Evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia

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Summary

- Evolocumab (Repatha®▼, Amgen) 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 140 mg every two weeks or 420 mg every month (given as 3 x 140 mg injections within 30 minutes of each other). The two regimens are considered clinically equivalent. Evolocumab 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.

- Several phase three trials have compared evolocumab to placebo and ezetimibe in people with hypercholesterolaemia (heterozygous familial or non-familial) and mixed dyslipidaemia. Evolocumab was given as monotherapy, with statins, with ezetimibe, or with both statins and ezetimibe. One trial compared evolocumab to placebo in patients with heterozygous familial hypercholesterolaemia.

- Evolocumab-treated patients in all trials had greater reductions in baseline LDL-C than those who received placebo or ezetimibe. Reductions were similar for both the bi-weekly and monthly dosing regimens. There was limited evidence of any effect on cardiovascular outcomes.

- The safety profile of evolocumab was comparable to comparators (placebo and ezetimibe). The most common adverse events were nasopharyngitis, upper respiratory tract infection, headache and back pain. There were no differences in the rates of serious adverse events, or events leading to discontinuation.

- There was no difference between evolocumab and comparators in rates of musculoskeletal adverse events, renal or hepatic disorders, or new onset diabetes.

- Evolocumab costs £170.10 for each 140 mg dose, equating to £4,422.60 per patient per year for bi-weekly dosing or £6,123.60 for the monthly regimen. 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.

- Evolocumab 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 statin plus ezetimibe, or who cannot be given statins.

- Evolocumab will compete directly with alirocumab (Praluent®▼, Sanofi) another monoclonal anti-PCSK9 antibody 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.[1-3]

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.[1,2]

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.[1-3]

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.[1-3]

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.[1-5]

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.[1,2,4]

Evolocumab (Repatha[®▼], Amgen Ltd) is a human monoclonal antibody which selectively binds circulating PCSK9, preventing it from binding to low density lipoprotein (LDL) receptors in the liver.[6,7] 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.

Evolocumab is licensed for treatment of adults aged 18 and over 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 lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of the statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Evolocumab is also licensed in combination with other lipid-lowering therapies for adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia.

This document will review the evidence for the use of evolocumab and alirocumab for the treatment of primary hypercholesterolaemia and dyslipidaemia. Treatment for homozygous FH is commissioned by NHS England, and is not covered here.

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.[2,4]

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.[5]

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.[8]

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.[9]

Clinical evidence

The clinical trial programme for evolocumab is extensive, encompassing around 19 phase III trials. This report focuses on the six published reports of seven completed studies, five of which assess the efficacy of evolocumab in patients with primary hypercholesterolaemia and mixed dyslipidaemia.[10-14] The remaining paper reports the results of two studies focusing on evolocumab safety.[15]

Five published trials assess the efficacy of evolocumab for the reduction of LDL-C in various populations. All five had similar designs which were appropriate for the therapeutic setting. All were randomised, double-blind, parallel-group trials with placebo and/or active controls. Most were 12 weeks in length although one, the DESCARTES trial, lasted one year. Inclusion criteria varied somewhat, but all participants were adults with elevated LDL-C. Patient characteristics were generally well balanced at baseline.

Evolocumab was administered either once every two weeks or once monthly. The co-primary endpoints in most trials were change in LDL-C between baseline and 12 weeks, and the change in LDL-C between baseline and weeks 10-12, averaged. This mean value was intended to show information on average LDL-C levels during the evolocumab dosing interval. LDL-C was either calculated using the Friedewald formula (as is common in clinical practice) or measured using a reflexive approach. The reflexive method also uses the Friedewald formula, but where results are below a specified threshold switches to direct quantification using ultracentrifugation.[7] The EMA considered this approach appropriate. Trial designs and results are summarised in Appendix 1. All trials analysed outcomes in all patients who were randomised to a treatment group and received at least one dose of study medication (modified intention-to-treat [mITT], population).

The MENDEL-2 trial (n=614) was a 12 week study which compared the efficacy of evolocumab Q2W and monthly to placebo and ezetimibe.[10] Patients had baseline LDL-C ≥100-190 mg/dL (2.6-4.9 mmol/L) and were not taking any other lipid-lowering medications. The design was intended to eliminate any confounding introduced by statin use or intolerance. Participants were randomised to receive evolocumab Q2W or monthly plus oral placebo, ezetimibe 10 mg plus a bi-weekly or monthly subcutaneous placebo, or both oral and subcutaneous placebo.

