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SYSTEMATIC REVIEW

# Systematic review of published Phase 3 data on anti-PCSK9 monoclonal antibodies in patients with hypercholesterolaemia

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## AIMS

Two anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies, alirocumab and evolocumab, have been approved for the treatment of hypercholesterolaemia in certain patients. We reviewed data from Phase 3 studies to evaluate the efficacy and safety of these antibodies.

## METHODS

We systematically reviewed Phase 3 English-language studies in patients with hypercholesterolaemia, published between 1 January 2005 and 20 October 2015. Congress proceedings from 16 November 2012 to 16 November 2015 were also reviewed.

## RESULTS

We identified 12 studies of alirocumab and nine of evolocumab, including over 10 000 patients overall. Most studies enrolled patients with hypercholesterolaemia and used anti-PCSK9 antibodies with statins. The ODYSSEY FH I, FH II and HIGH FH alirocumab studies and the RUTHERFORD-2 evolocumab study exclusively recruited patients with heterozygous familial hypercholesterolaemia. Two evolocumab studies focused mainly on homozygous familial hypercholesterolaemia (HoFH): TESLA Part B and TAUSSIG (a TESLA sub-study); only those data for HoFH are reported here. All comparator studies demonstrated a reduction in LDL cholesterol (LDL-C) with the anti-PCSK9 antibodies. No head-to-head studies were conducted between alirocumab and evolocumab. Up to 87% of patients receiving alirocumab and up to 98% receiving evolocumab reached LDL-C goals. Both antibodies were effective and well tolerated across a broad population of patients and in specific subgroups, such as those with type 2 diabetes.

## CONCLUSIONS

Using anti-PCSK9 antibodies as add-on therapy to other lipid-lowering treatments or as monotherapy for patients unable to tolerate statins may help patients with high cardiovascular risk to achieve their LDL-C goals.

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## Tables of Links

| TARGETS |
|---|
| **Enzymes** [2] |
| Hydroxymethylglutaryl-CoA reductase |
| Proprotein convertase subtilisin/kexin type 9 |
| **Other protein targets** [3] |
| NPC1 like 1 |

| LIGANDS | |
|---|---|
| Alirocumab | Ezetimibe |
| Atorvastatin | Rosuvastatin |
| Evolocumab | Simvastatin |

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

## Introduction

Despite declining rates, cardiovascular (CV) disease (CVD) remains the leading cause of mortality and morbidity in Europe [4, 5]. It is now clear that correcting elevated plasma LDL cholesterol (LDL-C) is an effective way to reduce CV risk [6, 7].

In practice, a large proportion of patients with very high CV risk do not reach the target LDL-C level recommended in Europe ($<1.8$ mmol $l^{-1}$ [70 mg $dl^{-1}$]) despite receiving treatment with statins, as shown by the EUROASPIRE IV study [5, 7]. Inadequate control of LDL-C in clinical practice indicates a need for more effective treatments. It may also indicate poor adherence to treatment, which is a particular concern in patients with very high CV risk [8, 9] and in those with comorbidities such as diabetes and hypertension, who need to take multiple medications [9]. In addition, statins are not well tolerated by 10–15% of patients [10].

High LDL-C levels can be influenced by lifestyle to some extent, but are mainly due to polymorphisms at numerous genetic loci [11–13]. The highly penetrant genetic mutations affecting the LDL receptor (LDLR) and apolipoprotein B have long been known to cause familial hypercholesterolaemia [14]. In 2003, a third locus associated with this inherited condition was identified: proprotein convertase subtilisin/kexin type 9 (PCSK9) [15]. The PCSK9 protein binds to LDLRs, targeting them for lysosomal degradation; this prevents the receptors from binding LDL-C and removing it from the circulation and therefore raises serum LDL-C concentrations [16]. The use of monoclonal antibodies that target PCSK9 in order to reduce plasma LDL-C is a new approach for the treatment of hypercholesterolaemia and may help address the unmet clinical need of achieving LDL-C targets for the majority of patients with high CV risk. Two fully human anti-PCSK9 monoclonal antibodies have recently been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA): alirocumab and evolocumab [17–20]. Other PCSK9 inhibitors are in development [21, 22].

In the USA, alirocumab and evolocumab are indicated for use in adults with heterozygous familial hypercholesterolaemia (HeFH) or clinical atherosclerotic CVD, such as heart attack or stroke, who require additional LDL-C lowering [17, 18]. Alirocumab and evolocumab are both used in addition to diet and maximum tolerated statin therapy [17, 18]. Evolocumab is also approved for use in combination with other LDL-C-lowering therapies in patients with homozygous familial hypercholesterolaemia (HoFH). In Europe, alirocumab and evolocumab are approved as an adjunct to diet for use in adults with primary hypercholesterolaemia (HeFH and non-familial) or mixed dyslipidaemia who do not achieve target LDL-C with other lipid-lowering medication and in patients with statin intolerance [19, 20]. Evolocumab is also approved for use in combination with other lipid-lowering therapies in patients aged 12 years and older with HoFH [20].

PCSK9 is predominantly synthesized in the liver and is secreted into the circulation, where it has a half-life of approximately 5 minutes [23]. The anti-PCSK9 monoclonal antibodies bind circulating PCSK9, preventing PCSK9-mediated degradation of the LDLR. In the absence of PCSK9, the number of receptors on the cell surface increases and more circulating LDL-C is removed [16]. Upon saturation of circulating PCSK9, any unbound antibody binds to PCSK9 as it is synthesized and released from the liver cells [24]. At this stage, increases in the antibody concentrations do not reduce LDL-C further but extend the duration of LDL-C lowering [19, 25, 26]. Eventually, the amount of circulating PCSK9 saturates the circulating unbound antibody and LDL-C levels return to baseline [24, 25]. Alirocumab and evolocumab have the same mechanism of action. Both antibodies are cleared more quickly in patients receiving concomitant statins [19, 20] because statins increase the production of PCSK9 [27, 28]. This elevation in PCSK9 levels is thought to result from statin-induced intracellular cholesterol depletion via sterol regulatory element binding proteins, which in turn promotes transcription of PCSK9 [24, 28]. Despite this effect, the reduction in LDL-C in patients receiving the recommended dose of either antibody is similar whether or not they are receiving concomitant statins [19, 20].

Following Phase 2 trials of alirocumab, which found a dose of 150 mg every 2 weeks (Q2W) to be more effective than a higher dose of 200 mg or 300 mg every 4 weeks (Q4W) [29, 30], a pooled study of Phase 3 trials evaluated two regimens of alirocumab with concomitant statins: 150 mg Q2W and 75 mg Q2W with a criteria-based uptitration to 150 mg Q2W at week 12 (which led to an additional 14% LDL-C reduction) [31]. As a result of these studies, the titration regimen was recommended for all patients except those requiring LDL-C reductions of more than 60%, in whom 150 mg Q2W should be the starting dose [19]. The efficacy of alirocumab does not appear to be influenced by age, body mass index, intensity of statin treatment or baseline

levels of LDL-C, HDL cholesterol (HDL-C) or triglycerides [32]. The starting dose of evolocumab for adults with primary hypercholesterolaemia or mixed dyslipidaemia is also based on clinical trial data and is either 140 mg Q2W or 420 mg Q4W; the two doses are clinically equivalent [20, 33–35]. For those with HoFH, 420 mg Q4W is recommended initially, with up-titration to 420 mg Q2W if a clinically meaningful response is not achieved after 12 weeks [20]. Pooled analyses of Phase 2 data showed that the approved dosing regimens of alirocumab [36] and evolocumab [37] were not associated with any discernible adverse event (AE) signal.

The aim of this systematic review was to assess the available data from Phase 3 studies that evaluated the efficacy and safety of anti-PCSK9 monoclonal antibodies in patients with elevated LDL-C levels.

## Methods

### Literature search

Embase and PubMed databases were searched to identify English-language Phase 3 studies of anti-PCSK9 antibodies in patients with elevated LDL-C, published from 1 January 2005 to 20 October 2015. We also searched abstracts books published from 16 November 2012 to 16 November 2015 from the International Symposium on Atherosclerosis and annual congresses of the following societies: American College of Cardiology, American Diabetes Association, American Heart Association, European Atherosclerosis Society, European Association for the Study of Diabetes, European Society of Cardiology and the National Lipid Association. Complete search strings are listed in Supporting Information File S1.

### Inclusion and exclusion criteria

For inclusion, studies had to have enrolled patients with elevated baseline LDL-C concentrations (according to their CV risk) into a Phase 3 trial of an anti-PCSK9 antibody and reported data on LDL-C. All Phase 3 studies (including randomized controlled trials, randomized trials, non-randomized trials, single-arm studies and pooled analyses that reported Phase 3 trial data separately) were included. Reports of pooled Phase 2 and Phase 3 safety data for subgroups not covered in reports of Phase 3 studies were also included. *In vitro* studies, animal studies and any other preclinical studies were excluded, as were editorials, letters, case reports, commentaries, interview-based research, legal cases, newspaper articles, debates, general or independent central reviews, opinions, protocols, workshops, assay studies, cytogenetic studies, surgical studies and educational material for patients. Publications containing no unique data (for example, where the results of a clinical study were reported in multiple publications) were also excluded.

### Screening and data extraction

The systematic review process complied with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [38]. The abstracts of publications identified in the initial search were screened independently by two authors to ascertain whether they met the predefined inclusion criteria. The full texts of all publications that were deemed potentially eligible for inclusion were reviewed independently by the two authors to confirm their eligibility. Conflicts between the authors would have been resolved by a third author but this was not necessary. Data were extracted from full-text publications, where available.

### Data extraction

Data on patient demographics and disease characteristics, outcomes and safety for patients receiving treatment with anti-PCSK9 antibodies, and the methodology and timings used to evaluate LDL-C levels, were extracted.

## Results

### Systematic literature search

Once duplicates were removed, the searches of the Embase and PubMed databases returned 979 results (Figure 1), 930 of which were excluded at the title/abstract screening stage. The main reasons for exclusion were papers not describing original data (409 records) or not describing data on anti-PCSK9 antibodies (246). Of the 49 records selected for full-text evaluation, 28 were excluded. The most common reason for exclusion at this stage was article type (e.g. letter or commentary). At the data extraction stage, four further records were excluded because they were found to contain data duplicating other included articles [39–42]. Seventeen records fulfilled the criteria for inclusion. The congress abstract search identified 909 abstracts, 19 of which were selected for inclusion. We also identified five relevant articles that were indexed in PubMed shortly after the search was completed [43–47]. These were included at the data extraction stage, replacing two congress abstracts presenting the same data [48, 49].

The 39 records that were included in the review described 12 Phase 3 studies of alirocumab and nine Phase 3 studies of evolocumab, involving more than 10 000 patients overall (Table 1), and 15 pooled analyses of efficacy from Phase 3 studies or pooled analyses of safety from Phase 2 and Phase 3 studies. Table 2 summarizes the study populations, including CV risk at baseline. No head to head studies were conducted between alirocumab and evolocumab.

LDL-C concentrations were largely measured at week 24 in the alirocumab studies (with earlier interim measurements in some studies) but at week 12 in the evolocumab studies, with some also measuring LDL-C concentrations at weeks 10, 24 and 52. The assays and their schedules are listed in Table 3.

The baseline characteristics of the patients enrolled in the included studies are shown in Tables 2 and 4.

### Efficacy of anti-PCSK9 antibodies

*Patients with hypercholesterolaemia or mixed dyslipidaemia.* The studies demonstrated that the use of anti-PCSK9 antibodies was associated with a rapid (within 1–2 weeks of treatment initiation) and persistent reduction in LDL-C as measured against the comparators (Table 5).

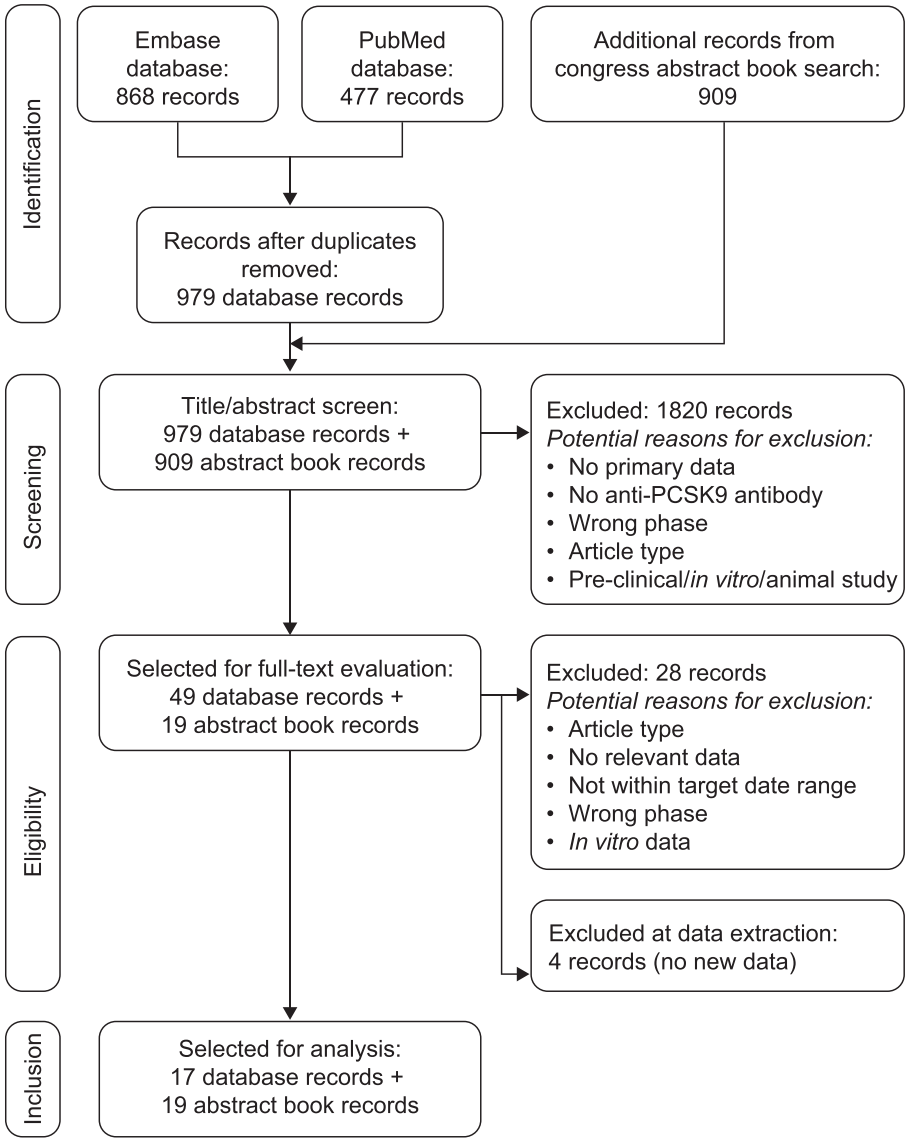



**Figure 1**

PRISMA flow diagram. PCSK9, proprotein convertase subtilisin/kexin type 9; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

