):</b> -26%, p&lt;0.0001</p> <p><b>Fasting TG:</b> -17%, p&lt;0.0001</p> <p><b>HDL-C:</b> 4.6%, p&lt;0.0001</p> <p><b>Apo-A1:</b> 2.8%, p&lt;0.0001</p>	<p>Patients were continued on 150 mg alicrocumab dose for the duration of the study.</p> <p>Alirocumab was administered using a prefilled syringe, whereas in all the other PIII studies alicrocumab was administered using a prefilled pen.</p> <p>Although the follow-up period was longer than for most other trials of alicrocumab, the duration of follow-up is still relatively short for a treatment intended for long-term use.</p> <p>There was a greater reduction in LDL-C with alicrocumab versus placebo in trial than in other placebo-controlled trials.</p> <p>A <i>post hoc</i> sub-group analysis showed that the difference between alicrocumab and placebo groups in the primary outcome at week 24 was similar in patients with HeFH and those without it.</p>

Trial	Study design	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Duration of study	Outcome measures and effect size (ITT population)	Additional comments
<b>COMBO I</b> <b>(completed)</b> <sup>12</sup> <a href="https://www.clinicaltrials.gov/ct2/show/study/NCT01644175">NCT01644175</a>	Randomised, double-blind, placebo-controlled, parallel group study.	<p><b>Inclusion</b></p> Adults aged ≥18 years with hypercholesterolaemia and established CHD or CHD risk equivalents - not adequately controlled on stable maximally-tolerated daily dose of statin for ≥4 weeks prior to screening, with or without other LMT. (LDL-C ≥70 mg/dL (1.81 mmol/L) with CVD, or LDL-C ≥100 mg/dL (2.59 mmol/L) without CVD) <p><b>Exclusion</b></p> Fasting serum triglycerides ≥400 mg/dL (4.52 mmol/L), currently taking statins other than atorvastatin (max 80 mg), rosuvastatin (40 mg) or simvastatin (40 mg), except for patients on 80 mg for >1 year, who are eligible).	n=316 HeFH; 0% Non-FH: 100% Male: 66% Mean age: 63 years Weight (Kg): 95 BMI (Kg/m <sup>2</sup> ): 32 Any CV history/risk factors: 99% CHD: 78% CHD risk equivalents: 43% Categorisation of CV risk per protocol: Very high 100% High 0% Moderate 0% Hypertension: 89% T1DM: 0% T2DM: 43% Family history of premature CHD: 35% Current smoker: 19% Statin use at baseline 63% Calculated mean LDL-C: 102 mg/dL (2.6 mmol/L)	Alirocumab 75 mg SC Q2W with possible up-titration at week 12 to 150 mg SC Q2W (n=209)  Placebo SC Q2W (n=107)	52 week randomized treatment period, and 8 week follow-up period	<p><b>Primary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 24 (± SE)</b>            Alirocumab: -48.2% (± 1.9)            Placebo: -2.3% (± 2.7)            Difference alirocumab vs. placebo -45.9% (± 1.3 [95% CI -52.5 to -39.3]); p&lt;0.0001</p> <p><b>Secondary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 52</b>            Difference vs. placebo -43%; p&lt;0.0001</p> <p><b>Mean change from baseline vs placebo at week 24;</b></p> <p><b>Measured LDL-C:</b> -46%, p&lt;0.0001  <b>Total-C:</b> -25%, p&lt;0.0001  <b>Apo B:</b> -36%, p&lt;0.0001  <b>Non-HDL-C:</b> -38%, p&lt;0.0001  <b>Lp (a):</b> -15%, p&lt;0.0001  <b>Fasting TG:</b> -0.6%, p=0.8699  <b>HDL-C:</b> 7.3%, p&lt;0.0001  <b>Apo-A1:</b> 5.8%, p=0.0002</p>	A sensitivity analysis that excluded one site with serious GCP non-compliance resulted in a difference vs. placebo of -45.8 (95% CI -52.4, -39.2) in the primary outcome.