The LAPLACE-2 trial (n=2,067) had a similar design, except that evolocumab was given with background statin therapy.[11] Enrolled patients had LDL-C ≥80 mg/dL (2.1 mmol/L) at baseline. Prior to the 12 week study period there was a 4 week lipid stabilisation phase, during which time patients were randomised to receive open-label oral statins at moderate or high intensity. The chosen statins were atorvastatin (10 mg or 80 mg), simvastatin (40 mg) or rosuvastatin (5 mg or 40 mg). Patients were then further randomised to receive placebo or evolocumab. Those in the atorvastatin groups could also be randomised to receive ezetimibe. This design resulted in 24 treatment groups in total (see appendix 1) comparing the effect of evolocumab to placebo and ezetimibe, on a background of the various statins.

The DESCARTES trial (n=901) recruited patients with LDL-C ≥75 mg/dL and assigned them to either diet alone, atorvastatin (10 mg or 80 mg), or both atorvastatin 80 mg and ezetimibe, based on their level or risk at baseline.[12] Patients in each group were

then randomised to receive monthly injections of either evolocumab 420 mg or placebo. At 52 weeks (including an initial 4 week lipid stabilisation phase) the DESCARTES trial is the longest available phase III study of evolocumab efficacy.

The GAUSS-2 trial (n=307) enrolled patients with an LDL-C level above their individualised treatment goal and a documented intolerance to at least two statins.[13] Intolerance was defined as an inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects. Other adverse effects of statins, such as gastrointestinal effects or liver function changes, were not considered to constitute intolerance. Patients were randomised to receive either daily ezetimibe or evolocumab Q2W or monthly for 12 weeks.

The RUTHERFORD-2 trial (n=415) is the only published phase III study to assess the efficacy of evolocumab in people with HeFH.[14] Participants were adults already taking a stable dose of a statin (with or without other lipid-modifying drug regimens) and were randomised to receive either evolocumab or placebo on a fortnightly or monthly regimen.

Evolocumab produced greater reductions in LDL-C than either placebo or ezetimibe in all trials (see table 1 and appendix 1). Reductions were around 55-60% at the end of 12 weeks treatment, compared to typical reductions of 15-20% in the groups assigned to ezetimibe. LDL-C reductions in the 52 week DESCARTES trial were slightly lower than in the 12 weeks studies at 45-50%. The efficacy in the Q2W and monthly dosing groups was comparable at both 12 weeks and average over weeks 10-12. Significant reductions in other lipid parameters were also observed, including ApoB, total cholesterol, non-HDL-C and triglycerides. HDL-C levels were seen to increase.

The EMA also performed a pooled analysis of outcomes from MENDEL-2, LAPLACE-2, GAUSS-2 and RUTHERFORD-2, the results of which confirmed the findings of the individual trials (see table 1).

Table 1. Treatment differences after 12 weeks (pooled data)[7]

Co-primary endpoint	Method	Biweekly	Monthly
Treatment difference vs. placebo			
Mean of weeks 10 & 12	Reflexive LDL-C	-66%	-65%
	Calculated LDL-C	-68%	-67%
Week 12	Reflexive LDL-C	-67%	-60%
	Calculated LDL-C	-69%	-62%
Treatment difference vs. ezetimibe			
Mean of weeks 10 & 12	Reflexive LDL-C	-39%	-40%
	Calculated LDL-C	-40%	-42%
Week 12	Reflexive LDL-C	-40%	-38%
	Calculated LDL-C	-41%	-39%

Safety

The final published paper reports the results of two open-label safety studies of evolocumab, OSLER-1 (56 weeks) and OSLER-2 (48 weeks). Patients in OSLER-1 had completed one of five phase II trials, while those in OSLER-2 had completed one of seven phase III studies. The only other entry criteria were that participants must not have experienced an adverse event leading to study discontinuation, did not have an unstable medical condition, and were not expected to require unblinded lipid measurement or modification of lipid-modifying therapy during the first twelve weeks of the study.

Participants were randomised to evolocumab 420 mg monthly or placebo, although patients in OSLER-2 could also choose to receive the 140 mg Q2W regimen. All participants also received standard therapy; at baseline 70% of participants were taking a statin, and 12-15% were taking ezetimibe. Around 10% in each group had known FH. The combined study population comprised 4,465 people, of whom 2,976 were randomised to evolocumab. At the end of the randomised period all participants were switched to open-label evolocumab for long-term study of safety and efficacy.

The primary endpoint in both trials was the incidence of adverse events (AEs). Adjudicated cardiovascular events were collected as a pre-specified exploratory outcome. The incidence of AEs was similar in the evolocumab and placebo groups (69.2% vs. 64.8%), and the incidence of serious AEs was 7.5% in both arms. Seventy-one people (2.4%) discontinued evolocumab treatment due to an AE. New evolocumab-binding antibodies were detected in 0.3% of patients in both groups; no evolocumab-neutralising antibodies were detected.

Injection site reactions were reported in 4.3% of patients receiving evolocumab. Muscle-related AEs occurred at similar rates in both trial arms (6.4% vs. 6.0%). Neurocognitive events were rare, but were more common with evolocumab (0.9% vs. 0.3%). Such events included delirium, cognitive and attention disorders, dementia, amnesiac conditions, disturbance in thinking and perception, and mental impairment disorders.