The majority of studies reported efficacy according to achievement of LDL-C goal (Table 5 and Figure 2). Generally, rates of goal achievement were highest when anti-PCSK9 antibodies were used in combination with statins and when baseline LDL-C was low. Across the alirocumab–statin combination studies, the highest rate of LDL-C goal achievement (87%) was in the subset of patients from the OPTIONS I study, who received alirocumab with atorvastatin 20 mg [50]. The lowest rate (64%) was in the alirocumab 150 mg Q4W arm of the ODYSSEY CHOICE II study, in which one-third of patients were not receiving concomitant lipid-lowering therapy [51]. All of these alirocumab combination studies included patients with high or very high CV risk. In studies of patients receiving evolocumab in combination with statins, rates for LDL-C goal achievement were highest (98%) in the YUKAWA-2 study [44] and lowest in the GAUSS-2 study [52]. Overall, LDL-C goals were achieved by 46% of the 140 mg Q2W group and 42% of the 420 mg Q4W group of GAUSS-2; however, patients were statin-intolerant, with high LDL-C at baseline (5.0 mmol $l^{-1}$ [193 mg $dl^{-1}$]) and nearly two-thirds of patients were not receiving concomitant lipid-lowering therapy at baseline [52]. The DESCARTES and GAUSS-2 trials showed that evolocumab was effective across patients with high, moderately high, moderate and low CV risk according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III classification [52, 53]. The highest rates for LDL-C goal achievement in DESCARTES (90% with evolocumab plus 10 mg atorvastatin; 84% with evolocumab monotherapy) were in the groups with the lowest proportion of high-risk individuals (10% and 5%, respectively); however, over two-thirds of patients in the subgroup with the greatest proportion of high-risk patients

## Table 1

Studies selected for inclusion of review of Phase 3 data on effect of anti-PCSK9 antibodies on LDL-C levels in patients with hypercholesterolaemia

| Study name | Design | Duration | Anti-PCSK9 antibody dose regimen(s) | Control arm(s) | Patients | Concomitant treatment (all study arms) |
|---|---|---|---|---|---|---|
| **Alirocumab** | | | | | | |
| **ODYSSEY MONO [40, 81]** | Randomized, double-blind, double-dummy, active-controlled, parallel-group | Treatment: 24 weeks<br>Follow-up: 8 weeks | Alirocumab 75 mg Q2W (increased, per protocol, at week 12 to 150 mg Q2W if week-8 LDL-C $\geq$ 1.8 mmol $l^{-1}$ [70 mg $dl^{-1}$] plus ezetimibe placebo QD | Alirocumab placebo Q2W plus ezetimibe 10 mg QD | 103 randomized (1:1) | None |
| **OPTIONS I [50]** | Multicentre, randomized, double-blind, double-dummy, parallel-group | Screening: 2–6 weeks<br>Treatment: 24 weeks<br>Follow-up: 8 weeks (median for patients who did not complete, 9.5–12.4 weeks) | Alirocumab 75/150 mg Q2W (increased, per protocol, at week 12 to 150 mg Q2W if week-8 LDL-C $\geq$ 1.8 mmol $l^{-1}$ [70 mg $dl^{-1}$] or $\geq$ 2.6 mmol $l^{-1}$ [100 mg $dl^{-1}$] in patients with or without documented CVD, respectively) | Ezetimibe 10 mg + atorvastatin 20 or 40 mg; atorvastatin 40 or 80 mg; rosuvastatin 40 mg | 355 randomized (1:1:1:1) | 47.6% of patients received atorvastatin 20 mg QD; 52.4% of patients received atorvastatin 40 mg QD |
| **OPTIONS II [46]** | Randomized | 24 weeks | Alirocumab 75 mg Q2W (alirocumab was increased, per protocol, at week 12 to 150 mg Q2W if the target LDL-C value was not met) | Ezetimibe 10 mg QD or double-dose rosuvastatin | 305 randomized (1:1:1) | 47.5% of patients received rosuvastatin 10 mg QD; 52.5% of patients received rosuvastatin 20 mg QD |
| **ODYSSEY COMBO II [74]** | Double-blind, double-dummy, active-controlled | 104 weeks<br>Final efficacy data: up to week 52<br>Safety data: up to the date of the last patient's week-52 visit | Alirocumab 75 mg Q2W (increased, per protocol, at week 12 to 150 mg Q2W if week-8 LDL-C $\geq$ 1.8 mmol $l^{-1}$ [70 mg $dl^{-1}$]) | Ezetimibe 10 mg | 720 randomized (2:1) | All patients received maximum tolerated daily statin therapy. 66.7% of patients received high-intensity statins (atorvastatin 40/80 mg QD or rosuvastatin 20/40 mg QD); 2.1% of patients received simvastatin 80 mg QD |
| **ODYSSEY COMBO I [70]** | Multicentre, randomized, placebo-controlled | 52 weeks | Alirocumab 75 mg Q2W (increased, per protocol, at week 12 to 150 mg Q2W if week-8 LDL-C $\geq$ 1.8 mmol $l^{-1}$ [70 mg $dl^{-1}$]) | Placebo | 316 randomized (2:1 ) | All patients received maximum tolerated daily statin therapy. 61.7–64.5% of patients received high-intensity statins at screening (atorvastatin 40–80 mg QD, rosuvastatin 20–40 mg QD, or simvastatin 80 mg QD) |
| **ODYSSEY LONG TERM[a] [57, 75]** | Multicentre, randomized, double-blind, placebo-controlled, parallel-group | 78 weeks | Alirocumab 150 mg Q2W | Placebo | 2341 randomized (2:1) | 100% ($n$ = 2339) of patients received maximum tolerated daily statin therapy. 46.8% were receiving high-intensity statins (atorvastatin 40–80 mg QD, rosuvastatin 20–40 mg QD, or simvastatin 80 mg QD) |

(*continues*)

## Table 1

(Continued)

| Study name | Design | Duration | Anti-PCSK9 antibody dose regimen(s) | Control arm(s) | Patients | Concomitant treatment (all study arms) |
|---|---|---|---|---|---|---|
| **ODYSSEY FH I and II [43]** | Multicentre, randomized, double-blind | 78 weeks<br>After study end, patients could either enter the open-label extension (3 years, ongoing) or were followed for a further 8 weeks | Alirocumab 75 mg Q2W (increased, per protocol, at week 12 to 150 mg Q2W if week-8 LDL-C $\geq$1.8 mmol $l^{-1}$ [70 mg $dl^{-1}$]) | Placebo | 735 randomized (2:1) | 82.7–91.5% of patients received high-intensity statin therapy (atorvastatin 40–80 mg QD, rosuvastatin 20–40 mg QD, or simvastatin 80 mg QD); 56.0–67.1% of patients received ezetimibe |
| **ODYSSEY HIGH FH[a] [56]** | Randomized, double-blind | 78 weeks | Alirocumab 150 mg Q2W | Placebo | 107 randomized (2:1) | Maximum tolerated statin with or without LLT |
| **ODYSSEY CHOICE I[a] [55]** | Randomized | 24 weeks | Alirocumab 300 mg Q4W | Placebo | 803 randomized | 31.9% of patients received no statins; 68.1% of patients received statins |
| **ODYSSEY CHOICE II[a] [51]** | Randomized | 24 weeks | Alirocumab 150 mg Q4W (increased, per protocol, to 150 mg Q2W if the week 8 LDL-C targets of <1.8 mmol $l^{-1}$ [70 mg $dl^{-1}$] or <2.6 mmol $l^{-1}$ [100 mg $dl^{-1}$], depending on CV risk, were not met, or if week 8 LDL-C was reduced by <30% from baseline) | Placebo | 233 randomized | 28.8–29.3% of patients received no LLT, 59.3–60.3% received ezetimibe, 5.2–10.3% received fenofibrate |
| **ODYSSEY ALTERNATIVE [45]** | Randomized | 24 weeks (optional open-label extension) | Alirocumab 75 mg Q2W (increased, per protocol, at week 12 to 150 mg Q2W depending on CV risk and LDL-C level at week 8) | Ezetimibe 10 mg QD or atorvastatin 20 mg QD | 314 randomized (2:2:1; 361 patients received a placebo run-in before randomization; patients reporting muscular AEs were excluded) | None |
| **Evolocumab** | | | | | | |
| **DESCARTES [53]** | Multicentre, randomized, double-blind, placebo-controlled | Run-in: 4–12 weeks<br>Treatment: 52 weeks | Evolocumab 420 mg Q4W for 48 weeks | Placebo | 905 randomized (2:1) | Of the 901 patients who received a study drug, 12.3% received background LLT with diet alone; 42.5% received 10 mg atorvastatin QD; 24.2% received 80 mg atorvastatin QD; 21.0% received 80 mg atorvastatin + 10 mg ezetimibe QD |
| **TAUSSIG[a,b] [33, 47]** | Single-arm, open-label, Phase 2/3 (interim sub-analysis) | Follow-up: 12, 24 and 48 weeks | Evolocumab 420 mg Q2W (420 mg Q4W after 12 weeks at investigator discretion) plus apheresis Q2W | None | 100 | None (but receiving apheresis) |
| **MENDEL-2 [71]** | Multicentre, randomized, blinded, placebo-controlled, active-comparator | 12 weeks | Evolocumab 140 mg Q2W; evolocumab 420 mg Q4W | Placebo Q2W; placebo Q4W; ezetimibe Q2W; ezetimibe Q4W | 614 randomized (2:2:1:1:1:1) | None |

(*continues*)

## Table 1

(Continued)

| Study name | Design | Duration | Anti-PCSK9 antibody dose regimen(s) | Control arm(s) | Patients | Concomitant treatment (all study arms) |
|---|---|---|---|---|---|---|
| **RUTHERFORD-2 [58]** | Multicentre, randomized, double-blind, placebo-controlled | 12 weeks | Evolocumab 140 mg Q2W; evolocumab 420 mg Q4W | Placebo Q2W; placebo Q4W | 331 randomized (2:1) | All patients received statins. 87% of patients were taking high-intensity statins (80 mg simvastatin QD, ≥ 40 mg atorvastatin QD, ≥ 20 mg rosuvastatin QD, or any dose of statin together with ezetimibe); 62% of patients were taking ezetimibe |
| **LAPLACE-2 [72]** | Multicentre, randomized, double-blind, placebo- and ezetimibe-controlled | 12 weeks | Evolocumab 140 mg Q2W; evolocumab 420 mg Q4W | Placebo; ezetimibe 10 mg QD | 1899 randomized (2:2:1:1) | 29% of patients were taking high-intensity statin therapy (atorvastatin > 40 mg QD or rosuvastatin > 20 mg QD, simvastatin 80 mg or any statin plus ezetimbe); 41% of patients were taking non-intensive statin therapy; 30% of patients were using no statin |
| **TESLA PART B [34]** | Randomized, double-blind, placebo-controlled | Treatment: 12 weeks | Evolocumab 420 mg | Placebo | 50 randomized (2:1) | All patients received statins at baseline; 94% received high- intensity statin therapy (≥40 mg atorvastatin QD, ≥ 20 mg rosuvastatin QD); 92% of patients received ezetimibe |
| **GAUSS-2 [52]** | Randomized, double-blind, placebo- and ezetimibe-controlled | 12 weeks | Evolocumab 140 mg Q2W with placebo Q2W or Q4W; evolocumab 420 mg Q4W with placebo Q2W or Q4W | Ezetimibe 10 mg QD | 307 randomized (2:2:1:1) | 33% of patients received LLT; 18% received a low-dose statin |
| **YUKAWA 2 [44]** | Randomized | Atorvastatin treatment: 4 weeks Evolocumab treatment: 12 weeks | Evolocumab 140 mg Q2W or 420 mg Q4W | Placebo | 404 randomized (1:1:1:1) | Of the 202 patients analysed at week 12, 49.5% received 5 mg atorvastatin; and 50.5% received 20 mg atorvastatin |
| **OSLER-2 [54]** | Randomized, open-label, controlled extension study | Randomized treatment: 48 weeks | Evolocumab 140 mg Q2W; evolocumab 420 mg Q4W | Standard therapy | 3141 randomized (2:1) | Statins and/or ezetimibe; data for OSLER-2 not reported separately |

[a]Data published in congress abstracts

[b]Study ongoing

AE, adverse event; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; OLE, open-label extension; QD, daily; Q2W, every 2 weeks; Q4W, every 4 weeks. LDL-C concentrations are presented in mmol $l^{-1}$ and mg $dl^{-1}$; where the publication provided only concentrations in either mg $dl^{-1}$ or mmol $l^{-1}$, a conversion factor of 38.67 was used [97].