Trial	Study design	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Duration of study	Outcome measures and effect size (ITT population)	Additional comments
<p><b>COMBO II</b> (on-going)<sup>13</sup> <a href="https://www.clinicaltrials.gov/ct2/show/study/NCT01644188">NCT01644188</a></p>	<p>Randomised, double-blind, double-dummy, active-controlled, parallel group study.</p>	<p><b>Inclusion</b> Adults aged ≥18 years with hypercholesterolaemia and established CHD or CHD risk equivalents - not adequately controlled on stable maximally-tolerated daily dose of statin for ≥4 weeks prior to screening, without other LMT. (LDL-C ≥70 mg/dL (1.81 mmol/L) with CVD, or LDL-C ≥100 mg/dL (2.59 mmol/L) without CVD)</p> <p><b>Exclusion</b> Fasting serum triglycerides ≥400 mg/dL (4.52 mmol/L), currently taking statins other than atorvastatin (max 80 mg), rosuvastatin (40 mg) or simvastatin (40 mg), except for patients on 80 mg for &gt;1 year, who are eligible).</p>	<p>n=720 HeFH; 0% Non-FH: 100% Male: 74% Mean age: 62 years Weight (Kg): 89 BMI (Kg/m<sup>2</sup>): 30 Any CV history/risk factors: 100% CHD: 90% CHD risk equivalents: 31% Categorisation of CV risk per protocol: Very high 100% High 0% Moderate 0% Hypertension: 81% T1DM: 0.3% T2DM: 31% Family history of premature CHD: 21% Current smoker: 22% Statin use at baseline 69% Calculated mean LDL-C: 107 mg/dL (2.8 mmol/L)</p>	<p>Alirocumab 75 mg SC Q2W - with possible up-titration at week 12 to 150 mg SC Q2W + oral placebo (n=479)</p> <p>Ezetimibe 10 mg PO + SC placebo (n=241)</p>	<p>104 week randomized treatment period, and 8 week follow-up period.</p>	<p><b>Primary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 24 (± SE)</b> Alirocumab: -50.6% (± 1.4) Ezetimibe: -20.7% (± 1.9) Difference alicrocumab vs. ezetimibe -29.8% (± 2.3 [95% CI -34.4 to -25.3]); p&lt;0.0001</p> <p><b>Secondary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 52</b> Difference vs. ezetimibe -31%; p&lt;0.0001</p> <p><b>Mean change from baseline vs ezetimibe at week 24;</b></p> <p><b>Measured LDL-C:</b> -30%, p&lt;0.0001 <b>Total-C:</b> -15%, p&lt;0.0001 <b>Apo B:</b> -22%, p&lt;0.0001 <b>Non-HDL-C:</b> -23%, p&lt;0.0001 <b>Lp (a):</b> -22%, p&lt;0.0001 <b>Fasting TG:</b> -0.3%, p=0.9117 <b>HDL-C:</b> 8.1%, p&lt;0.0001 <b>Apo-A1:</b> 6.3%, p&lt;0.0001</p>	<p>This was the only trial to compare alicrocumab with ezetimibe in patients who were receiving background statin therapy at the maximally tolerated dose, without any other LMT.</p> <p>At baseline 17 (2.4%) patients were taking LMTs other than dietary supplements.</p>

Trial	Study design	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Duration of study	Outcome measures and effect size (ITT population)	Additional comments