Cardiovascular AEs occurred in 29 (0.95%) evolocumab-treated patients compared to 31 (2.2%) in the placebo group (hazard ratio at 1 year 0.47, 95% CI 0.28 to 0.78). Reported cardiovascular AEs included cardiovascular death, coronary events and cerebrovascular events. The data appear to be confounded somewhat by the inclusion of three deaths labelled "non-cardiovascular" in the placebo group.

Pooled safety data

The EMA published further pooled data relating to 6,026 patients enrolled in any phase of the clinical trial programme who received any dose of evolocumab.[7] Of these, 2,458 received evolocumab for at least 1 year and 1,124 were exposed for 2 years or more. The rate of treatment-emergent AEs (TEAEs) was found to be similar in the evolocumab and comparator groups at approximately 50%. Serious TEAEs occurred in 2-3% of trial participants, and 1-2% discontinued treatment due to TEAEs. The most common AEs included nasopharyngitis, upper respiratory tract infection, headache and back pain.

The rate of AEs was higher in patients previously found to be intolerant to statins, at 65% in the evolocumab group and 69% in those taking placebo.[7] Myalgia was less common in evolocumab-treat patients (9%) than in those receiving placebo (14%), and more common in this subgroup than in the general trial population (2.5%). Likewise, rates of headache and back pain were more common in this subgroup.

Across all trials, the incidence of AEs was slightly higher among patients who received monthly evolocumab (54%) than Q2W dosing (44%). The difference was not accounted for by any one AE or class of AEs, although injection site bruising was more common with the monthly regimen (18 reports, 0.9%) than with fortnightly dosing (0 reports). AEs related to the injection devices were uncommon and not usually severe. Anti-evolocumab antibodies were rare (n=15) and not associated with any AEs such as hypersensitivity. No evolocumab-neutralising antibodies were detected.

There were no demonstrated effects on musculoskeletal events, hepatic or renal disorders or incidence of diabetes. The effect of evolocumab on cardiovascular AEs was similar to that observed in the published extension study (hazard ratio at 1 year 0.50, 95% CI 0.29 to 0.86). However, cardiovascular events were not the primary outcome measure in any trial, and there were only 103 events collected during the clinical trial program. These figures should therefore be interpreted with caution.

Dosage and administration

Prior to initiating therapy with evolocumab, secondary causes of hyperlipidaemia or mixed dyslipidaemia, such as nephrotic syndrome or hypothyroidism, should be excluded. Use in children younger than 18 is not recommended, as safety and efficacy have not been established for indications other than homozygous FH. Evolocumab is licensed in children aged 12 and older for the treatment of homozygous FH only.

Evolocumab is supplied as a 140 mg/mL solution for injection, available in single-use pre-filled pens and syringes each containing 1mL. The recommended dose is either 140 mg every two weeks or 420 mg monthly. The 420 mg dose should be administered using three pre-filled pens or syringes administered consecutively and within 30 minutes of one another. The two doses are considered clinically equivalent. Evolocumab is suitable for self-administration, after appropriate training.

Administration should be by subcutaneous injection into the abdomen, thigh or upper arm, and injection sites should be rotated. Evolocumab must not be given intravenously or intramuscularly.

Cost analysis

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

The pre-filled syringe costs £170.10 for a single 140 mg dose, while the pre-filled pen costs £340.20 for a pack of two single-use devices each containing a single 140 mg dose (all prices exclude VAT).[16]

Evolocumab is intended for life-long use.[6,17] It will be an additional treatment option for adults with primary hypercholesterolaemia (HeFH and non-FH) or mixed dyslipidaemia, as an adjunct to diet:

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

Accurately estimating the numbers of patients who might be eligible for treatment with evolocumab 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).[18] 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 evolocumab or ezetimibe.

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

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.[19] In the NTAG area in in the first quarter of 2015/16 a total of 27,900 items of ezetimibe were prescribed at a cost of around £742,000.

Evolocumab 140 mg Q2W costs £4,422.60 per patient per year while the monthly dose costs £6,123.60 per patient per year. This compares to £343.03 per patient 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 evolocumab instead of ezetimibe this would result in an approximate incremental cost of between £4,081 (Q2W dosing) and £5,782 (monthly dosing) per patient per year. In some patients evolocumab may be used in addition to ezetimibe plus statins, and therefore the costs would be additive.

Evolocumab will compete directly with another recently launched PCSK9 antibody, alirocumab (Praluent®▼, Sanofi).[20] The incremental cost of prescribing alirocumab second-line instead of ezetimibe would £4,018 per patient per year.

Points to consider

Evolocumab, and the recently launched alirocumab, represent the first available treatment options for people with hypercholesterolaemia or mixed dyslipidaemia despite optimised lipid-modifying therapy.