## Table 2

Inclusion criteria and baseline cardiovascular risk in the Phase 3 trials of anti-PCSK9 antibodies in patients with hypercholesterolaemia

| Study name | Patient population and CV risk as specified by inclusion criteria | CV risk definitions used/criteria for diagnosis of FH | Overall cardiovascular risk at baseline in enrolled population |
|---|---|---|---|
| **Alirocumab** | | | |
| **ODYSSEY MONO [40, 81]** | Hypercholesterolaemia (LDL-C 2.6–4.9 mmol $l^{-1}$ [100–190 mg $dl^{-1}$]) and moderate CV risk | SCORE | Moderate (10-year risk of fatal CV events of ≥ 1% and < 5%); (SCORE: alirocumab, 2.97; ezetimibe, 2.68) |
| **OPTIONS I [50]** | High CV risk with LDL-C ≥ 2.6 mmol $l^{-1}$ (100 mg $dl^{-1}$) or very high with LDL-C ≥ 1.8 mmol $l^{-1}$ (70 mg $dl^{-1}$) risk despite atorvastatin | SCORE | High or very high |
| **OPTIONS II [46]** | CVD and LDL-C ≥ 1.8 mmol/l (70 mg $dl^{-1}$) or CV risk factors and LDL-C ≥ 2.6 mmol $l^{-1}$ (100 mg $dl^{-1}$), (i.e. high risk, despite baseline rosuvastatin) | Not reported | High |
| **ODYSSEY COMBO II [74]** | CVD and LDL-C ≥ 1.8 mmol $l^{-1}$ (70 mg $dl^{-1}$) or CHD risk equivalents and LDL-C ≥ 2.6 mmol $l^{-1}$ (100 mg $dl^{-1}$); hypercholesterolaemia not controlled by statins, high CV risk | Hypercholesterolaemia and established CHD or CHD risk equivalents | 98.6% had CV history or risk factors |
| **ODYSSEY COMBO I [70]** | CVD and LDL-C ≥ 1.8 mmol $l^{-1}$ (70 mg $dl^{-1}$) or CHD risk equivalents and LDL-C ≥ 2.6 mmol $l^{-1}$ (100 mg $dl^{-1}$); on maximum tolerated statin therapy | Hypercholesterolaemia and established CHD or CHD risk equivalents | High |
| **ODYSSEY LONG TERM[a] [57, 75]** | LDL-C ≥ 1.8 mmol $l^{-1}$ (70 mg $dl^{-1}$) and HeFH (i.e. high risk) or high CV risk | HeFH diagnosed either by genetic analysis or clinical criteria; risk evels assessed using CHD or CHD risk equivalents | High |
| **ODYSSEY FH I and II [43]** | HeFH with LDL-C above ESC/EAS goal concentrations (i.e. high CV risk) | HeFH diagnosed either by genotyping or by clinical criteria (Simon Broome or WHO/Dutch Lipid Network criteria with a score of >8 points) | High (all patients had HeFH) |
| **ODYSSEY HIGH FH[a] [56]** | HeFH and severe HeFH (LDL-C ≥ 4.2 mmol $l^{-1}$ [160 mg $dl^{-1}$] ) despite maximum tolerated statins | Severe HeFH defined as HeFH and LDL-C ≥ 4.1 mmol $l^{-1}$ (160 mg $dl^{-1}$) despite maximum tolerated statin therapy | High or very high (all patients had HeFH) |
| **ODYSSEY CHOICE I[a] [55]** | Hypercholesterolaemia at moderate–very high CV risk receiving maximum tolerated statin/at moderate CV risk not receiving statin/ moderate–very high CV risk with statin intolerance | Moderate, high or very high risk defined as patients who were intolerant to ≥2 statins, one at the lowest daily starting dose and another at any dose | Moderate–very high |

(*continues*)

## Table 2

(Continued)

| Study name | Patient population and CV risk as specified by inclusion criteria | CV risk definitions used/criteria for diagnosis of FH | Overall cardiovascular risk at baseline in enrolled population |
|---|---|---|---|
| **ODYSSEY CHOICE II[a] [51]** | Hypercholesterolaemia with moderate–very high CV risk and SAMS/moderate risk without SAMS | Not reported | Moderate–very high |
| **ODYSSEY ALTERNATIVE [45]** | LDL-C ≥ 2.6 mmol/l (100 mg $dl^{-1}$) and moderate–high CV risk or LDL-C ≥ 1.8 mmol/l (70 mg $dl^{-1}$) and very high CV risk. Statin intolerance/SAMS | Not reported | Not reported |
| **Evolocumab** | | | |
| **DESCARTES [53]** | LDL-C ≥ 1.9 mmol $l^{-1}$ (75 mg $dl^{-1}$), various levels of CV risk | NECP ATP III guidelines | High: evolocumab, 26.0%; placebo, 26.2%<br>Moderately high: evolocumab, 9.3%; placebo, 9.6%<br>Moderate: evolocumab, 33.9%; placebo, 32.1%<br>Low: evolocumab, 30.7%; placebo, 32.1% |
| **TAUSSIG [a,b,c] [33, 47]** | HoFH (i.e. very high CV risk), some receiving lipid apheresis | Clinical or genetic diagnosis of severe FH | Very high (all patients had HoFH) |
| **MENDEL-2 [71]** | LDL-C ≥ 2.6 mmol $l^{-1}$ (100 mg $dl^{-1}$) and low CV risk | Framingham CHD risk scores [92] | Low |
| **RUTHERFORD-2 [58]** | LDL-C ≥ 2.6 mmol $l^{-1}$ (100 mg $dl^{-1}$) and HeFH (i.e. high CV risk) | Simon Broome criteria | High (all patients had HeFH) |
| **LAPLACE-2 [72]** | Hypercholesterolaemia 2.1–3.9 mmol $l^{-1}$ (80–150 mg $dl^{-1}$), various levels of CV risk | NCEP ATP III | Coronary artery disease: evolocumab, 23.8%placebo, 22.0%;ezetimibe, 17.2% |
| **TESLA PART B [34]** | LDL-C ≥ 3.4 mmol $l^{-1}$ (131 mg $dl^{-1}$) and HoFH (i.e. very high CV risk) | HoFH diagnosed either by genetic analysis or clinical criteria (history of an untreated LDL-C concentration > 13 mmol/l [500 mg $dl^{-1}$] plus either xanthoma before 10 years of age or evidence of HeFH in both parents) | Very high (all patients had HoFH) |
| **GAUSS-2 [52]** | LDL-C above NCEP goal concentrations, statin intolerance, various levels of CV risk | NCEP ATP III | High: evolocumab, 50–57%; control, 63%<br>Moderately high: evolocumab, 16%; control, 10–16%<br>Moderate: evolocumab, 16–19%; control, 16–18%<br>Low: evolocumab, 12–16%; control, 6–10% |
| **YUKAWA 2 [44]** | LDL-C ≥ 2.6 mmol/l (100 mg $dl^{-1}$), hyperlipidaemia or mixed dyslipidaemia and high CV risk | Japan Atherosclerosis Society criteria | High |

(continues)

**Table 2**
(Continued)

| Study name | Patient population and CV risk as specified by inclusion criteria | CV risk definitions used/criteria for diagnosis of FH | Overall cardiovascular risk at baseline in enrolled population |
|---|---|---|---|
| **OSLER-2 [54]** | Patients who completed one of the parent studies could enrol, providing they had not discontinued treatment owing to an AE, had stable disease and were not expected to require dose adjustments or unblended lipid measurements | Risk assessed according to parent trial | Various |

[a]Data published in congress abstracts
[b]Although the TAUSSIG study enrolled patients with severe hypercholesterolaemia, including those with HeFH, the data included in this systematic review are only from patients with HoFH
[c]Study ongoing
ATP, Adult Treatment Panel; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; SAMS, statin-associated muscle symptoms; SCORE, European Systematic Coronary Risk Estimation; WHO, World Health Organization. LDL-C concentrations are presented in mmol $l^{-1}$ and mg $dl^{-1}$; where the publication provided only concentrations in either mg $dl^{-1}$ or mmol $l^{-1}$, a conversion factor of 38.67 was used (i.e. mg $dl^{-1}$/38.67 = concentration in mmol $l^{-1}$) [97]. For the purposes of this review, we assumed that patients with HeFH had a high CV risk and those with HoFH had a very high CV risk.

(64% were high-risk in the subgroup of patients who received evolocumab plus 80 mg atorvastatin and 10 mg ezetimibe) also achieved their LDL-C goal [53].

The proportions of patients receiving monotherapy who achieved their LDL-C goal ranged from 42%, which was observed in the ODYSSEY ALTERNATIVE study of alirocumab monotherapy in patients with moderate–very high CV risk and statin intolerance to 84% in the subgroup receiving evolocumab monotherapy in DESCARTES (of whom 5% had high CV risk defined using the NCEP ATP III classification) [45, 53]. The difference in baseline LDL-C levels may have influenced this difference in outcomes: mean baseline LDL-C was 4.9 mmol $l^{-1}$ (191 mg $dl^{-1}$) in the ODYSSEY ALTERNATIVE study and 2.7 mmol $l^{-1}$ (104 mg $dl^{-1}$) in DESCARTES.

Four studies did not report the proportion of patients who achieved their LDL-C goal [33, 34, 47, 54, 55]. ODYSSEY CHOICE I showed that the mean reduction in LDL-C was greater than 50% [55].

*Patients with familial hypercholesterolaemia.* All the multi-arm studies showed a significant reduction in LDL-C with the anti-PCSK9 antibody being investigated *vs.* the comparator (Table 5).

The ODYSSEY FH studies of alirocumab in combination with statins enrolled patients with HeFH. Mean placebo-corrected LDL-C reductions of 51–58% were observed, with 72–81% of patients achieving their LDL-C goal [43]. In the ODYSSEY HIGH FH study, fewer patients (41%) met LDL-C goals, probably reflecting the study inclusion requirement for patients to have severe HeFH (patients with LDL-C $\geq$ 4.1 mmol $l^{-1}$ [160 mg $dl^{-1}$] despite maximally tolerated statin with or without lipid-lowering therapy) [56]. In the ODYSSEY LONG TERM study of alirocumab, 17.7% of patients had HeFH [57]. Data were not reported according to the aetiology of hypercholesterolaemia, but the authors stated that the percentage change in LDL-C was similar across subgroups. Overall, the calculated decrease in LDL-C level from baseline to week 24 was 61.0% with alirocumab; 79% of patients achieved their LDL-C goal (Table 5 and Figure 2) [57].

In the RUTHERFORD-2 study of evolocumab monotherapy in patients with HeFH, 68% of patients in the evolocumab 140 mg Q2W arm and 63% in the evolocumab 420 mg Q4W arm achieved their LDL-C goal (Table 5 and Figure 2) [58]. TESLA part B [34] and an interim subgroup analysis of TAUSSIG (itself a subgroup analysis of TESLA part B; [33, 47]) both reported data for evolocumab in patients with HoFH (it should be noted that patients with HeFH and LDL-C $\geq$ 3.4 mmol $l^{-1}$ [130 mg $dl^{-1}$] who had not been diagnosed with coronary heart disease [CHD] or CHD risk equivalents; or LDL-C $\geq$ 2.6 mmol $l^{-1}$ [100 mg $dl^{-1}$] who had been diagnosed with CHD or CHD risk equivalent; or who were receiving apheresis [59], were also included in these studies but data for those patients have not been reported). HoFH is a rare disease [60] and at the time of this review, there were no Phase 3 data for alirocumab in this population. The proportion of patients achieving their LDL-C goal was not reported in either evolocumab study, and the mean LDL-C reductions were less than 50% (decrease from baseline at week 12: TESLA part B, 23.1% with evolocumab *vs.* 7.9% with placebo

## Table 3

Assays used in studies of effect of anti-PCSK9 antibodies on LDL-C levels in patients with hypercholesterolaemia

| Study name | LDL-C assays | | Anti-drug antibody assays |
|---|---|---|---|
| | Method | Time-point(s) | |
| **Alirocumab** | | | |
| **ODYSSEY MONO [40, 81]** | Friedewald method | Weeks 12 and 24 | Assessed by the Regeneron Clinical Bioanalysis Group (Regeneron Pharmaceuticals, Tarrytown, NY, USA), at baseline, weeks 12 and 24; follow-up week 32 |
| **OPTIONS I [50]** | Lipid analysis done at a central laboratory LDL-C levels determined using Friedewald formula unless triglyceride levels > 4.5 mmol $l^{-1}$ (400 mg $dl^{-1}$), in which cases β-quantification was used | Week 24 | Assessed using a validated immunoassay with adequate sensitivity by Regeneron Pharmaceuticals, Inc., at baseline, weeks 12 and 24; follow-up week 32 |
| **OPTIONS II [46]** | Not reported | Week 24 | Assessed using a validated immunoassay by Regeneron Pharmaceuticals, Inc., at weeks 4, 8, 12, 16 and 24; follow-up week 32 |
| **ODYSSEY COMBO II [74]** | LDL-C levels determined using Friedewald formula unless triglyceride levels > 4.5 mmol $l^{-1}$ (400 mg $dl^{-1}$), in which cases β-quantification was used | Week 24 | Assessed by Medpace Reference Laboratories, Cincinnati, Ohio |
| **ODYSSEY COMBO I [70]** | Lipid analysis done at a central laboratory LDL-C levels determined using Friedewald formula | Week 24 | Assay details not reported Assessed at baseline, weeks 12, 24 and 52; follow-up week 60 |
| **ODYSSEY LONG TERM[a] [57, 75]** | LDL-C levels determined using Friedewald formula unless triglyceride levels > 4.5 mmol $l^{-1}$ (400 mg $dl^{-1}$), in which cases β-quantification was used | Week 24 | Not reported |
| **ODYSSEY FH I and II [43]** | LDL-C levels determined using Friedewald formula and β-quantification | Week 24 | Samples collected at clinic visits, prior to administration of study drug, at baseline, weeks 12, 24, 52 and 78 and follow-up<br>Assayed using a validated assay by Regeneron Pharmaceuticals, Inc. |
| **ODYSSEY HIGH FH[a] [56]** | Not reported | Week 24 | Not reported |
| **ODYSSEY CHOICE I[a] [55]** | Not reported | Week 24 | Not reported |
| **ODYSSEY CHOICE II[a] [51]** | Not reported | Week 24 | Not reported |
| **ODYSSEY ALTERNATIVE [45]** | LDL-C levels determined using Friedewald formula | Week 24 | Not reported |

(*continues*)