<b>OPTIONS I</b> <b>(completed)</b> <sup>14</sup> <a href="#">NCT01730040</a>	Randomised, double-blind, double-dummy, active-controlled, parallel group study.	<p><b>Inclusion</b></p> <p>Adults aged ≥18 years with hypercholesterolaemia and established CHD or CHD risk equivalents <u>or</u> with HeFH with or without high CV risk - not adequately controlled on atorvastatin 20 mg or 40 mg with or without other LMT for ≥4 weeks prior to screening. (LDL-C ≥70 mg/dL (1.81 mmol/L) with CVD, or LDL-C ≥100 mg/dL (2.59 mmol/L) without CVD)</p> <p><b>Exclusion</b></p> <p>History of HoFH, LDL-C ≥250 mg/dL, fasting serum triglycerides ≥400 mg/dL (4.52 mmol/L), currently taking statins other than atorvastatin, currently taking ezetimibe.</p>	<p>n=355</p> <p>HeFH; 9%</p> <p>Non-FH: 91%</p> <p>Male: 65%</p> <p>Mean age: 63 years</p> <p>Weight (Kg): 90</p> <p>BMI (Kg/m<sup>2</sup>): 31</p> <p>Any CV history/risk factors: 100%</p> <p>CHD: 56%</p> <p>CHD risk equivalents: 28%</p> <p>Categorisation of CV risk per protocol:</p> <p>Very high 60%</p> <p>High 40%</p> <p>Moderate 0%</p> <p>Hypertension: 78%</p> <p>T1DM: 0.3%</p> <p>T2DM: 31%</p> <p>Family history of premature CHD: 24%</p> <p>Current smoker: 19%</p> <p>Statin use at baseline 100%</p> <p>Calculated mean LDL-C: 105 mg/dL (2.7 mmol/L)</p>	<p><u>Baseline atorvastatin 20 mg</u></p> <p>Alirocumab 75/150 mg SC Q2W + atorvastatin 20 mg (n=57)</p> <p>Ezetimibe 10 mg + atorvastatin 20 mg (n=55)</p> <p>Atorvastatin 40 mg (n=57)</p> <p><u>Baseline atorvastatin 40 mg</u></p> <p>Alirocumab 75/150 mg SC Q2W + atorvastatin 40 mg (n=47)</p> <p>Ezetimibe 10 mg PO + atorvastatin 40 mg (n=47)</p> <p>Atorvastatin 80 mg PO (n=47)</p> <p>Rosuvastatin 40 mg PO (n=45)</p>	24 week randomized treatment period, and 8 week follow-up period.	<p><b>Primary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 24 (± SE)</b></p> <p><u>Baseline atorvastatin 20 mg</u></p> <p>Alirocumab + ATV: -44.1 (±4.5)</p> <p>Ezetimibe + ATV mg: -20.5 (±4.7)</p> <p>Atorvastatin 40 mg: -5.0 (±4.6)</p> <p>Alirocumab vs. ezetimibe -23.6% (±6.6 [95% CI -40.7 to -6.5]); p=0.0004</p> <p>Alirocumab vs. atorvastatin 40 mg -39.1% (±6.4 [95% CI -55.9 to -22.2]); p&lt;0.0001</p> <p><u>Baseline atorvastatin 40 mg</u></p> <p>Alirocumab + ATV: -54.0 (±4.3)</p> <p>Ezetimibe + ATV: -22.6 (±4.3)</p> <p>Atorvastatin 80 mg: -4.8 (±4.2)</p> <p>Rosuvastatin 40 mg: -21.4 (±4.2)</p> <p>Alirocumab vs. ezetimibe -31.4% (±6.1 [95% CI -47.7 to -15.4]); p&lt;0.0001</p> <p>Alirocumab vs. atorvastatin 80 mg -49.2% (±6.1 [95% CI -65.0 to -33.5]); p&lt;0.0001</p> <p>Alirocumab vs. rosuvastatin 40 mg -32.6% (±6.0 [95% CI -48.4 to -16.9]); p&lt;0.0001</p>	<p>The relevance of this study is uncertain as included patients were not on maximum tolerated doses of statins.</p> <p>In the baseline atorvastatin 20 mg arms -a sensitivity analysis that excluded one site with serious GCP non-compliance resulted in a difference of -23.6 (95% CI -36.6, -10.6) versus ezetimibe and -39.1 (95% CI -51.8, -26.3) versus atorvastatin up-titration.</p> <p>In the baseline atorvastatin 40 mg arms - the sensitivity analysis resulted in a difference of -33.7 (95% CI -45.9, -21.5) versus ezetimibe, -33.7 (95% CI -45.8, -21.6) versus rosuvastatin 40 mg, and -51.3 (95% CI -63.4, -39.1) versus atorvastatin up-titration.</p>

Trial	Study design	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Duration of study	Outcome measures and effect size (ITT population)	Additional comments