The evidence for the clinical efficacy and safety of evolocumab is limited, with the majority of the evidence for efficacy derived from five phase III trials, each lasting 12 weeks. One phase III trials lasted 52 weeks, which the EMA considered to be the minimum acceptable trial length for a drug intended to be used for life. Extension studies are ongoing. All trials showed that evolocumab produced large reductions in LDL-C compared to both placebo and ezetimibe and on a background of diet alone, statins, or statins plus ezetimibe.

The safety profile of evolocumab was comparable to the comparators. The most common AEs were nasopharyngitis, upper respiratory tract infection, headache and back pain. Rates of serious AEs and AEs leading to discontinuation were low.

There is limited evidence that evolocumab has any effect on cardiovascular outcomes. Rates appear to be lower than in control groups, but the number of events collected was low. A 5 year cardiovascular outcomes trial is currently underway, and is expected to complete in February 2018. The primary outcome measure will be a composite of time to cardiovascular death, myocardial infarction, hospitalisation for unstable angina, stroke or coronary revascularisation.[21]

Evolocumab is expensive at £4,400 to £6,100 per patient per year depending on dose compared to £342 for ezetimibe. The incremental cost of using evolocumab instead of ezetimibe is roughly £4,100 to £5,800 per patient per year. In cases where they are added to background therapy this cost will be additive. Alirocumab, the other licensed PCSK9 inhibitor, costs £4,360 per patient per year, an incremental cost of £4000 over ezetimibe. There may be additional costs incurred to either administer each dose or provide suitable training for patients to self-administer.

Unlike existing lipid-modifying drugs evolocumab must be injected, which may reduce tolerability. The monthly regimen offers the advantage of less frequent dosing but increases the injection burden by requiring three injections to be given in quick succession. It is also considerably more expensive than the fortnightly dosing schedule due to the higher relative dose. Evolocumab is suitable for self-administration, given appropriate training.

Evolocubmab 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 statin plus ezetimibe, or who cannot be given statins.

Evolocumab will compete directly with alirocumab (Praluent®▾, Sanofi). 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 published phase 3 trials of evolocumab

Trial	Study design	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Duration of study	Outcome measures and effect size (mITT population)	Additional comments
MENDEL-2[10] NCT01763827	Double-blind RCT	**Inclusion** Adults aged 18-80 with fasting LDL-C ≥100 mg/dL (2.6 mmol/L) and <190 mg/dL (4.9 mmol/L), triglycerides ≤400 mg/dL, and 10-year Framingham coronary heart disease risk score ≤10%. **Exclusion** Heart failure; history of CHD; recent VTE; uncontrolled cardiac arrhythmia or hypertension; diabetes mellitus; thyroid, liver, GI, endocrine or renal dysfunction; malignancies within 5 years (except non-melanoma skin cancers or carcinoma in situ); use of lipid-regulating drugs within three months.	n=614[22] Female – 66% Mean age – 53 years Coronary artery disease <1% T2DM <1% Triglycerides ≥150 mg/dL (≥1.7 mmol/L) 29% Low HDL-C – 24% Current cigarette use – 12% Hypertension – 29% Family history premature CHD – 10% Risk classification (ESC/EAS criteria) Very high – 8% High – 2% Moderate – 57% Low – 33% Statin use at baseline – 0 Mean LDL – 3.7 mmol/L Mean PCSK9 – 3.8 nmol/L	Oral placebo + SC placebo biweekly, n=76; Oral placebo + SC placebo monthly, n=78; Ezetimibe + SC placebo biweekly, n=77; Ezetimibe + SC placebo monthly, n=77; Oral placebo + evolocumab 140 mg biweekly, n=153; Oral placebo + evolocumab 420 mg monthly, n=153.	12 weeks treatment, plus additional 2 weeks follow-up.	**Co-primary endpoints:** ***Change in LDL-C from baseline to weeks 10&12 (averaged)*** *Biweekly administration:* Evolocumab: -56.9% (-59.0 to -54.8) Ezetimibe: -17.5% (-20.4 to -14.7) Placebo: -0.4% (-3.3 to 2.4) *Monthly administration* Evolocumab: -58.8% (-60.8 to -56.8) Ezetimibe: -19.1% (-21.9 to -16.4) Placebo: -1.4% (-4.4 to 1.7) ***Change in LDL-C from baseline to week 12*** *Biweekly administration:* Evolocumab: -57.0% (-59.5 to -54.6) Ezetimibe -17.8% (-21.0 to -14.5) Placebo: 0.1% (-3.2 to 3.4) *Monthly administration* Evolocumab: -56.1% (-58.3 to -53.9) Ezetimibe: -18.6% (-21.6 to -15.5) Placebo: -1.3% (-4.4 to 1.7)	