## Table 3

(Continued)

| Study name | LDL-C assays | | Anti-drug antibody assays |
|---|---|---|---|
| | Method | Time-point(s) | |
| **Evolocumab** | | | |
| **DESCARTES [53]** | LDL-C levels determined using Friedewald formula unless triglyceride levels > 4.5 mmol $l^{-1}$ (400 mg $dl^{-1}$) or LDL-C < 1.0 mmol $l^{-1}$ (39 mg $dl^{-1}$), in which cases reflexive testing via ultracentrifugation was used | Week 12 and week 52 | Assayed at baseline and weeks 12, 24, 36 and 52 |
| **TAUSSIG[a,c] [33, 47]** | Not reported | Weeks 12, 24 and 48 | Not reported |
| **MENDEL-2 [71]** | LDL-C levels determined using Friedewald formula unless triglyceride levels > 4.5 mmol $l^{-1}$ (400 mg $dl^{-1}$) or LDL-C < 1.0 mmol $l^{-1}$ (39 mg $dl^{-1}$), in which cases preparative ultracentrifugation was used | Weeks 10 and 12 | Immunoassays conducted by EMD Millipore Corporation (St. Charles, MO) and Amgen Inc. |
| **RUTHERFORD-2 [58]** | LDL-C levels determined using Friedewald formula unless triglyceride levels ≥ 4.5 mmol $l^{-1}$ (400 mg $dl^{-1}$) or LDL-C levels < 1.0 mmol $l^{-1}$ (39 mg $dl^{-1}$), in which cases preparative ultracentrifugation was used | Weeks 10 and 12 | Binding/neutralizing antibodies assessed at baseline and week 12 |
| **LAPLACE-2[b] [72]** | LDL-C levels determined using Friedewald formula unless triglyceride levels ≥ 4.5 mmol $l^{-1}$ (400 mg $dl^{-1}$)[b] or LDL-C levels < 1.0 mmol $l^{-1}$ (39 mg $dl^{-1}$), in which cases preparative ultracentrifugation was used | Weeks 10 and 12 | Binding/neutralizing antibodies assessed at baseline and week 12 |
| **TESLA PART B [34]** | Lipid analysis done at a central laboratory LDL-C levels determined using Friedewald formula with preparative ultracentrifugation | Week 12 (mean of weeks 6 and 12 also reported) | Assessed and analysed at each visit by a central Laboratory (Millipore [Billerica, MA, USA]) |
| **GAUSS-2 [52]** | LDL-C levels determined using Friedewald formula unless triglyceride levels > 4.5 mmol $l^{-1}$ (400 mg $dl^{-1}$) or LDL-C < 1.0 mmol $l^{-1}$ (39 mg $dl^{-1}$), in which cases preparative ultracentrifugation was used | Weeks 10 and 12 | Binding/neutralizing antibodies assessed but details of assay/ scheduling not reported |
| **YUKAWA 2 [44]** | Not reported | Weeks 10 and 12 | Not reported |

(*continues*)

**Table 3**
(Continued)

| Study name | LDL-C assays | | Anti-drug antibody assays |
|---|---|---|---|
| | Method | Time-point(s) | |
| **OSLER-2 [54]** | LDL-C levels determined using Friedewald formula | Week 12 | Electrochemiluminescence-based immunoassay at baseline and every 4 weeks |

[a]Data published in congress abstracts
[b]Robinson *et al.* reported a triglyceride concentration of 400 mg $dl^{-1}$ as equivalent to 3.9 mmol $l^{-1}$ but reported a similar conversion factor to that we used. We have therefore amended the triglyceride concentration in mmol $l^{-1}$ to 4.5 mmol $l^{-1}$, in agreement with the conversion factor they report
[c]Study ongoing
LDL-C, low-density lipoprotein cholesterol. LDL-C concentrations are presented in mmol $l^{-1}$ and mg $dl^{-1}$; where the publication provided only concentrations in either mg $dl^{-1}$ or mmol $l^{-1}$, a conversion factor of 38.67 was used (i.e. mg $dl^{-1}$/38.67 = concentration in mmol $l^{-1}$). Triglyceride concentrations are presented in both mg $dl^{-1}$ and mmol $l^{-1}$; where the publication provided concentration in only mg $dl^{-1}$ or only in mmol $l^{-1}$ a conversion factor of 88.57 was used to convert between units (i.e. mg $dl^{-1}$/88.57 = concentration in mmol $l^{-1}$) [97].

[$P < 0.0001$]; TAUSSIG, 21% with evolocumab; Table 5) [33, 34, 47].

Overall, the percentage reduction in LDL-C was similar in patients with FH and those with non-familial hypercholesterolaemia, although rates of goal achievement were lower in patients with FH.

## *Efficacy across subgroups*

*Patients with type 2 diabetes.* A pooled analysis of five placebo-controlled Phase 3 alirocumab studies (ODYSSEY FH I and FH II, COMBO I, HIGH FH and LONG TERM) found that in patients with type 2 diabetes who received 75 mg alirocumab (up-titration to 150 mg if required), least-square mean LDL-C changes from baseline to week 24 were 43.4% for those treated with alirocumab *vs.* 0.3% for those who received placebo ($P < 0.001$). In patients without type 2 diabetes, reductions were 49.8% and 5.1%, respectively ($P < 0.0001$). The *P*-value for the effect of diabetes on LDL-C reduction was 0.02. Dose increase at week 12 was more common in patients without diabetes than in those with diabetes, which could explain these results; in patients from studies in which alirocumab was given at 150 mg from the start, type 2 diabetes had no significant effect on LDL-C reduction [61].

A pooled analysis of data from the MENDEL-2, LAPLACE-2, RUTHERFORD-2 and GAUSS-2 evolocumab studies found that mean changes in LDL-C in patients with type 2 diabetes ($n = 417$; 57–60% across dosing regimens) were similar to those in individuals without the disease ($n = 2729$; 61–62%). Goal achievement in patients with diabetes was high, with 87–88% of patients achieving LDL-C levels below 1.8 mmol $l^{-1}$ (70 mg $dl^{-1}$) [62]. A second pooled analysis of four Phase 3 trials also found that evolocumab reduced LDL-C to a similar extent in patients with and without type 2 diabetes [63].

*Other patient subgroups.* A pooled analysis of data from six alirocumab studies (ODYSSEY COMBO I and II, FH I and II, HIGH FH and LONG TERM) showed that alirocumab significantly reduced LDL-C levels compared with controls, regardless of whether or not patients were also receiving high-intensity statin treatment (atorvastatin 40–80 mg) and regardless of background lipid-lowering treatment [64].

An analysis of the efficacy of alirocumab in patients with and without moderate chronic kidney disease (CKD) across ten Phase 3 trials found that, in the majority of studies, alirocumab significantly lowered LDL-C by approximately 40–70% *vs.* the comparator treatment. The exception was the ALTERNATIVE trial, in which there was no significant reduction in LDL-C with alirocumab *vs.* the control for patients with moderate CKD; however, patient numbers were small [65].

A pooled analysis of data from ten Phase 3 trials found that alirocumab was significantly better than the control in lowering LDL-C levels, regardless of baseline triglyceride or HDL-C concentrations [66]. Similarly, a pooled analysis of data from four Phase 3 studies found that evolocumab significantly reduced LDL-C compared with the control in patients with high LDL-C at baseline (≥4.1 mmol $l^{-1}$ [159 mg $dl^{-1}$] on statin treatment or ≥6.1 mmol $l^{-1}$ [236 mg $dl^{-1}$] not on statin) [67]. A pooled analysis of data from Phase 3 trials has shown

## Table 4

Other baseline characteristics of patients with hypercholesterolaemia in Phase 3 trials of anti-PCSK9 antibodies

| Study name | Age (years), mean ± SD | Proportion of men | LDL-C at baseline, mean ± SD | Other CV risk factors |
|---|---|---|---|---|
| **Alirocumab** | | | | |
| **ODYSSEY MONO [40, 81]** | Alirocumab, 60.8 ± 4.6<br>Ezetimibe, 59.6 ± 5.3 | Alirocumab, 53.8%<br>Ezetimibe, 52.9% | Alirocumab, 3.6 ± 0.7 mmol $l^{-1}$ (141 ± 27 mg $dl^{-1}$)<br>Ezetimibe, 3.6 ± 0.6 mmol $l^{-1}$ (138 ± 23 mg $dl^{-1}$) | Diabetes:<br>Alirocumab, 5.8%<br>Ezetimibe, 2.0% |
| **OPTIONS I [50]** | Alirocumab, 62.2–64.2<br>Control groups, 57.5–65.7 | Alirocumab, 57.9–66.0%<br>Control groups, 56.4–76.6% | Alirocumab + atorvastatin (20 mg), 2.7 ± 0.9 mmol $l^{-1}$ (104 ± 35 mg $dl^{-1}$)<br>Alirocumab + atorvastatin (40 mg), 3.0 ± 1.0 mmol $l^{-1}$ (116 ± 37 mg $dl^{-1}$)<br>Ezetimibe + atorvastatin (20 mg), 2.6 ± 0.8 mmol $l^{-1}$ (100 ± 30 mg $dl^{-1}$)<br>Ezetimibe + atorvastatin (40 mg), 2.6 ± 0.8 mmol $l^{-1}$ (99 ± 29 mg $dl^{-1}$)<br>Atorvastatin (40 mg), 2.6 ± 0.8 mmol $l^{-1}$ (100 ± 30 mg $dl^{-1}$)<br>Atorvastatin (80 mg), 2.8 ± 1.0 mmol $l^{-1}$ (109 ± 38 mg $dl^{-1}$)<br>Rosuvastatin (40 mg), 2.8 ± 1.0 mmol $l^{-1}$ (110 ± 39 mg $dl^{-1}$) | Type 2 diabetes:<br>Alirocumab, 53.2–57.9%<br>Control groups, 34.0–54.4%<br>Hypertension:<br>Alirocumab, 76.6–77.2%<br>Control groups, 73.3–81.8% |
| **OPTIONS II [46]** | Alirocumab, 57.9–62.2<br>Control groups, 60.4–63.1 | Alirocumab, 51.9–63.3%<br>Control groups, 52.4–71.7% | Alirocumab + rosuvastatin (10 mg), 2.8 ± 0.7 mmol $l^{-1}$ (107 ± 26 mg $dl^{-1}$)<br>Alirocumab + rosuvastatin (20 mg), 3.1 ± 0.8 mmol $l^{-1}$ (118 ± 32 mg $dl^{-1}$)<br>Ezetimibe + rosuvastatin (10 mg), 2.7 ± 1.1 mmol $l^{-1}$ (102 ± 42 mg $dl^{-1}$)<br>Ezetimibe + rosuvastatin (20 mg), 3.1 ± 1.2 mmol $l^{-1}$ (119 ± 48 mg $dl^{-1}$)<br>Rosuvastatin (20 mg), 2.7 ± 0.9 mmol $l^{-1}$ (106 ± 36 mg $dl^{-1}$)<br>Rosuvastatin (40 mg), 2.9 ± 1.1 mmol $l^{-1}$ (113 ± 43 mg $dl^{-1}$) | Type 2 diabetes:<br>Alirocumab, 33.3–38.8%<br>Control groups, 32.1–58.3%<br>CHD history:<br>Alirocumab, 49.6–59.3%<br>Control groups, 52.1–67.9%<br>CHD risk equivalent:<br>Alirocumab, 20.4–32.7%<br>Control groups, 20.8–31.3% |
| **ODYSSEY COMBO II [74]** | Alirocumab, 61.7 ± 9.4<br>Ezetimibe, 61.3 ± 9.2 | Alirocumab, 75.2%<br>Ezetimibe, 70.5% | Alirocumab, 2.8 ± 0.9 mmol $l^{-1}$ (108 ± 34 mg $dl^{-1}$)<br>Ezetimibe, 2.7 ± 0.9 mmol $l^{-1}$ (104 ± 34 mg $dl^{-1}$) | CV history or risk factors:<br>Alirocumab, 99.6%<br>Ezetimibe, 100%<br>Type 2 diabetes:<br>Alirocumab, 30.4%<br>Ezetimibe, 31.5% |
| **ODYSSEY COMBO I [70]** | Alirocumab, 63.0 ± 9.5<br>Placebo, 63.0 ± 8.8 | Alirocumab, 62.7%<br>Placebo, 72.0% | Alirocumab, 2.6 ± 0.76 mmol $l^{-1}$ (100 ± 30 mg $dl^{-1}$)<br>Placebo, 2.7 ± 0.91 mmol $l^{-1}$ (106 ± 35 mg $dl^{-1}$) | CHD history:<br>Alirocumab, 78.5%<br>Placebo, 77.6%<br>CHD risk equivalents:<br>Alirocumab, 40.7%<br>Placebo, 47.7% |

(*continues*)

## Table 4

(Continued)

| Study name | Age (years), mean ± SD | Proportion of men | LDL-C at baseline, mean ± SD | Other CV risk factors |
|---|---|---|---|---|
| | | | | Type 2 diabetes:<br>Alirocumab, 45.0%<br>Placebo, 39.3% |
| **ODYSSEY LONG TERM[a] [57, 75]** | Alirocumab, 60.4 ± 10.4<br>Placebo, 60.6 ± 10.4 | Alirocumab, 63.3%<br>Placebo, 60.2% | Alirocumab, 3.2 ± 1.1 mmol $l^{-1}$<br>(123 ± 43 mg $dl^{-1}$)<br>Placebo, 3.2 ± 1.1 mmol $l^{-1}$<br>(122 ± 41 mg $dl^{-1}$) | CHD history:<br>Alirocumab, 67.9%<br>Placebo, 70.1%<br>CHD risk equivalents:<br>Alirocumab, 41.1%<br>Placebo, 41.0%<br>Type 2 diabetes:<br>Alirocumab, 34.9%<br>Placebo, 33.9% |
| **ODYSSEY FH I [43]** | Alirocumab, 52.1 ± 12.9<br>Placebo, 51.7 ± 12.3 | Alirocumab, 55.7%<br>Placebo, 57.7% | Alirocumab, 3.7 ± 0.1 mmol $l^{-1}$<br>(145 ± 3 mg $dl^{-1}$)<br>Placebo, 3.7 ± 0.1 mmol $l^{-1}$<br>(144 ± 4 mg $dl^{-1}$) (LS mean ± SE) | CHD:<br>Alirocumab, 45.5%<br>Placebo, 47.9%<br>Type 2 diabetes:<br>Alirocumab, 9.9%<br>Placebo, 15.3%<br>Hypertension:<br>Alirocumab, 43.0%<br>Placebo, 43.6% |
| **ODYSSEY FH II [43]** | Alirocumab, 53.2 ± 12.9<br>Placebo, 53.2 ± 12.5 | Alirocumab, 51.5%<br>Placebo, 54.9% | Alirocumab, 3.5 ± 0.1 mmol $l^{-1}$<br>(135 ± 3 mg $dl^{-1}$)<br>Placebo, 3.5 ± 0.1 mmol $l^{-1}$<br>(134 ± 5 mg $dl^{-1}$)<br>(LS mean ± SE) | CHD:<br>Alirocumab, 34.7%<br>Placebo, 37.8%<br>Type 2 diabetes:<br>Alirocumab, 4.2%<br>Placebo, 3.7%<br>Hypertension:<br>Alirocumab, 34.1%<br>Placebo, 29.3% |
| **ODYSSEY HIGH FH[a] [56]** | Not reported | Not reported | Alirocumab, 5.1 ± 1.5 mmol $l^{-1}$<br>(196 ± 58 mg $dl^{-1}$)<br>Placebo, 5.2 ± 1.1 mmol $l^{-1}$<br>(201 ± 43 mg $dl^{-1}$) | Not reported |
| **ODYSSEY CHOICE I[a] [55]** | Not reported | Not reported | Not reported | Not reported |
| **ODYSSEY CHOICE II[a] [51]** | 63 | 56% | Alirocumab 150 mg Q4W,<br>4.2 ± 1.8 mmol $l^{-1}$<br>(164 ± 69 mg $dl^{-1}$)<br>Alirocumab 75 mg Q2W,<br>4.0 ± 1.2 mmol $l^{-1}$<br>(155 ± 45 mg $dl^{-1}$)<br>Placebo, 4.1 ± 1.2 mmol $l^{-1}$<br>(159 ± 47 mg $dl^{-1}$) | CHD, 51%<br>Type 2 diabetes, 17% |