<p><b>OPTIONS II</b> <b>(completed)</b> <a href="https://clinicaltrials.gov/ct2/show/study/NCT01730053">NCT01730053</a></p>	<p>Randomised, double-blind, double-dummy, active-controlled, parallel group study.</p>	<p><b>Inclusion</b> Adults aged ≥18 years with hypercholesterolaemia and established CHD or CHD risk equivalents <u>or</u> with HeFH with or without high CV risk - not adequately controlled on rosuvastatin 10 mg or 20 mg with or without other LMT for ≥4 weeks prior to screening. (LDL-C ≥70 mg/dL (1.81 mmol/L) with CVD, or LDL-C ≥100 mg/dL (2.59 mmol/L) without CVD)</p> <p><b>Exclusion</b> History of HoFH, LDL-C ≥250 mg/dL, fasting serum triglycerides ≥400 mg/dL (4.52 mmol/L), currently taking statins other than atorvastatin, currently taking ezetimibe.</p>	<p>n=305 HeFH; 13% Non-FH: 87% Male: 61% Mean age: 61 years Weight (Kg): 89 BMI (Kg/m2): 31 Any CV history/risk factors: 100% CHD: 58% CHD risk equivalents: 26% Categorisation of CV risk per protocol: Very high 63% High 37% Moderate 0% Hypertension: 73% T1DM: 0.7% T2DM: 41% Family history of premature CHD: 30% Current smoker: 18% Statin use at baseline 100% Calculated mean LDL-C: 111 mg/dL (2.9 mmol/L)</p>	<p><u>Baseline rosuvastatin 10 mg</u></p> <p>Alirocumab 75/150 mg SC Q2W + rosuvastatin 10 mg (n=48)</p> <p>Ezetimibe 10 mg + rosuvastatin 10 mg (n=47)</p> <p>Rosuvastatin 20 mg (n=48)</p> <p><u>Baseline rosuvastatin 20 mg</u></p> <p>Alirocumab 75/150 mg SC Q2W + rosuvastatin 20 mg (n=53)</p> <p>Ezetimibe 10 mg PO + rosuvastatin 20 mg (n=50)</p> <p>Rosuvastatin 40 mg PO (n=52)</p>	<p>24 week randomized treatment period, and 8 week follow-up period.</p>	<p><b>Primary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 24 (± SE)</b></p> <p><u>Baseline rosuvastatin 10 mg</u> Alirocumab + ATV: -50.6 (±4.2) Ezetimibe + ATV mg: -14.4 (±4.4) Rosuvastatin 20 mg: -16.3 (±4.1)</p> <p>Alirocumab vs. ezetimibe -36.1% (±6.1 [95% CI -51.5 to -20.7]); p&lt;0.0001</p> <p>Alirocumab vs. rosuvastatin 40 mg -34.2% (±5.9 [95% CI -49.2 to -19.3]); p&lt;0.0001</p> <p><u>Baseline rosuvastatin 20 mg</u> Alirocumab + ATV: -36.3 (±7.1) Ezetimibe + ATV mg: -11.0 (±7.2) Rosuvastatin 40 mg: -15.9 (±7.1)</p> <p>Alirocumab vs. ezetimibe -25.3% (±10.1 [95% CI -50.9 to 0.3]); p=0.0136</p> <p>Alirocumab vs. rosuvastatin 40 mg -20.3% (±10.1 [95% CI -45.8 to 5.1]); p=0.0453</p>	<p>The relevance of this study is uncertain as included patients were not on maximum tolerated doses of statins.</p> <p>In the baseline rosuvastatin 10 mg arms -a sensitivity analysis that excluded the site with serious GCP non-compliance resulted in a difference of (-36.1 (95% CI -48.1, -24.1) versus ezetimibe, and -34.2 (95% CI -45.9, -22.5) versus rosuvastatin up-titration).</p> <p>In the baseline rosuvastatin 20 mg arms - the sensitivity analysis resulted in a difference of -27.6 (95% CI -48.2, -7.0) versus ezetimibe and -23.4 (95% CI -43.9, -3.0) versus rosuvastatin up-titration.</p>