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LAPLACE-2[11] NCT01763866	Double-blind RCT	**Inclusion[23]** Age 18 to 80 years, inclusive, intensive statin dose + fasting LDL-C ≥80 mg/dL (2.1 mmol/L) OR non-intensive statin dose + fasting LDL-C ≥100 mg/dL (2.6 mmol/L) OR no statin + fasting LDL-C ≥150 mg/dL (4.0 mmol/L) Fasting triglycerides ≤400 mg/dL (4.5 mmol/L) **Exclusion[23]** Heart failure, last known LVEF <30%; serious cardiac disease; T1DM; newly diagnosed or poorly controlled T2DM; uncontrolled hypertension; drugs affecting lipid levels; hyper- or hypothyroidism; renal or hepatic impairment; Active infection; Major hematologic, renal, metabolic, GI, or endocrine disruption; VTE (within 3 mo); current/prior history of statin intolerance; Requires, per investigator's opinion, maximal statin dosage;	n=1,896[22] Female – 46% Mean age – 60years Coronary artery disease 23% T2DM 16% Triglycerides ≥150 mg/dL (≥1.7 mmol/L) 29% Low HDL-C – 28% Current cigarette use – 15% Hypertension –57% Family history premature CHD – 20% Risk classification (ESC/EAS criteria) Very high – 43% High – 5% Moderate – 43% Low – 9% Statin use at baseline – 100% Mean LDL 2.8– mmol/L Mean PCSK9 – 4.9 nmol/L	**Groups 1-6** Atorvastatin 10 mg *Plus* SC placebo Q2W + oral placebo, n=56 *Or* SC placebo monthly + oral placebo, n=55 *Or* SC placebo Q2W + ezetimibe 10 mg, n=56 *Or* SC placebo monthly + ezetimibe 10 mg, n=55 *Or* Evolocumab 140 mg Q2W + oral placebo, n=110 *Or* Evolocumab 420 mg monthly + oral placebo, n=110 **Groups 7-12** Atorvastatin 80 mg *Plus* SC placebo Q2W + oral placebo, n=55 *Or* SC placebo monthly + oral placebo, n=55	4 week lipid-stabilisation phase (oral statins only) 12 weeks active treatment with oral statins plus evolocumab / ezetimibe/ placebo	**Co-primary endpoints:** ***Change in LDL-C from baseline to weeks 10&12 (averaged)*** ***% change (95% CI)*** • **Treatment difference (% change) vs. placebo or ezetimibe** *Atorvastatin 80 mg +* Pbo + pbo Q2W: 13.1% (5.3 to 21) Pbo + Pbo monthly: 9.8% (3.1 to 16.5) Ezetimibe + pbo Q2W: -16.9% (-24.5 to -9.2) Ezetimibe + pbo monthly: -21.3% (-28.0 to -14.5) Evolocumab Q2W + pbo: -61.8% (-67.3 to -56.3) • % change vs. pbo: -74.9% (-84.5 to -65.4) • % change vs. ezetimibe: -44.9% (-54.3 to -35.6) Evolocumab monthly + pbo: -65.1% (-69.8 to -60.3) • % change vs. pbo: -74.8% (-83.0 to -66.6) • % change vs. ezetimibe: -43.8% (-52.1 to -35.6) *Rosuvastatin 40 mg +* Pbo Q2W: 6.6% (0.4 to 12.7) Pbo monthly: 0% (-7.0 to 6.9) Evolocumab Q2W: -59.1% (-63.5 to -54.7) • % change vs. pbo: -65.7% (-73.2 to -58.1) Evolocumab monthly: -62.9% (-67.8 to -58.1) • % change vs. pbo: -62.9% (-	Outcomes at 12 weeks (co-primary endpoint) not reported; treatment differences vs. placebo and ezetimibe reported in isolation. Sequential testing to account for multiple endpoints.