(*continues*)

## Table 4

(Continued)

| Study name | Age (years), mean ± SD | Proportion of men | LDL-C at baseline, mean ± SD | Other CV risk factors |
|---|---|---|---|---|
| **ODYSSEY ALTERNATIVE [45]** | Alirocumab, 64.1 ± 9.0<br>Ezetimibe, 62.8 ± 10.1<br>Atorvastatin, 63.4 (8.9) | Alirocumab, 55.6%<br>Ezetimibe, 53.6%<br>Atorvastatin, 55.6% | Alirocumab, 4.9 ± 1.9 mmol $l^{-1}$ (191 ± 73 mg $dl^{-1}$)<br>Ezetimibe, 5.0 ± 1.8 mmol $l^{-1}$ (194 ± 71 mg $dl^{-1}$)<br>Atorvastatin, 4.8 ± 1.5 mmol $l^{-1}$ (187 ± 60 mg $dl^{-1}$) | CHD:<br>Alirocumab, 50.8%<br>Ezetimibe, 43.2%<br>Atorvastatin, 44.4%<br>Type 2 diabetes:<br>Alirocumab, 28.6%<br>Ezetimibe, 19.2%<br>Atorvastatin, 23.8%<br>Hypertension:<br>Alirocumab, 67.5%<br>Ezetimibe, 61.6%<br>Atorvastatin, 55.6% |
| **Evolocumab** | | | | |
| **DESCARTES [53]** | Evolocumab, 55.9 ± 10.8<br>Placebo, 56.7 ± 10.1 | Evolocumab, 48.4%<br>Placebo, 46.4% | Evolocumab, 2.7 ± 0.6 mmol $l^{-1}$ (104 ± 22 mg $dl^{-1}$)<br>Placebo, 2.7 ± 0.6 mmol $l^{-1}$ (104 ± 22 mg $dl^{-1}$) | Type 2 diabetes:<br>Evolocumab, 10.4%<br>Placebo, 13.9%<br>Hypertension:<br>Evolocumab, 48.2%<br>Placebo, 49.3%<br>≥2 CV risk factors:<br>Evolocumab, 37.4%<br>Placebo, 42.4% |
| **TAUSSIG[a,b] [33, 47]** | 34 | 51% | 8.3 ± 3.3 mmol $l^{-1}$ (320 ± 128 mg $dl^{-1}$) | CHD: 46% |
| **MENDEL-2 [71]** | Evolocumab groups, 53<br>Placebo groups, 53–54 | Evolocumab groups, 32–34%<br>Control groups, 31–40% | Evolocumab Q2W (140 mg) + placebo QD, 3.7 ± 0.6 mmol $l^{-1}$ (142 ± 22 mg $dl^{-1}$)<br>Evolocumab QM (420 mg) + placebo QD, 3.7 ± 0.6 mmol $l^{-1}$ (144 ± 23 mg $dl^{-1}$)<br>Placebo Q2W + ezetimibe QD, 3.7 ± 0.6 mmol $l^{-1}$ (143 ± 24 mg $dl^{-1}$)<br>Placebo QM + ezetimibe QD, 3.7 ± 0.6 mmol $l^{-1}$ (144 ± 23 mg $dl^{-1}$)<br>Placebo Q2W + placebo QD, 3.6 ± 0.5 mmol $l^{-1}$ (140 ± 21 mg $dl^{-1}$)<br>Placebo QM + placebo QD, 3.7 ± 0.6 mmol $l^{-1}$ (144 ± 24 mg $dl^{-1}$) | Type 2 diabetes:<br>Evolocumab groups, 0%<br>Control groups, 0–1%<br>Hypertension:<br>Evolocumab groups, 33–35%<br>Control groups, 16–30%<br>Low HDL-C:<br>Evolocumab groups, 20–24%<br>Control groups, 18–34%<br>≥2 CV risk factors:<br>Evolocumab groups, 18–19%<br>Control groups, 11–26% |
| **RUTHERFORD-2 [58]** | Evolocumab Q2W, 52.6 ± 12.3<br>Placebo Q2W, 51.1 ± 14.2<br>Evolocumab Q4W: 51.9 ± 12.0<br>Placebo Q4W, 46.8 ± 12.1 | Evolocumab Q2W, 60%<br>Placebo Q2W, 54%<br>Evolocumab Q4W, 58%<br>Placebo Q4W, 56% | Evolocumab Q2W, 4.2 ± 1.3 mmol $l^{-1}$ (162 ± 50 mg $dl^{-1}$)<br>Placebo Q2W, 3.9 ± 0.9mmol $l^{-1}$ (151 ± 35 mg $dl^{-1}$)<br>Evolocumab Q4W, 4.0 ± 1.1 mmol $l^{-1}$ (155 ± 43 mg $dl^{-1}$)<br>Placebo Q4W, 3.9 ± 1.1 mmol $l^{-1}$ (151 ± 43 mg $dl^{-1}$) | Coronary artery disease:<br>Evolocumab Q2W, 35%<br>Placebo Q2W, 30%<br>Evolocumab Q4W 35%<br>Placebo Q4W, 18% |

(*continues*)

## Table 4

(Continued)

| Study name | Age (years), mean ± SD | Proportion of men | LDL-C at baseline, mean ± SD | Other CV risk factors |
|---|---|---|---|---|
| **LAPLACE-2 [72]** | Evolocumab, 59.6 ± 9.9<br>Placebo, 59.9 ± 10.2<br>Ezetimibe, 60.8 ± 9.3 | Evolocumab, 56.0%<br>Placebo, 52.2%<br>Ezetimibe, 50.7% | Evolocumab, 2.8 ± 1.1 mmol $l^{-1}$ (110 ± 42 mg $dl^{-1}$)<br>Placebo, 2.8 ± 1.0 mmol $l^{-1}$ (108 ± 40 mg $dl^{-1}$)<br>Ezetimibe, 2.8 ± 1.0 mmol $l^{-1}$ (109 ± 37 mg $dl^{-1}$) | Diabetes:<br>Evolocumab, 15.7%<br>Placebo, 13.3%<br>Ezetimibe, 19.9% |
| **TESLA PART B [34]** | Evolocumab, 30 ± 12<br>Placebo, 32 ± 14 | Evolocumab, 52%<br>Placebo, 50% | Evolocumab, 9.2 ± 3.5 mmol $l^{-1}$ (356 ± 135 mg $dl^{-1}$)<br>Placebo, 8.7 ± 3.8 mmol $l^{-1}$ (336 ± 147 mg $dl^{-1}$)<br>(determined using ultracentrifugation; Friedewald formula values also presented) | Type 2 diabetes: 6%<br>Hypertension:<br>Evolocumab, 12%<br>Placebo, 6%<br>Low HDL-C:<br>Evolocumab, 64%<br>Placebo, 81%<br>≥2 CV risk factors:<br>Evolocumab, 52%<br>Placebo, 63% |
| **GAUSS-2 [52]** | Evolocumab groups, 61–63<br>Control groups, 60–62 | Evolocumab groups, 55%<br>Control groups, 47–57% | Evolocumab Q2W (140 mg) + placebo QD, 5.0 ± 1.5 mmol $l^{-1}$ (192 ± 57 mg $dl^{-1}$)<br>Evolocumab QM (420 mg) + placebo QD, 5.0 ± 1.6 mmol $l^{-1}$ (192 ± 61 mg $dl^{-1}$)<br>Ezetimibe QD + placebo Q2W, 5.0 ± 1.7 mmol $l^{-1}$ (195 ± 64 mg $dl^{-1}$)<br>Ezetimibe QD + placebo QM, 5.0 ± 1.3 mmol $l^{-1}$ (195 ± 52 mg $dl^{-1}$) | Type 2 diabetes:<br>Evolocumab groups, 15–19%<br>Control groups, 22–31%<br>Hypertension:<br>Evolocumab groups, 55%<br>Control groups, 59–75%<br>Low HDL-C:<br>Evolocumab groups, 28–36%<br>Control groups, 35%<br>≥2 CV risk factors:<br>Evolocumab groups, 37–52%<br>Control groups, 39–69% |
| **YUKAWA 2 [44]** | Evolocumab, 62 ± 11<br>Placebo, 61 ± 10 | Evolocumab, 60%<br>Placebo, 61% | Evolocumab, 2.8 ± 0.9 mmol $l^{-1}$ (109 ± 35 mg $dl^{-1}$)<br>Placebo, 2.7 ± 0.7 mmol $l^{-1}$ (103 ± 28 mg $dl^{-1}$) | Diabetes:<br>Evolocumab, 47%<br>Placebo, 51%<br>Cerebrovascular/peripheral artery disease:<br>Evolocumab, 12%<br>Placebo, 14%<br>≥2 CV risk factors:<br>Evolocumab, 56%<br>Placebo, 58% |
| **OSLER-2 [54]** | Data for OSLER-2 not reported separately | Data for OSLER-2 not reported separately | Evolocumab, 2.9 mmol $l^{-1}$ (114 mg $dl^{-1}$) | Data for OSLER-2 not reported separately |

[a]Data published in congress abstracts

[b]Study ongoing

CHD, coronary heart disease; CV, cardiovascular; LDL-C, LDL cholesterol; LS, least-squares; Q2W, every 2 weeks; Q4W, every 4 weeks; QD, daily; QM, monthly. LDL-C concentrations are presented in mmol $l^{-1}$ and mg $dl^{-1}$; where the publication provided only concentrations in either mg $dl^{-1}$ or mmol $l^{-1}$, a conversion factor of 38.67 was used (i.e. mg $dl^{-1}$/38.67 = concentration in mmol $l^{-1}$) [97].

## Table 5

Efficacy of anti-PCSK9 antibodies in patients with hypercholesterolaemia

| Study name | Mean change in LDL-C levels from baseline | LDL-C goal achievement according to EAS/ESC guidelines (<70 mg dl$^{-1}$ [very high CV risk] or <100 mg dl$^{-1}$ [high CV risk]) |
|---|---|---|
| **Alirocumab** | | |
| **ODYSSEY MONO [40, 81]** | Week 24:<br>Alirocumab, −47.2%<br>Ezetimibe, −15.6% ($P < 0.0001$) | Week 24<br>Alirocumab, 70%<br>Ezetimibe, not reported |
| **OPTIONS I [50]** | Week 24 (atorvastatin 20 and 40 mg regimens respectively):<br>Add-on alirocumab, −44.1% and −54.0%<br>($P < 0.001$ *vs.* all comparators)<br>Add-on ezetimibe, −20.5% and −22.6%<br>Doubling of atorvastatin dose, −5.0% and −4.8%<br>Switching atorvastatin 40 mg to rosuvastatin 40 mg, −21.4% | Week 24 (atorvastatin 20 and 40 mg regimens respectively):<br>Add-on alirocumab, 87.2% and 84.6%<br>Add-on ezetimibe, 68.4% and 65.1% ($P = 0.0284$ and 0.0011 *vs.* alirocumab)<br>Doubling of atorvastatin dose, 34.5% and 18.5% ($P < 0.0001$ *vs.* alirocumab)<br>Switching atorvastatin 40 mg to rosuvastatin 40 mg, 62.2% ($P = 0.0025$ *vs.* alirocumab) |
| **OPTIONS I I [46]** | Week 24, 10 mg rosuvastatin group:<br>Alirocumab, −50.6%<br>Ezetimibe, −14.4%<br>Double-dose rosuvastatin, −16.3% ($P < 0.0001$ for alirocumab *vs.* comparators)<br>Week 24, 20 mg rosuvastatin group:<br>Alirocumab, −36.3%<br>Ezetimibe, −11.0% ($P = 0.0136$ *vs.* alirocumab; significance threshold $P < 0.0125$)<br>Double-dose rosuvastatin, −15.9% ($P = 0.0453$; significance threshold $P < 0.0125$) | Week 24, 10 mg rosuvastatin group:<br>Alirocumab, 85%<br>Ezetimibe, 57%<br>Double-dose rosuvastatin, 45% ($P < 0.001$ for alirocumab *vs.* comparators)<br>Week 24, 20 mg rosuvastatin group:<br>Alirocumab, 67%<br>Ezetimibe, 52% ($P = 0.1177$ *vs.* alirocumab)<br>Double-dose rosuvastatin, 40.1% ($P = 0.0022$) |
| **ODYSSEY COMBO II [74]** | Week 24<br>Alirocumab, −50.6%<br>Ezetimibe, −20.7% ($P < 0.0001$) | Week 24<br>Alirocumab, 77%<br>Ezetimibe, 46% ($P < 0.0001$)[a] |
| **ODYSSEY COMBO I [70]** | Week 24<br>Alirocumab, −48.2%<br>Placebo, −2.3% ($P < 0.0001$) | Week 24<br>Alirocumab, 75%<br>Placebo, 9%[a] |
| **ODYSSEY LONG TERM [57]** | Week 24<br>Alirocumab, −61.0%<br>Placebo, 0.8% ($P < 0.001$)<br>The difference between the alirocumab and placebo groups in the percentage change in LDL-C level from baseline to week 24 was similar in patients with heterozygous familial hypercholesterolemia and those without | Week 23<br>Alirocumab, 79%<br>Placebo, 8.0%[a] |
| ***Patients with and without diabetes*[b] [75]** | Placebo-corrected LDL-C reduction at 24 weeks:<br>Patients with diabetes, −59%<br>Patients without diabetes, −63% ($p$ for interaction = 0.0957) | Not reported |
| **ODYSSEY FH I [43]** | Mean placebo-corrected LDL-C reduction:<br>Week 24, −57.9%, $P < 0.0001$<br>Week 78, −51.8% | Week 24:<br>Alirocumab, 72%<br>Placebo, 2.4% |
| **ODYSSEY FH II [43]** | Mean placebo-corrected LDL-C reduction<br>Week 24, −51.4%, $P < 0.0001$<br>Week 78, −52.1% | Week 24:<br>Alirocumab, 81%<br>Placebo, 11% |