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<p><b>ALTERNATIVE</b></p> <p><b>(on-going)</b></p> <p><a href="#">NCT01709513</a></p>	<p>Randomised, double-blind, double-dummy, active-controlled, parallel group study.</p>	<p><b>Inclusion</b></p> <p>Adults aged ≥18 years with hypercholesterolaemia or HeFH with moderate, high or very high CV risk and a history of statin intolerance (inability to tolerate ≥2 different statins due to unexplained muscle-related symptoms – one statin had to have been at the lowest approved starting dose)- receiving a stable dose of LMT for ≥4 weeks prior to screening.</p> <p>(LDL-C ≥70 mg/dL (1.81 mmol/L) with very high CV risk, or LDL-C ≥100 mg/dL (2.59 mmol/L) with high- or moderate CV risk.</p> <p><b>Exclusion</b></p> <p>10-year risk of fatal CV events (SCORE risk) &lt;1% at screening, use statin above lowest approved dose, or skeletal muscle-related AE(s), within 4 weeks prior to screening, use of fibrates, other than fenofibrate, within 6 weeks</p>	<p>n=314</p> <p>HeFH; 15%</p> <p>Non-FH: 85%</p> <p>Male: 55%</p> <p>Mean age: 63 years</p> <p>Weight (Kg): 84</p> <p>BMI (Kg/m<sup>2</sup>): 29</p> <p>Any CV history/risk factors: 100%</p> <p>CHD: 47%</p> <p>CHD risk equivalents: 23%</p> <p>Categorisation of CV risk per protocol:</p> <p>Very high 54%</p> <p>High 28%</p> <p>Moderate 14%</p> <p>Hypertension: 62%</p> <p>T1DM: 0%</p> <p>T2DM: 24%</p> <p>Family history of premature CHD: 36%</p> <p>Current smoker: 7%</p> <p>Statin use at baseline 5%</p> <p>Calculated mean LDL-C: 191 mg/dL (5.0 mmol/L)</p>	<p>Alirocumab 75 mg SC Q2W plus oral placebo - with possible up-titration at week 12 to 150 mg SC Q2W (n=125)</p> <p>Ezetimibe 10 mg PO daily plus SC placebo (n=126)</p> <p>Atorvastatin 20 mg PO daily plus SC placebo (n=63)</p>	<p>24 week randomized treatment period, and 8 week follow-up period, or entry in to open-label extension study</p>	<p><b>Primary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 24 (± SE)</b></p> <p>Alirocumab: -45.0% (± 2.2)</p> <p>Ezetimibe: -14.6% (± 2.2)</p> <p>Difference alirocumab vs. ezetimibe -30.4% [95% CI -36.6 to -24.2]; p&lt;0.0001</p> <p><b>Secondary outcomes</b></p> <p>Mean change from baseline vs ezetimibe at week 24;</p> <p><b>Measured LDL-C:</b> -33%, p&lt;0.0001</p> <p><b>Total-C:</b> -21%, p&lt;0.0001</p> <p><b>Apo B:</b> -25%, p&lt;0.0001</p> <p><b>Non-HDL-C:</b> -26%, p&lt;0.0001</p> <p><b>Lp (a):</b> -19%, p&lt;0.0001</p> <p><b>Fasting TG:</b> -6%, p=0.1426</p> <p><b>HDL-C:</b> 0.9%, p=0.6997</p> <p><b>Apo-A1:</b> 1.9%, p=0.2768</p>	<p>Patients reporting muscle symptoms during run-in were not randomized as these were assumed to be non-statin-related.</p> <p>The atorvastatin 20 mg rechallenge arm was included to validate the definition of statin intolerance used for patients' eligibility.</p> <p>However, 70% of the supposedly 'statin-intolerant' patients who received atorvastatin completed the 24 week double-blind phase of the trial, suggesting that a majority of these were able to tolerate statins, for at least the duration of this study.</p> <p>A sensitivity analysis that excluded the site with serious GCP non-compliance resulted in a difference vs. ezetimibe of -30.7% (95% CI -36.9, -24.6) in the primary outcome.</p>