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		personal or family history of hereditary muscular disorders.		*Or* SC placebo Q2W + ezetimibe 10 mg, n=56 *Or* SC placebo monthly + ezetimibe 10 mg, n=54 *Or* Evolocumab 140 mg Q2W + oral placebo, n=110 *Or* Evolocumab 420 mg monthly + oral placebo, n=110 **Groups 13-16** Rosuvastatin 5 mg *Plus* SC placebo Q2W, n=58 *Or* SC placebo monthly, n=57 *Or* Evolocumab 140 mg Q2W + oral placebo, n=114 *Or* Evolocumab 420 mg monthly + oral placebo, n=115 **Groups 17-20** Rosuvastatin 40 mg		71.4 to -54.5) *Atorvastatin 10 mg +* Pbo + pbo Q2W: 8.5% (4.1 to 13.0) Pbo + Pbo monthly: 0.4% (-4.8 to 5.5) Ezetimibe + pbo Q2W: -23.9% (-28.5 to -19.3) Ezetimibe + pbo monthly: -19.0 (-24.0 to -13.9) Evolocumab Q2W + pbo: -61.4% (-64.6 to -58.2) • % change vs. pbo: -70.0% (-75.4 to -64.5) • % change vs. ezetimibe: -37.5% (-43.0 to -32.0) Evolocumab monthly + pbo: -62.5% (-66.1 to -58.9) • % change vs. pbo: -62.8% (-69.1 to -56.6) • % change vs. ezetimibe: -43.5% (-49.7 to -37.3) *Simvastatin 40 mg +* Pbo Q2W: 3.3% (-3.4 to 10.0) Pbo monthly: 6.0% (-3.5 to 15.5) Evolocumab Q2W: -66.2% (-72.0 to 60.4) • % change vs. pbo: -69.4% (-74.9 to -64.0) Evolocumab monthly: -62.4% (-70.0 to -54.9) • % change vs. pbo: -68.5% (-79.7 to -60.2) *Rosuvastatin 5 mg +* Pbo Q2W: 7.6% (2.8 to 12.3) Pbo monthly: 2.8% (-2.1 to 7.7)	

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				Plus SC placebo Q2W, n=56 *Or* SC placebo monthly, n=56 *Or* Evolocumab 140 mg Q2W + oral placebo, n=111 *Or* Evolocumab 420 mg monthly + oral placebo, n=112 **Groups 21-24** Simvastatin 40 mg *Plus* SC placebo Q2W, n=56 *Or* SC placebo monthly, n=55 *Or* Evolocumab 140 mg Q2W + oral placebo, n=112 *Or* Evolocumab 420 mg monthly + oral placebo, n=115		Evolocumab Q2W: -59.3% (-62.8 to -55.9) • % change vs. pbo: -66.9% (-72.7 to -61.1) Evolocumab monthly: -63.8% (-67.3 to -60.3) • % change vs. pbo: -66.6% (-72.6 to -60.6) ***Change in LDL-C from baseline to week 12*** Absolute changes in LDL-C not presented. Treatment differences vs. pbo/ezetimibe available only. *Atorvastatin 80 mg +* Evolocumab Q2W + pbo: • % change vs. pbo: -76.3% (-86.9 to -65.7) • % change vs. ezetimibe: -47.2% (-57.5 to -36.9) Evolocumab monthly + pbo: • % change vs. pbo: -70.5% (-79.8 to -61.2) • % change vs. ezetimibe: -38.9% (-48.2 to -29.6) *Rosuvastatin 40 mg +* Evolocumab Q2W + pbo: • % change vs. pbo: -68.3% (-77.0 to -59.6) Evolocumab monthly + pbo: • % change vs. pbo: -55.0% (-65.3 to -44.7)	

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						Atorvastatin 10 mg + Evolocumab Q2W + pbo: • % change vs. pbo: -71.4% (-77.6 to -65.3) • % change vs. ezetimibe: -39.6% (-45.8 to -33.4) Evolocumab monthly + pbo: • % change vs. pbo: -59.2% (-65.9 to -52.4) • % change vs. ezetimibe: -41.1% (-47.8 to -34.4) *Simvastatin 40 mg +* Evolocumab Q2W + pbo: • % change vs. pbo: -70.6% (-76.7 to -64.4) Evolocumab monthly + pbo: • % change vs. pbo: -60.4% (-69.1 to -51.7) *Rosuvastatin 5 mg +* Evolocumab Q2W + pbo: • % change vs. pbo: -68.2% (-74.7 to -61.7) Evolocumab monthly + pbo: • % change vs. pbo: -64.5% (-70.8 to -58.1)	