(*continues*)

## Table 5

(Continued)

| Study name | Mean change in LDL-C levels from baseline | LDL-C goal achievement according to EAS/ESC guidelines (<70 mg dl$^{-1}$ [very high CV risk] or <100 mg dl$^{-1}$ [high CV risk]) |
|---|---|---|
| **ODYSSEY HIGH FH[b] [56]** | Week 24, LS mean reduction:<br>Alirocumab, −45.7%<br>Placebo, −6.6%, $P < 0.0001$ | Week 24:<br>Alirocumab, 41%<br>Placebo, 5.7% |
| **ODYSSEY CHOICE I[b] [55]** | Week 24, mean placebo-corrected LDL-C reduction:<br>Patients not receiving statins, −52.4%<br>Patients receiving statins, −58.7% | Not reported |
| **ODYSSEY CHOICE II[b] [51]** | Week 24: LS mean difference from placebo: −56.4%, $P < 0.0001$ | Week 24<br>Alirocumab, 64%<br>Placebo, 1.8% |
| **ODYSSEY ALTERNATIVE [45]** | Week 24 LS mean change from baseline:<br>Alirocumab −45.0%<br>Ezetimibe −14.6%, $P < 0.0001$ (atorvastatin not reported) | Week 24:<br>Alirocumab 42%<br>Ezetimibe, 4.4% ($P < 0.0001$) |
| **Evolocumab** | | |
| **DESCARTES [53]** | Mean placebo-corrected LDL-C reduction (overall):<br>Week 12, −57.5%<br>Week 52, −57.0%<br>Mean placebo-corrected LDL-C reduction (week 52, evolocumab group)<br>Diet-alone, −55.7%<br>10 mg atorvastatin, −61.6%<br>80 mg atorvastatin, −56.8%<br>80 mg atorvastatin + 10 mg ezetimibe, −48.5%<br>($P < 0.001$ for all comparisons) | Week 52:<br>Evolocumab groups: 82%<br>Placebo groups, 6.4%[a]<br>Week 52 by evolocumab group:<br>Diet-alone group, 84%<br>10 mg atorvastatin group, 90%<br>80 mg atorvastatin, 81%<br>80 mg atorvastatin + 10 mg ezetimibe, 67%[a] |
| **TAUSSIG[b,c] [33, 47]** | Week 12: −20.9%<br>Week 24: −23.4%<br>Week 48: −18.6% | Not reported |
| **MENDEL-2 [71]** | Week 12 (Q2W and Q4W regimens, respectively)<br>Evolocumab, −57.0% and −56.1%<br>Placebo, 0.1% and −1.3%<br>Ezetimibe, −17.8% and −18.6% | Means weeks 10 and 12 (Q2W and Q4W regimens, respectively):<br>Evolocumab, 72% and 69%<br>Placebo, 0% and 1%<br>Ezetimibe, 2% and 1%[a] |
| **RUTHERFORD-2 [58]** | Week 12 (Q2W and Q4W regimens, respectively):<br>Evolocumab, −61.3% and −55.7%<br>Placebo, −2.0% and 5.5% ($P < 0.0001$) | Week 12 (Q2W and Q4W regimens, respectively):<br>Evolocumab 68% and 63%<br>Placebo, 2% and 2%<br>(both $P < 0.0001$) |
| **LAPLACE-2 [72]** | Week 12 mean placebo-corrected LDL-C reduction (Q2W and Q4W regimens, respectively):<br>With atorvastatin 80 mg, −76.3% and −70.5%<br>With rosuvastatin 40 mg, −68.3% and −55.0%<br>Atorvastatin 10 mg, −71.4% and −59.2%<br>With simvastatin 40 mg, −70.6% and −60.4% | Means weeks 10 and 12 (Q2W and Q4W regimens, respectively):<br>Evolocumab groups:<br>Atorvastatin 80 mg, 94% and 93%<br>Rosuvastatin 40 mg, 94% and 95%<br>Atorvastatin 10 mg, 88% and 86%<br>Simvastatin 40 mg, 94% and 86% |

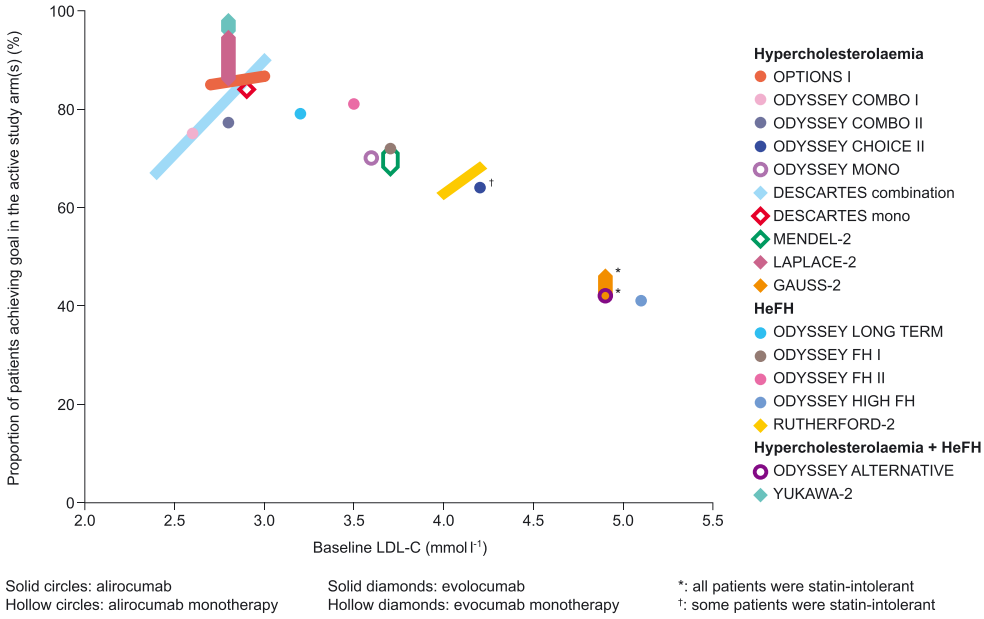
(continues)

## Table 5

(Continued)

| Study name | Mean change in LDL-C levels from baseline | LDL-C goal achievement according to EAS/ESC guidelines (<70 mg dl$^{-1}$ [very high CV risk] or <100 mg dl$^{-1}$ [high CV risk]) |
|---|---|---|
| | With rosuvastatin 5 mg, −68.2% and −64.5%<br>Week 12 mean ezetimibe-corrected LDL-C reduction (Q2W and Q4W regimens, respectively):<br>With atorvastatin 80 mg, −47.2% and −38.9%<br>With atorvastatin 10 mg, −39.6% and −41.1%<br>Evolocumab administered Q2W and Q4W was effective in all pre-specified subgroups relative to placebo and ezetimibe, with no notable differences observed between subgroups. (inc ATP III risk) | Rosuvastatin 5 mg, 89% and 90%[a]<br>Placebo groups:<br>Atorvastatin 80 mg, 14% and 9%<br>Rosuvastatin 40 mg, 39% and 29%<br>Atorvastatin 10 mg, 6% and 6%<br>Simvastatin 40 mg, 2% and 4%<br>Rosuvastatin 5 mg, 7% and 5%[a]<br>Ezetimibe groups:<br>Atorvastatin 80 mg, 51% and 62%<br>Atorvastatin 10 mg, 20% and 17%[a] |
| **TESLA PART B [34]** | Week 12<br>Evolocumab, −23.1%<br>Placebo, 7.9% ($P < 0.0001$) | Not reported |
| **GAUSS-2 [52]** | Mean of weeks 10 and 12:<br>Ezetimibe QD + placebo Q2W: −19.2%<br>Evolocumab 140 mg Q2W + placebo QD: −56.1%<br>Ezetimibe QD + placebo QM: −16.6%<br>Evolocumab 420 mg QM + placebo QD: −55.3%<br>(all $P < 0.001$ for evolocumab *vs.* ezetimibe) | Means weeks 10 and 12 (Q2W and Q4W regimens, respectively):<br>Evolocumab, 45.5% and 42.0% ($P < 0.001$)<br>Placebo, 2.0% and 0.0%[a] |
| **YUKAWA 2 [44]** | Week 12 mean placebo-corrected LDL-C reduction (Q2W and Q4W regimens, respectively):<br>With atorvastatin 5 mg, −74.9% and −69.9%<br>With atorvastatin 20 mg, −75.9% and −66.9% | Week 12 (Q2W and Q4W regimens, respectively):<br>With atorvastatin 5 mg, 98% and 96%<br>With atorvastatin 20 mg, 96% and 98%[a] |
| **OSLER-2 [54]** | Week 12 mean standard-of-care-corrected LDL-C reduction<br>Evolocumab, −64% | Not reported |

[a]Goal defined as LDL-C < 70 mg dl$^{-1}$ for all patients
[b]Data reported in congress abstracts
[c]Study ongoing
ATP, Adult Treatment Panel; LDL-C, LDL cholesterol; NCEP, National Cholesterol Education Program; QD, daily; QM, monthly; Q2W, every 2 weeks; Q4W, every 4 weeks.




## Figure 2

LDL-C goal achievement according to baseline LDL-C level. HeFH, heterozygous familial hypercholesterolaemia; LDL-C, LDL cholesterol. Figure includes only studies that reported LDL-C goal achievement. LDL-C levels in mg $dl^{-1}$ are converted to mmol $l^{-1}$ by dividing by 38.67 [97]

that evolocumab substantially reduces LDL-C regardless of baseline PCSK9 levels [68].

A pooled analysis of nine Phase 3 alirocumab studies, across which 20–65% of patients had previously experienced a myocardial infarction (MI) or ischaemic stroke, showed that there was no interaction between previous MI or stroke and LDL-C reduction [69].

Finally, a pooled analysis of four Phase 3 studies found that evolocumab reduced LDL-C regardless of age, gender, presence of metabolic syndrome and cardiovascular risk level [63].

## *Adverse events*

In general, adverse event (AE) rates were similar in the active and control arms of both combination and monotherapy studies of patients with non-familial hypercholesterolaemia (Table 6). The most common AEs across the alirocumab and evolocumab studies were musculoskeletal events, nasopharyngitis and upper respiratory tract infections. The patterns of these AEs in the alirocumab studies were mixed, with just three reporting increased rates of nasopharyngitis with alirocumab *vs.* control (ODYSSEY MONO, ODYSSEY COMBO I and ODYSSEY CHOICE II; the biggest across-arm difference was reported in ODYSSEY MONO: 23.1% with alirocumab *vs.* 15.7% with control) [40, 51, 70]. An increase in musculoskeletal events was only reported in ODYSSEY CHOICE II (24.1–28.7% *vs.* 20.7% [51]) and there was no clear signal that upper respiratory tract infection was more common with alirocumab than with controls.

The distribution of AEs in the evolocumab studies also varied across studies. A higher percentage of patients experienced musculoskeletal events, nasopharyngitis and upper respiratory tract infections in the evolocumab arms than in the control arms in the DESCARTES, RUTHERFORD-2 and TESLA part B studies; the biggest difference in incidence of nasopharyngitis and musculoskeletal events were in RUTHERFORD-2 (9% *vs.* 5% and 5% *vs.* 1%, respectively), while in both DESCARTES and TESLA part B, 9% of patients in the evolocumab arms experienced upper respiratory tract infections, *vs.* 6% in the control arms [34, 53, 58]. However, in the other comparator studies in which these AEs were reported (MENDEL, LAPLACE, GAUSS-2 and YUKAWA-2), there were either no discernible differences in the frequencies of events across active and control arms, or higher incidences in the control arms than in the evolocumab arms [44, 52, 71, 72]. In several alirocumab studies, injection site reactions were more common in the active arms than in the comparator arms, with the largest incidences seen in ODYSSEY CHOICE I (incidences with alirocumab, 5.4–18.5% across arms *vs.* control, 5.7–8.3%) and ODYSSEY CHOICE II (alirocumab, 3.5 and 13.8% in the 75 mg Q2W and 150 mg Q4W arms, respectively, *vs.* control, 0%) [51, 55]. However, in ODYSSEY MONO, injection site reactions were less frequent in the alirocumab arm compared with the control (2% *vs.* 4%) and, in OPTIONS I, rates were similar across arms (2–3%) [40, 50]. Across the evolocumab studies, the incidences of injection site reactions were similar in the active and control arms.