Trial	Study design	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Duration of study	Outcome measures and effect size (ITT population)	Additional comments
<p><b>MONO</b></p> <p><b>(completed)</b> 15,16</p> <p><a href="#">NCT01644474</a></p>	Randomised, double-blind, double-dummy, active-controlled, parallel group study.	<p><b>Inclusion</b></p> <p>Adults aged ≥18 years with hypercholesterolaemia and moderate CV risk (10-yr risk of fatal CVD of ≥ 1% and &lt; 5%) not receiving a statin or any other LMT</p> <p>(LDL-C between 100 mg/dL (2.59 mmol/L and 190 mg/dL (4.9 mmol/L)</p> <p><b>Exclusion</b></p> <p>History of HoFH, HeFH or established CHD, DM associated with a risk SCORE ≥5% or any additional risk factor, fasting serum triglycerides ≥400 mg/dL (4.52 mmol/L).</p>	<p>n=103</p> <p>HeFH: 0%</p> <p>Non-FH: 100%</p> <p>Male: 53%</p> <p>Mean age: 60 years</p> <p>Weight (Kg): 86</p> <p>BMI (Kg/m2): 29</p> <p>Any CV history/risk factors: 99%</p> <p>CHD: 0%</p> <p>CHD risk equivalents: 0%</p> <p>Categorisation of CV risk per protocol:</p> <p>Very high 0%</p> <p>High 0%</p> <p>Moderate 100%</p> <p>Hypertension: 31%</p> <p>T1DM: 0%</p> <p>T2DM: 4%</p> <p>Family history of premature CHD: 4%</p> <p>Current smoker: 11%</p> <p>Statin use at baseline 0%</p> <p>Calculated mean LDL-C: 140 mg/dL (3.7 mmol/L)</p>	<p>Alirocumab 75 mg SC Q2W plus oral placebo - with possible up-titration at week 12 to 150 mg SC Q2W (n=52)</p> <p>Ezetimibe 10 mg PO daily plus SC placebo (n=51)</p>	24 week randomized treatment period, and 8 week follow-up period, or entry in to open-label extension study	<p><b>Primary outcomes</b></p> <p><b>Change in calculated LDL-C from baseline to week 24 (± SE)</b></p> <p>Alirocumab: -47.2% (± 3.0)</p> <p>Ezetimibe: -15.6% (± 3.1)</p> <p>Difference alicrocumab vs. ezetimibe -31.6% (± 4.3 [95% CI -40.2 to -23.0]); p&lt;0.0001</p> <p><b>Secondary outcomes</b></p> <p>Mean change from baseline vs ezetimibe at week 24;</p> <p><b>Measured LDL-C:</b> n/a</p> <p><b>Total-C:</b> -19%, p&lt;0.0001</p> <p><b>Apo B:</b> -26%, p&lt;0.0001</p> <p><b>Non-HDL-C:</b> -26%, p&lt;0.0001</p> <p><b>Lp (a):</b> -4%, p=0.4013</p> <p><b>Fasting TG:</b> 1%, p=0.1827</p> <p><b>HDL-C:</b> 4.4%, p=0.1116</p> <p><b>Apo-A1:</b> 5.3%, p=0.0371</p>	<p>Only patients whose LDL-C remained ≥100 mg/dL after 8 weeks were to be up-titrated to alicrocumab 150 mg Q2W at week 12 however, there was an administrative error and all patients with LDL-C ≥70 mg/dL were up-titrated at week 12. Of the 14 patients up-titrated, Nevertheless, the week 12 results when all patients in the alicrocumab arm were receiving 75mg Q2W, were similar to the week 24 results. Difference alicrocumab vs. ezetimibe -28.5% (± 4.0 [95% CI -35.7 to -21.2]); p&lt;0.0001</p> <p>This trial may be considered supportive of the of the LDL-C-lowering effect observed in other phase 3 trials, as monotherapy with alicrocumab may not be appropriate in the absence of robust CV outcomes data.</p>