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DESCARTES[1][2] NCT01516879	Double-blind RCT	**Inclusion criteria** Male or female ≥ 18 to ≤ 75 years, fasting LDL-C ≥ 75 mg/dL (2.0 mmol/L) at initial visit and, at end of the lipid stabilization period ≥ 75 - 100 mg/dL (with CHD or risk equivalent), < 130 mg/dL (3.4 mmol/L) without CHD or risk equivalent, OR ≥75 mg/dL (2.0 mmol/L) for subjects on maximal lipid-lowering therapy; fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L). **Exclusion criteria** CHD risk equivalent not receiving statin therapy, LDL-C at screening ≤ 99 mg/dL; heart failure, or LVEF < 30%; Uncontrolled cardiac arrhythmia; cardiac disease; T1DM or newly diagnosed or poorly controlled T2DM; drugs affecting lipid levels other than statins or ezetimibe; hyperthyroidism or hypothyroidism; Moderate to severe renal dysfunction; Active liver disease or hepatic dysfunction; CK > 3 times ULN	**Placebo (n=302)** Age – 56.7 years Male – 46.4%, BMI 30.5 White – 82.1 *ATP-III risk category*: High – 26.2% Moderately high – 9.6% Moderate – 33.9% Low – 30.7% Coronary artery disease – 13.9%, T2DM – 13.9% Current smoker – 15.9% Hypertension – 49.3% Family history premature CHD – 21.9% ≥2 risk factors – 42.4% **Evolocumab (n=599)** Age – 55.9 years Male – 48.8%, BMI 29.9 White – 79.5 *ATP-III risk category*: High – 26.0% Moderately high – 9.3% Moderate – 33.9% Low – 30.7% Coronary artery disease – 15.7%, T2DM – 10.4% Current smoker –14.5% Hypertension – 48.2% Family history premature CHD – 23.7% ≥2 risk factors –37.4%	**Diet alone** *Plus* Evolocumab 420 mg Q4W, n=74 *Or* Placebo Q4W, n=38 **Diet + atorvastatin 10 mg** *Plus* Evolocumab 420 mg Q4W, n=256 *Or* Placebo Q4W, n=129 **Diet + atorvastatin 80 mg** *Plus* Evolocumab 420 mg Q4W, n=146 *Or* Placebo Q4W, n=73 **Diet + atorvastatin 80 mg + ezetimibe 10 mg** *Plus* Evolocumab 420 mg Q4W, n=126 *Or* Placebo Q4W, n=63	Lipid stabilisation (diet + statins/ ezetimibe) – 4-12 weeks Randomised period (evolocumab/placebo) – 52 weeks	**Primary endpoint: % change in LDL-C at week 52** **Diet alone** Evolocumab 420 mg Q4W: -51.5±2.4 Placebo Q4W: 4.2±3.5 TD: -55.7±4.2 **Diet + atorvastatin 10 mg** Evolocumab 420 mg Q4W: -54.7±1.5 Placebo Q4W: 6.9±2.2 TD: -61.6±2.6 **Diet + atorvastatin 80 mg** Evolocumab 420 mg Q4W: -46.7±3.1 Placebo Q4W: 10.1±4.3 TD: -56.8±5.3 **Diet + atorvastatin 80 mg + ezetimibe 10 mg** Evolocumab 420 mg Q4W: -50.1±1.2 Placebo Q4W: 6.8±1.8 TD: -57.0±2.1	

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GAUSS-2[13] NCT01763905	Double-blind RCT	**Inclusion** Adults aged 18-80 on no or low-dose statins, LDL-C above their NCEP Adilt Treatment Panel III goal, previous intolerance to ≥2 statins (defined as inability to tolerate any dose or increase above the lowest tablet strength due to intolerable muscle-related side-effects). **Exclusion** Heart failure or left ventricular ejection fraction <30%, ACS or serious arrhythmia, T1 or T2DM that is poorly controlled or newly diagnosed, uncontrolled hypertension or thyroid disease, moderate or severe renal dysfunction, hepatic dysfunction, use of systemic steroids (other than hormone replacement) or cyclosporine, use of niacin >200 mg/day, red yeast rice, or prescription lipid-lowering medications other than low-dose statins, ezetimibe or bile-acid sequestrants in the prior 6 weeks	n=307[22] Female – 46% Mean age – 60 years Coronary artery disease 23% T2DM 16% Triglycerides ≥150 mg/dL (≥1.7 mmol/L) 29% Low HDL-C – 28% Current cigarette use – 15% Hypertension – 57% Family history premature CHD – 20% Risk classification (ESC/EAS criteria) Very high – 43% High – 5% Moderate – 43% Low – 9% Statin use at baseline – 100% Mean LDL – 2.8 mmol/L Mean PCSK9 – 4.9 nmol/L	Ezetimibe + SC placebo biweekly, n=51; Ezetimibe + SC placebo monthly, n=51; Oral placebo + evolocumab 140 mg biweekly, n=103; Oral placebo + evolocumab 420 mg monthly, n=102.	12 weeks	**Co-primary endpoints:** ***Change in LDL-C from baseline to weeks 10&12 (averaged)*** *Biweekly administration:* Ezetimibe: –19.2% (-23.9 to -14.5) Evolocumab: -56.1% (-59.7 to -52.5) TD -36.9 (-42.3 to -31.6, p<0.001) *Monthly administration* Ezetimibe: -16.6% (-20.6 to -12.6) Evolocumab: -55.3% (-58.3 to -52.3) TD -38.7 (-43.1 to -34.3, p<0.001) ***Change in LDL-C from baseline to week 12*** *Biweekly administration:* Ezetimibe: -18.3% (-23.1 to -13.1) Evolocumab: -56.1% (-59.9 to -52.4) TD -38.1 (-43.7 to -32.4, p<0.001) *Monthly administration* Ezetimibe: -15.1% (-19.3 to -10.9) Evolocumab: -52.6% (-55.7 to -49.5) TD -37.6 (-42.2 to -32.9, p<0.001)	

