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PCSK9 inhibition update 2016

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Introduction

Reducing circulating low density lipoprotein cholesterol (LDL-C) reduces the risk of cardiovascular disease. Current approaches to reduce LDL-C include statins, which inhibit cholesterol synthesis and up-regulate hepatic cell-surface LDL receptors (LDL-R), and ezetimibe, which blocks cholesterol absorption. Serum proprotein convertase subtilisin/kexin 9 (PCSK9) is a serine protease that binds to LDL receptors through a two step process, increasing their degradation and thereby reducing the rate at which LDL is removed from circulation.[1] Both statins and ezetimibe elevate serum PCSK9 protein levels in patients, which could attenuate their efficacy by reducing the amount of cholesterol cleared from circulation.[2] Though PCSK9 was first identified less than a decade ago, it seems to be an important regulator of LDL metabolism. PCSK9 'gain-of-function' mutations are rare, autosomal dominant traits that cause familial hypercholesterolemia and predispose to atherosclerotic cardiovascular disease. The more common 'loss-of-function' mutations cause low LDL-cholesterol and atheroprotection.[3,4]

PCSK9 inhibition

PCSK9 inhibition through gene silencing by antisense oligonucleotides or by the action of small peptides and antibodies is a novel therapeutic approach to treatment of hypercholesterolemia. Initial observations of reduction in atherosclerosis in mice, rats, and primates with PCSK-9 inhibition prompted human trials. Of the many approaches to PCSK9 inhibition, monoclonal antibodies are the furthest advance in their clinical development; small molecule oral inhibitors seem a remote prospect.[5]

Gene silencing

To determine whether PCSK9 inhibition in mice could enhance LDL-C lowering effect of both statins and ezetimibe, a study utilized small interfering RNAs (siRNAs) to knock down PCSK9, together with ezetimibe, rosuvastatin, and an ezetimibe - rosuvastatin combination. Ezetimibe, rosuvastatin, and ezetimibe/rosuvastatin combined lowered serum cholesterol but induced the expression of PCSK9 as well as hepatic cholesterol biosynthesis. PCSK9 knockdown in combination with any treatment arm led to greater reductions in serum non-HDL-C with a near-uniform reduction of all LDL-C subfractions. In addition to reducing serum cholesterol, the combined rosuvastatin/ezetimibe/PCSK9 siRNA exhibited a significant reduction in serum apoB and triglyceride levels, suggesting that PCSK9 inhibitors, in combination with current therapies, have the potential to achieve greater reductions in both serum cholesterol and triglycerides.[2]

Monoclonal antibodies (PCSK Mabs)

PCSK Mabs are human monoclonal antibodies that bind specifically to human PCSK9 and prevent its interaction with LDL-R, thereby decreasing LDL-C. There are 3 PCSK Mabs being actively studied in clinical trials: (i) Regeneron/Sanofi Product ALIROCUMAB/SAR236553 (Alirocumab, PraluentTM), (ii) Amgen Product EVOLOCUMAB (evolocumab, RepathaTM), and (iii) Pfizer Product RN 316 (bococizumab). Both alirocumab and evolocumab have been tested in phase I, phase II and phase III trials. Pfizer's bococizumab has been slow to start but fast catching up with cardiovascular outcomes phase III trials of other two products.

Alirocumab (PraluentTM)

Alirocumab is a specific monoclonal antibody to PCSK9 that significantly reduced LDL-C levels in healthy volunteers and in subjects with hypercholesterolemia in phase I studies. It was subsequently tested in phase II studies in patients with primary hypercholesterolemia with impressive results.[6]

Preclinical experience

In rats and monkeys, alirocumab distribution is restricted to intravascular compartment following IV administration. It is degraded into small peptides and individual amino acids with a mean half life of 98-121 hours in rats and 51-61hours in monkeys.