Alirocumab studies in patients with familial hypercholesterolaemia also reported similar rates of AEs in the alirocumab and placebo arms [43, 56]. However, a pooled analysis of ODYSSEY studies (FH I and II, HIGH FH and LONG TERM [HeFH population]) found that injection-site reactions were more common in the alirocumab arm than in the placebo arm (5.9% and 4.2%, respectively) [73]. In RUTHERFORD-2 (which included only patients with HeFH), the incidences

## Table 6

Safety of anti-PCSK9 antibodies in patients with hypercholesterolaemia

| Study name | Adverse events (% of patients) | Serious adverse events | Major CV events | Adverse events leading to discontinuation | ADA testing and results | Mortality |
|---|---|---|---|---|---|---|
| **Alirocumab** | | | | | | |
| **ODYSSEY MONO [40, 81]** | TEAEs:<br>Alirocumab, 69.2%;<br>Ezetimibe, 78.4% | TE SAEs:<br>Alirocumab, 1.9%<br>Ezetimibe; 2.0% | Not reported | TEAEs:<br>Alirocumab, 9.6%<br>Ezetimibe, 7.8% | TE ADA- positive response:<br>Alirocumab, 12%<br>Ezetimibe, 0%<br>No neutralizing antibodies were detected in any patient | No deaths in either group |
| **OPTIONS I [50]** | TEAEs:<br>Alirocumab, 65.4%;<br>Ezetimibe, 64.4%;<br>Atorvastatin, 63.8% | TE SAEs:<br>5.4% of patients overall, with no discernible pattern across study arms | Adjudicated CV events:<br>Alirocumab, 1.0%<br>Ezetimibe, 1.0%<br>Atorvastatin, 0% | TEAEs:<br>Alirocumab, 6.7%<br>Ezetimibe, 4.0%<br>Atorvastatin, 5.4% | Baseline testing: 1 patient in the pooled alirocumab add-on group and 4 in the control groups<br>TE ADA-positive responses: pooled alirocumab, add-on group, 5.1% (3 patients had persistent responses, 1 had a transient response and 1 had an indeterminate response; 1 had a positive neutralizing antibody assay response)<br>Pooled statin dose increase/switch to rosuvastatin group, 1 patient | Two patients in the ezetimibe add-on group on the atorvastatin baseline regimen died during the study (from acute respiratory distress syndrome and cardiac arrest) |
| **OPTIONS II [46]** | TEAEs:<br>Alirocumab, 56.3%<br>Ezetimibe, 53.5%<br>Double-dose rosuvastatin, 67.3% | TE SAEs:<br>Alirocumab, 5.8%<br>Ezetimibe, 7.9%<br>Double-dose rosuvastatin, 7.9% | Adjudicated CV events:<br>Alirocumab, 0%<br>Ezetimibe, 1.0%;<br>Double-dose rosuvastatin, 1.0% | TEAEs:<br>Alirocumab, 4.9%<br>Ezetimibe,7.9%<br>Double-dose rosuvastatin, 5.0% | Baseline testing:<br>Two patients in the alirocumab add-on group were negative at baseline, but positive post-dose<br>The antibodies did not appear to affect LDL-C lowering | One death in the ezetimibe + rosuvastatin 20 mg group, due to subdural haematoma (adjudicated as a CV death) |
| **ODYSSEY COMBO II [74]** | TEAEs:<br>Alirocumab, 71.2%<br>Ezetimibe, 67.2% | TE SAEs:<br>Alirocumab, 18.8%<br>Ezetimibe, 17.8% | Alirocumab, 4.8%<br>Ezetimibe, 3.7% | Alirocumab, 7.5%<br>Ezetimibe, 5.4% | Not reported | TEAE leading to death:<br>Alirocumab, 0.4% (2 patients; both cardiac origin)<br>Ezetimibe, 1.7%<br>(4 patients; 2 cardiac origin) |
| **ODYSSEY COMBO I [70]** | TEAEs:<br>Alirocumab, 75.8%<br>Placebo, 75.7% | TE SAEs:<br>Alirocumab, 12.6%<br>Placebo, 13.1% | CV TEAEs[a] confirmed by adjudication:<br>Alirocumab, 2.9%<br>Placebo, 2.8% | TEAEs:<br>Alirocumab, 6.3%<br>Placebo, 7.5% | Basline testing: 3 (1.5%) patients in the alirocumab group and 2 patients in the placebo group (2.0%) tested positive at baseline.<br>Alirocumab, TE ADAs, 6.6% (13 patients), in 7 of whom the antibodies were transient and resolved despite continued alirocumab treatment 4 of the | TEAE leading to death:<br>Alirocumab, 1.0% (2 patients)<br>Placebo, 2.8% (3 patients) |

(*continues*)

## Table 6

(Continued)

| Study name | Adverse events (% of patients) | Serious adverse events | Major CV events | Adverse events leading to discontinuation | ADA testing and results | Mortality |
|---|---|---|---|---|---|---|
| | | | | | patients in the alirocumab arm developed neutralizing antibodies | |
| **ODYSSEY LONG TERM[b] [57, 75]** | TEAEs:<br>Alirocumab, 81.0%<br>Placebo, 82.5% | TE SAEs:<br>Alirocumab, 18.7%<br>Placebo, 19.5% | CV AEs confirmed by adjudication:<br>Alirocumab, 4.6%<br>Placebo, 5.1%<br>Major CV AEs in *post hoc* analysis confirmed by adjudication:<br>Alirocumab, 1.7%<br>Placebo, 3.3% ($P = 0.02$) | Alirocumab, 7.2%<br>Placebo, 5.8% | Not reported | AE leading to death:<br>Alirocumab, 0.5% (8 patients)<br>Placebo, 1.3% (10 patients) |
| **ODYSSEY FH I [43]** | TEAEs:<br>Alirocumab, 81.7%<br>Placebo, 79.1% | TE SAEs:<br>Alirocumab, 13.7%<br>Placebo, 13.5% | CV events confirmed by adjudication:<br>Alirocumab, 2.5%<br>Placebo, 1.8% | TEAEs:<br>Alirocumab, 3.4%<br>Placebo, 6.1% | TE ADA-positive response:<br>Alirocumab, 5.5%<br>Placebo, 0.6%<br>0.6% of patients in the alirocumab arm developed neutralizing antibodies | TEAEs leading to death:<br>Alirocumab, 1.9% (6 patients; 2 metastatic cancer, 1 acute MI, 2 sudden cardiac death, 1 colonic pseudo-obstruction following abdominal surgery)<br>Placebo, 0% |
| **ODYSSEY FH II [43]** | TEAEs:<br>Alirocumab, 74.9%<br>Placebo, 81.5% | TE SAEs:<br>Alirocumab, 9.0%<br>Placebo, 9.9% | CV events confirmed by adjudication:<br>Alirocumab,1.2%<br>Placebo, 1.2% | TEAEs:<br>Alirocumab, 3.6%<br>Placebo, 1.2% | TE ADA-positive response:<br>Alirocumab, 8.6%<br>Placebo, 1.3%<br>0.6% of patients in the alirocumab arm developed neutralizing antibodies | No TEAEs leading to death in either group |
| **ODYSSEY HIGH FH[b] [56]** | TEAEs:<br>Alirocumab, 61.1%<br>Placebo, 71.4% | Not reported | Not reported | TEAEs leading to discontinuation:<br>Alirocumab, 4.2%<br>Placebo, 2.9% | Not reported | Not reported |
| **ODYSSEY CHOICE I[b] [55]** | TEAEs:<br>Alirocumab, 71.5–78.1%<br>Placebo, 61.1–75.0% | TE SAEs:<br>Alirocumab, 8.0–9.6%<br>Placebo, 9.7–10.2% | Not reported | TEAEs leading to discontinuation:<br>Alirocumab, 3.8–6.8%<br>Placebo, 5.6–6.4% | Not reported | No TEAEs leading to death in either group |
| **ODYSSEY CHOICE II[b] [51]** | TEAEs:<br>Alirocumab, 77.6%<br>Placebo, 63.8% | TE SAEs:<br>Alirocumab, 12.1%<br>Placebo, 6.9% | Not reported | TEAEs leading to discontinuation:<br>Alirocumab, 6.9%<br>Placebo, 3.4% | Not reported | No TEAEs leading to death in either group |
| **ODYSSEY ALTERNATIVE [45]** | TEAEs:<br>Alirocumab, 82.5%<br>Ezetimibe, 80.6%<br>Atorvastatin, 85.7% | TE SAEs:<br>Alirocumab, 9.5%<br>Ezetimibe, 8.1%<br>Atorvastatin, 11.1% | Adjudicated CV events:<br>Alirocumab, 3.2%<br>Ezetimibe, 0.8%<br>Atorvastatin, 1.6% | TEAEs leading to discontinuation:<br>Alirocumab 18.3%<br>Ezetimibe, 25.0%<br>Atorvastatin 25.4% | Not reported | No deaths in any group |

(*continues*)

## Table 6

(Continued)

| Study name | Adverse events (% of patients) | Serious adverse events | Major CV events | Adverse events leading to discontinuation | ADA testing and results | Mortality |
|---|---|---|---|---|---|---|
| **Evolocumab** | | | | | | |
| **DESCARTES [53]** | TEAEs:<br>Evolocumab, 74.8%<br>Placebo, 74.2% | TE SAEs:<br>Evolocumab, 5.5%<br>Placebo, 4.3% | Atherosclerotic events confirmed by adjudication:<br>Evolocumab, 1.0%<br>Placebo, 0.7% | Evolocumab, 2.2%<br>Placebo, 1.0% | No anti-evolocumab neutralizing antibodies were detected in any patient | Deaths:<br>Evolocumab, 0.3% (2 patients; 1 cardiac failure, 1 MI)<br>Placebo, 0% |
| **TAUSSIG [b,c] [33, 47]** | 85 AEs in 16 patients (of 37 analysed):<br>84 grade 1 or 2, 1 grade 3, 1 serious | 85 AEs in 16 patients (of 37 analysed):<br>84 grade 1 or 2,1 grade 3, 1 serious | Not reported | Not reported | Not reported | Not reported |
| **MENDEL-2 [71]** | TEAEs:<br>Evolocumab, 44%<br>Placebo, 44%<br>Ezetimibe, 46% | TE SAEs:<br>Evolocumab, 1.3%<br>Placebo, 0.6%<br>Ezetimibe, 0.6% | None | Evolocumab, 2.3%<br>Placebo, 3.9%<br>Ezetimibe, 3.2% | None reported | No deaths in any group |
| **RUTHERFORD-2 [58]** | TEAEs:<br>Evolocumab Q2W,55%<br>Placebo Q2W, 43%<br>Evolocumab Q4W, 57%<br>Placebo Q4W, 55% | TE SAEs:<br>Evolocumab Q2W, 3%<br>Placebo Q2W, 4%<br>Evolocumab Q4W, 4%<br>Placebo Q4W, 5% | CV events confirmed by adjudication:<br>Evolocumab Q2W, 2%<br>Placebo Q2W, 0%<br>Evolocumab Q4W, 1%<br>Placebo Q4W, 0% | None | No anti-evolocumab neutralizing antibodies were detected in any patient | No deaths in any group |
| **LAPLACE-2 [72]** | TEAEs:<br>Evolocumab, 36%<br>Ezetimibe, 40%<br>Placebo, 39% | TE SAEs:<br>Evolocumab, 2.1%<br>Ezetimibe, 0.9%<br>Placebo, 2.3% | CV events during the 12 week treatment period confirmed by adjudication:<br>Evolocumab, 0.4% (5 patients)<br>Ezetimibe, 0.9% (2 patients)<br>Placebo, 0.4% (2 patients) | Evolocumab, 1.9%<br>Ezetimibe, 1.8%<br>Placebo, 2.2% | Before study drug administration, 3 evolocumab-treated patients tested positive for binding antibodies; of these, 1 in the evolocumab 420 mg Q4W group had detectable binding antibodies at the end of study<br>No new cases of binding antibodies post-treatment were reported<br>Neutralizing antibodies were not detected | Deaths:<br>Evolocumab, 0%<br>Ezetimibe, 0%<br>Placebo, 0.2% (1 patient) |
| **TESLA PART B [34]** | TEAEs:<br>Evolocumab, 36%<br>Placebo, 63% | None | Not reported | None | Binding and neutralizing antibody tests negative for all patients (excluding 1 who had a positive binding antibody test at baseline and negative | No deaths in either group |

(*continues*)

## Table 6

(Continued)

| Study name | Adverse events (% of patients) | Serious adverse events | Major CV events | Adverse events leading to discontinuation | ADA testing and results | Mortality |
|---|---|---|---|---|---|---|
| | | | | | antibody testing at all other study assessments) | |
| **GAUSS-2 [52]** | TEAEs:<br>Evolocumab 140 mg Q2W + placebo QD, 61%<br>Ezetimibe QD + placebo Q2W, 69%<br>Evolocumab 420 mg Q4W + placebo QD, 71%; Ezetimibe QD + placebo Q4W, 77% | TE SAEs<br>Evolocumab 140 mg Q2W + placebo QD, 5%<br>Ezetimibe QD + placebo Q2W, 2%<br>Evolocumab 420 mg Q4W + placebo QD, 1%<br>Ezetimibe QD + placebo Q4W, 6% | Not reported | Evolocumab 140 mg Q2W + placebo QD, 6%<br>Ezetimibe QD + placebo Q2W, 8%<br>Evolocumab 420 mg Q4W + placebo QD, 11%<br>Ezetimibe QD + placebo Q4W, 18% | None reported | No deaths in any group |
| **YUKAWA-2 [44]** | Evolocumab, 46.5%<br>Atorvastatin + placebo, 51.0% | Evolocumab, 0.5%;<br>Atorvastatin + placebo, 2.5% | Positively adjudicated CV events:<br>Evolocumab, 0%<br>Atorvastatin + placebo, 0.5% | AEs leading to discontinuation:<br>Evolocumab, 0%<br>Atorvastatin + placebo, 0.5% | Binding antibodies detected in 1 patient in the evolocumab group and 0 in the atorvastatin + placebo group<br>No neutralizing antibodies were detected | Not reported |
| **OSLER-2 [54]** | Data for OSLER-2 not reported separately | Data for OSLER-2 not reported separately | Data for OSLER-2 not reported separately | Data for OSLER-2 not reported separately | Data for OSLER-2 not reported separately | Data for OSLER-2 not reported separately |

[a]Includes coronary heart disease death (including undetermined cause), non-fatal MI, fatal and non-fatal ischaemic stroke (including stroke not otherwise specified), congestive heart failure requiring hospitalization, ischaemia-driven coronary revascularization procedure

[b]Data reported in congress abstracts

[c]Study ongoing

ADA, anti-drug antibody; AE, adverse event; CV, cardiovascular; MI, myocardial infarction; QD, daily; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; TE, treatment emergent; TEAE, treatment-emergent adverse event.

of AEs were 55 and 57% in the evolocumab arms and 43 and 55% in the placebo arms (Table 6) [58].

In the TESLA part B study of patients with the rare genetic disease HoFH, the incidence of AEs was 36% in the evolocumab arm and 63% in the placebo arm (Table 6) [34].