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RUTHER-FORD-2[14] NCT01763918	Double-blind RCT	**Inclusion** Adults 18-80 with diagnosis of heterozygous FH at screening (Simon Broome criteria), on a stable dose of approved lipid-modifying therapy (ezetimibe, resins, stanols or niacin,). **Exclusion** Diagnosis of homozygous FH, lipoprotein or plasma apheresis in previous 4 months, heart failure or LVEF <30%, acute or unstable cardiac events within 3 months, planned cardiac surgery, treatment with fibrates within 6 weeks, T1DM, newly-diagnosed or poorly-controlled T2DM, uncontrolled hypertension, uncontrolled hypo- or hyperthyroidism, moderate to severe renal dysfunction, active liver disease, creatinine kinase >3X ULN, previous participation in study of PCSK9 inhibition.	n=329[22] Female – 42% Mean age – 62 years Coronary artery disease 29% T2DM 20% Triglycerides ≥150 mg/dL (≥1.7 mmol/L) 52% Low HDL-C – 33% Current cigarette use – 8% Hypertension – 59% Family history premature CHD – 32% Risk classification (ESC/EAS criteria) Very high – 52% High – 58% Moderate – 0% Low – 0% Statin use at baseline – 100% Mean LDL – 4.0 mmol/L Mean PCSK9 – 6.2 nmol/L	Placebo biweekly, n=55; Placebo monthly, n=55; Evolocumab 140 mg biweekly, n=111; Evolocumab 420 mg monthly, n=110.	12 weeks	**Co-primary endpoints:** ***Change in LDL-C from baseline to weeks 10&12 (averaged)*** *Biweekly administration:* Placebo: -1.1% (-5.8 to 3.7) Evolocumab: -61.2% (-64.6 to -57.9) TD -60.2% (-65.8 to -54.5, p<0.0001) *Monthly administration* Placebo: 2.3% (-2.5 to 7.1) Evolocumab: -63.3% (-66.6 to -59.9) TD -65.6% (-71.3 to -59.8, p<0.0001) ***Change in LDL-C from baseline to week 12*** *Biweekly administration:* Placebo: -2.0% (-6.9 to 2.9) Evolocumab: -61.3% (-64.7 to -57.8) TD -59.2% (-65.1 to -53.4, p<0.0001) *Monthly administration* Placebo: 5.5% (-0.9 to 12.0) Evolocumab: -55.7% (-6.2 to -51.3%) TD -61.3% (-69.0 to -53.6, p<0.0001)	Simon Broome criteria also used in UK for FH diagnosis.

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OSLER-1 & OSLER-2[15] NCT01439880 & NCT01854918	Open-label RCTs	Patients who had completed one of five phase 2 trials or seven phase 3 trials of evolocumab, provided they did not have an AE leading to discontinuation or an unstable medical condition, and were not expected to need unblended lipid measurement or adjustment of lipid-lowering therapy during the first 12 weeks.	**Evolocumab group**, n=2,976 Male – 50.1%, age – 58 Coronary artery disease 19.8% Diabetes 12.8% Triglycerides – 120mg/dL Mean HDL-C – 51 mg/dL Current cigarette use – 15.6% Hypertension – 51.9% Family history premature CHD – 24.3% Moderately high or high cardiac risk – 44.8% Statin use – 69.7% Ezetimibe – 12.6% Mean LDL 120 mg/dL **Standard therapy group**, n=1,489 Male – 51.4%, age – 58 Coronary artery disease 20.6% Diabetes 14.6% Triglycerides – 119mg/dL Mean HDL-C – 51 mg/dL Current cigarette use – 14.9% Hypertension – 52.2% Family history premature CHD – 24.3% Moderately high or high cardiac risk – 46.5% Statin use – 70.9% Mean LDL 120 mg/dL Ezetimibe – 15.4%	Evolocumab (Q2W or monthly) + local standard therapy, n=2,976 Local standard therapy alone, n=1,489	56 weeks (OSLER-1). 48 weeks (OSLER-2) All patients switched to open-label evolocumab at the end of randomised treatment, for ongoing safety & efficacy assessment	**Primary endpoint: incidence of adverse effects** *Any AE*: Evolocumab – 69.2% Standard therapy – 64.8% *Serious AE*: Evolocumab – 7.5% Standard therapy – 7.5% *Leading to evolocumab discontinuation*: Evolocumab – 2.4% Standard therapy – n/a *Muscle-related AE* Evolocumab – 6.4% Standard therapy – 6.0% *Injection-site reaction* Evolocumab – 4.3% Standard therapy – n/a *Cardiovascular events (death, MI, unstable angina, coronary revascularisation, stroke, TIA, hospitalisation for heart failure)* After 1 year, hazard ratio 0.47 (0.28 to 0.78), p=0.003 (in favour evolovumab)	Cardiovascular events prospectively collected but trials not specifically designed or powered for this endpoint. Interpret with caution.