*Serious adverse events, cardiac events, mortality and treatment discontinuation.* Serious AEs were rare in all studies (Table 6). The highest reported incidence of serious AEs was in ODYSSEY COMBO II and ODYSSEY LONG TERM (alirocumab 19%; ezetimibe 18%, placebo 20%) [57, 74]. In ODYSSEY LONG TERM, the authors noted that the serious AEs included allergic and neurologic AEs; however, numbers were small, with 0.5% and 0.4% of patients in the alirocumab and control arms, respectively, experiencing serious allergic AEs and 0.3% of patients in either arm experiencing serious neurologic AEs. No further details on serious AEs were given for ODYSSEY COMBO II. Few details of serious AEs were given in the evolocumab studies, apart from in DESCARTES. Of the 33 patients (5.5%) experiencing serious AEs in the evolocumab arm, only five AEs were experienced by more than one patient: angina pectoris, palpitations, ventricular extrasystoles, positional vertigo, back pain and pulmonary embolism (all two patients each; angina pectoris and pulmonary embolism also occurred in two patients and one patient, respectively, in the control arm) [53].

Major cardiac AEs were rare: the lowest reported incidence (0%) was seen in the control arms of OPTIONS I [50] and RUTHERFORD-2 [58], the alirocumab arm of OPTIONS II [46] and the evolocumab arm of YUKAWA-2 [44], and the highest was 5.1% in the placebo arm of ODYSSEY LONG TERM [57] (Table 6). Treatment discontinuations because of AEs were similarly rare (Table 6): the lowest rate was observed in YUKAWA-2 (evolocumab 0%; placebo 0.5%) and the highest in ODYSSEY ALTERNATIVE (alirocumab 18%; control groups 25%) [44, 45]. The rates of treatment-emergent AEs (TEAEs) leading to death were low in all studies; the highest incidences were reported in the control arm of OPTIONS I and the placebo arm of ODYSSEY COMBO I (2.0% and 2.8%, respectively) [50, 70].

*Patient subgroups.* Pooled analyses of Phase 3 studies have found that there are no differences in the incidence of AEs in patients with diabetes *vs.* those without for evolocumab [62]. Similar results were seen in the alirocumab ODYSSEY LONG TERM study [75] and in a pooled analysis of alirocumab [61], although patients with diabetes appeared less likely to experience injection-site reactions than those without. Pooled analyses of Phase 3 alirocumab studies have also found that AE incidence is not impacted by baseline triglyceride or HDL-C concentrations [66], by whether or not patients had previously had an MI or stroke [69], or by the presence or absence of CKD (although numerically higher treatment discontinuations were seen in patients with moderate CKD than in those without) [65].

Pooled safety data for patient subgroups from Phase 3 and Phase 2 studies show that the AE profile of evolocumab does not vary according to body weight [76] and that there are no noticeable differences in AE profiles when comparing patients aged 65 and older with those aged 75 and older [77]. Pooled Phase 2/3 analyses for alirocumab and evolocumab have shown that AEs are similar regardless of whether or not patients achieved very low LDL-C levels (<0.65 or <0.39 mmol $l^{-1}$ [<25 mg $dl^{-1}$ or <15 mg $dl^{-1}$] for alirocumab and <1.0 mmol $l^{-1}$ [<40 mg $dl^{-1}$] for evolocumab) [78, 79]. A pooled analysis of patients with statin intolerance from Phase 2 and Phase 3 studies of evolocumab found that safety signals in this subgroup were similar to those seen in previous analyses in broader populations [80].

### *Anti-drug antibody production*

Anti-drug antibody assessment was reported in six alirocumab and five evolocumab studies (Table 6). Pre-existing immunoreactivity to alirocumab was evident in 0.7–3.2% of patients in the ODYSSEY COMBO I and OPTIONS I studies [50, 70]. In ODYSSEY COMBO I, 6.6% of patients had a treatment-emergent positive response (i.e. developed antibodies to alirocumab following treatment) in the anti-alirocumab antibody assay; however, in more than half of these patients, the antibodies were transient despite continued treatment with alirocumab. Four of the patients developed neutralizing antibodies, but these were transient and resolved within 24 weeks [70]. In OPTIONS I, anti-drug antibody development was observed in five patients in the pooled alirocumab add-on group, three of whom had persistent antibody responses and one of whom developed neutralizing antibodies [50]. In OPTIONS II, treatment-emergent antibody development occurred in two patients; in one the response was transient and in the other it was indeterminate (i.e. it was only detected at the final sampling point); the antibodies did not appear to affect LDL-C lowering [46]. In the alirocumab arms of the ODYSSEY FH studies, 6–9% of patients developed anti-drug antibodies and 0.6% developed neutralizing antibodies [43]. In ODYSSEY MONO, six patients in the alirocumab arm (12%) developed anti-drug antibodies, five of whom had a persistent response; however, neutralizing antibodies that could affect the pharmacokinetics, efficacy or safety of alirocumab were not detected [40]. Treatment-emergent anti-drug antibodies were not detected in patients in the evolocumab arms of DESCARTES, RUTHERFORD-2 or TESLA part B [34, 53, 58]. In YUKAWA-2 one patient developed an anti-evolocumab antibody, and in LAPLACE-2 three patients in the evolocumab group tested positive for anti-drug antibodies before study drug administration, one of whom had detectable anti-drug antibodies at the end of the study; neutralizing antibodies were not detected in any patient [44, 72].

## Discussion

The studies included in our systematic review show that the anti-PCSK9 monoclonal antibodies alirocumab and evolocumab are well tolerated and effective in lowering LDL-C, thereby helping patients with hypercholesterolaemia or mixed dyslipidaemia to achieve LDL-C goals. Both alirocumab and evolocumab have been demonstrated to reduce LDL-C goals across a broad patient population that encompassed a wide range of CV risk levels, and various comorbidities such as diabetes and CKD. We also noted an

apparent inverse relationship between baseline LDL-C and goal achievement, suggesting that these agents have a consistent effect that is independent of baseline LDL-C levels. Statin intolerance may influence goal achievement, with the ODYSSEY ALTERNATIVE and GAUSS-2 studies of patients with intolerance to statins reporting lower levels of goal achievement than other studies, but the data are still encouraging given the very high baseline LDL-C concentrations in patients enrolled in these studies.

For both alirocumab and evolocumab, rates of AEs, serious AEs and major cardiovascular AEs were similar to those in the respective control arms. The incidence of AEs was lower when alirocumab was used as a monotherapy than when it was used in combination with statins, which could reflect differences in the patient baseline characteristics: patients in the monotherapy study had a lower CV risk level than patients in the combination studies and would be expected to be receiving fewer concomitant medicines. In contrast to alirocumab, there was no discernible pattern in AE incidence according to whether evolocumab was used as a monotherapy or in combination with statins.

Treatment-emergent anti-drug antibodies were also rare, but were reported in five alirocumab studies [40, 43, 46, 50, 70, 81]. The highest incidence of treatment-emergent antibodies was reported in the alirocumab arm of the ODYSSEY MONO study (12%). An immune signal following alirocumab administration is also noted in the summary of product characteristics, which states that, in the Phase 3 programme, allergic reactions were more common in the alirocumab groups than in the control groups (8% *vs*. 7%, respectively) [19]. A pooled safety analysis of nine placebo-controlled Phase 2 and Phase 3 studies also found that the incidence of local injection-site reactions was higher with alirocumab than with placebo (7% *vs*. 5%), even though the incidence of AEs was generally similar across the alirocumab and placebo study arms [42].

In the evolocumab studies that investigated the presence of such antibodies, neutralizing treatment-emergent anti-drug antibodies were not detected, and treatment-emergent binding antibodies were reported in just one patient (in the evolocumab arm of YUKAWA-2) [44]. The anti-drug antibody assays used were sensitive; several studies detected drug binding antibodies in patients who had not yet received evolocumab [34, 53, 72]. It should be noted, however, that different assays were used across the trials.

Overall efficacy and safety are being further evaluated for all anti-PCSK9 antibodies in ongoing long-term Phase 3 studies. A combined analysis of two randomized open-label extension studies (OSLER-1 and -2) involving 4465 patients who completed one of 12 Phase 2 or 3 evolocumab studies (and consented to participate in an extension study with an initial re-randomization after completion of the parent study) provides further relevant data that were not included in the safety section of our systematic review because it did not fulfil our inclusion criteria of including data for a patient subgroup not reported elsewhere [54]. This analysis also reported that no treatment-emergent neutralizing anti-drug antibodies were detected. Data on neurocognitive events will be of particular interest; OSLER-1 and -2 reported that although overall rates of AEs were similar in the active and control study arms, patients who received evolocumab were more likely to experience neurocognitive events (0.9% *vs*. 0.3% in the control arm) [54]. Similar data were seen for alirocumab in the ODYSSEY LONG TERM study (1.2% *vs*. 0.5% in the control arm) [57]. The effect of anti-PCSK9 antibodies on cognitive function is being investigated with a validated instrument (Cambridge Neuropsychological Test Automated Battery) in the evolocumab EBBINGHAUS trial (NCT02207634), a sub-analysis of a group of patients enrolled in the ongoing FOURIER study (NCT01764633 [82]), and will be monitored in other ongoing Phase 3 studies, such as the alirocumab ODYSSEY OUTCOMES study (NCT01663402).

The meta-analysis by Lipinksi *et al*. examined the effect of anti-PCSK9 antibodies on lipids, but grouped data for alirocumab and evolocumab and did not examine the effects of these agents in different patient subgroups [83]. Other meta-analyses and literature reviews have used CV events as efficacy/safety endpoints to compare studies, but data are currently very limited [84–87]. In contrast, because LDL-C reduction was the primary endpoint of the Phase 3 studies described here, the studies were statistically powered to assess the true efficacy of anti-PCSK9 antibodies regarding LDL-C lowering. Since completion of our systematic review, a meta-analysis of randomized clinical trials investigating the efficacy of evolocumab in patients with or without type 2 diabetes has been published [88]. The analysis found that the LDL-C-lowering effect of evolocumab was consistent in patients with and without type 2 diabetes. Outcomes data in this and other patient subgroups are awaited with interest.

Given that high LDL-C is recognized as a major risk factor for CVD [5, 89], we would expect the significant reductions in LDL-C seen in these trials to translate into a reduction in CV events. ODYSSEY LONG TERM, which had the longest follow-up of the alirocumab studies included in this review, reported promising data on major CV events, with significantly fewer events in the alirocumab group than in the placebo group (1.7% *vs*. 3.3%; $P = 0.02$) [57]. A combined prespecified exploratory analysis of OSLER-1 and -2 found that the rate of CV events at 1 year was significantly reduced with evolocumab compared with standard therapy (0.47% *vs*. 2.2%; $P = 0.003$) [54]. Results from ongoing Phase 3 studies on CV outcomes, such as the alirocumab ODYSSEY OUTCOMES study, the evolocumab FOURIER study and the bococizumab SPIRE studies, are eagerly awaited [82, 90–92].

The results from this analysis should be interpreted in the context of the study limitations. First, cross-trial comparisons should be made with caution because of the different methodologies used. For example, LDL-C was measured at different time points after drug administration. The parameters used to define CV risk also differed across the trials, with some using the SCORE system (which estimates CV mortality risk using a combination of age, sex, blood pressure, smoking status and total cholesterol [93]) and some using the NCEP ATP III classification (which defines high and very high CV risk as elevated LDL-C in combination with other risk factors [94]); one study used the Framingham coronary heart disease score [95]. Methodological differences among studies may be overcome to some extent by analysing the data according to patient group, because the standard of care within each group should be consistent. However, the baseline demographics of patients enrolled in the studies often varied considerably.

Even when comparing studies using the same agents, caution is required; indeed, whereas most of the alirocumab studies used a starting dose of 75 mg Q2W, increasing to 150 mg Q2W only if the response at week 8 was insufficient, the ODYSSEY LONG TERM study had a starting dose of 150 mg Q2W. Secondly, when interpreting LDL-C data, it is important to note that the Friedewald formula underestimates LDL-C at low concentrations and so its use may overestimate the effect of anti-PCSK9 antibodies [96]. Most of the included alirocumab studies used ultracentrifugation techniques if triglyceride concentrations exceeded 10.3 mmol $l^{-1}$ (912 mg $dl^{-1}$). Most evolocumab studies, however, also used ultracentrifugation if LDL-C concentrations were less than 1.0 mmol $l^{-1}$ (39 mg $dl^{-1}$), as well as if patients had high triglyceride levels. Lastly, by limiting inclusion to published Phase 3 studies to ensure that only robust data were analysed, this review has analysed data for only two anti-PCSK9 antibodies.

## Conclusions

This systematic literature review provides a detailed overview of all available published Phase 3 data, in addition to pooled Phase 2/3 data for patient subgroups, for alirocumab and evolocumab, the two fully human anti-PCSK9 monoclonal antibodies currently approved by the FDA and EMA. These drugs are being investigated further in two large study programmes, PROFICIO and ODYSSEY, respectively. Using anti-PCSK9 antibodies as 'add-on' therapy to statins or ezetimibe, or as monotherapy for patients unable to tolerate statins, will allow more patients to achieve their LDL-C goal, with few AEs or treatment discontinuations. Clinical trials to investigate the effect of anti-PCSK9 antibodies on CV events, and therefore their relevance in clinical practice, are currently underway, with results expected later this year.

## Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: IGB, OSD, UF, RD and WM received medical writing support from EH and KA for the submitted work, funded by Amgen. RD and UF have been employees of Amgen and own stocks in Amgen in the previous 3 years. IGB has received personal fees from Sanofi/Genzyme, Amgen, AstraZeneca, Bristol-Myers Squibb and Eli Lilly in the previous 3 years. KA and EH are employees of Oxford PharmaGenesis UK, which has received project funding from Amgen in the previous 3 years. OSD has received: grants, personal fees and non-financial support from Merck Sharp & Dohme, Amgen and Sanofi; grants and personal fees from AstraZeneca; grants from Pfizer; and personal fees from Abbott in the previous 3 years. WM has received: grants and personal fees from Siemens Diagnostics, Aegerion Pharmaceuticals, Amgen, AstraZeneca, Danone Research, Sanofi/Genzyme, Numares AG, BASF and Pfizer; grants from Abbott Diagnostics; personal fees from Hoffmann-La Roche, Merck Sharp & Dohme, Sanofi and Synageva; and has been employed by Synlab Holding Deutschland GmbH in the previous 3 years. No other relationships or activities could appear to have influenced the submitted work.

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## Contributors

All authors participated in the systemic review design and preparation of the manuscript. Ioanna Gouni-Berthold, Olivier S. Descamps, Uwe Fraass, Ricardo Dent and Winfried März are responsible for the critical interpretation of data. Elizabeth Hartfield and Kim Allcott executed the systematic review.

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