Phase I studies: Three phase 1 studies of ALIROCUMAB in healthy volunteers have been reported. Of these, two were randomized, single ascending-dose studies of either intravenous (n=40) or subcutaneous (n=32) administration of alirocumab versus placebo. These studies were followed by a randomized, placebo-controlled, multiple-dose trial in adults with heterozygous familial hypercholesterolemia (HeFH) who were receiving atorvastatin (n=21) and those with non-familial hypercholesterolemia who were receiving treatment with atorvastatin (n=30) (baseline LDL-C >100mg/dL) or a modified diet alone (n=10) (baseline LDL-C >130mg/dL). Alirocumab doses of 50, 100, or 150mg were administered subcutaneously on days 1, 29, and 43. Among subjects receiving alirocumab, there were no discontinuations because of adverse events (primary end point). Alirocumab significantly lowered LDL-C levels in all studies (secondary end point) [7]. In the multiple-dose study, alirocumab doses of 50, 100, and 150 mg reduced measured LDL-C levels in the combined atorvastatin-treated populations from baseline by −39.2, −53.7, and −61.0 percentage points respectively as compared with

placebo (P<0.001 for all comparisons). The magnitude of these effects was similar in familial and non-familial hypercholesterolemia. There was also a favourable trend on Lp(a), particularly in patients receiving atorvastatin. There was no apparent hepatotoxicity or discontinuations for any adverse effects (Table 1).[8]

Phase 2 studies

Study 1003: This multicentre, randomised, blind, placebo-controlled phase 2 trial assessed the efficacy and safety of various doses and dosing intervals of alirocumab (150mg, 200mg, or 300mg every 4weeks, or 150mg every 2weeks, or placebo every 2weeks) added to statins, to further lower LDL-C in 77 patients with HeFH with a baseline LDL-C >100mg/dl on stable diet and statin dose with or without ezetimibe. Randomisation was stratified by concomitant use of ezetimibe at baseline. The primary endpoint of mean percent reduction in LDL-C from baseline at week 12 was 28·9% for 150mg every 4weeks (p=0·0113), 31·54% for 200 mg every 4weeks (p=0·0035), 42·53% for 300 mg every 4weeks (p<0·0001), and 67·90% for 150mg every 2weeks (p<0·0001), compared with 10·65% with placebo. Over 80% achieved an LDL-C <70 mg/dL. LDL-C reductions averaged nearly 100mg/dL from baseline. No serious adverse event was reported with alirocumab. No increases of more than three times the upper limit of normal were reported for hepatic transaminases or creatinine kinase. The most common adverse event was injection-site reaction. Thus, alirocumab significantly reduced LDL-C levels in HeFH patients already on high-dose statin, with/without ezetimibe. More sustained LDL-C reducing efficacy was noted with 2weekly regime compared to higher doses administered every 4weeks (Table 2).[9]

Study 11565: To evaluate the LDL-C lowering efficacy of alirocumab in patients with primary hypercholesterolemia, a double-blind, randomized, parallel-group, placebo controlled trial of 12weeks duration was conducted in 183 patients with LDL-C ≥100mg/dl on stable-dose atorvastatin 10, 20, or 40mg. The treatment arms were SC placebo every 2weeks; alirocumab 50, 100, or 150 mg every 2 weeks; or 200 or 300 mg every 4weeks, alternating with placebo. Alirocumab demonstrated a clear dose-response relationship with respect to percentage LDL-C lowering for both 2weekly (40%, 64%, and 72%) and 4weekly (43% and 48%) administration (p<0.0001). Alirocumab also substantially reduced non-HDL-C, apoB, and Lp(a). It improved achievement of LDL-C targets, particularly with 2weekly regime. There were no signals for persistent or prevalent clinical or laboratory adverse events, including hepatic and muscle assessments. One patient on alirocumab had leukocytoclastic vasculitis, attributed to study drug that resolved with prednisolone.[10]

Study 11566: In another phase II study in 92 patients of primary hypercholesterolemia, alirocumab plus atorvastatin 80mg reduced LDL-C by 73%, representing a 56% additional reduction in LDL-C compared to Placebo + Atorvastatin 80mg. Addition of alirocumab allowed significantly more subjects to attain LDL-C levels of <100 mg/dL and <70mg/dL. A similar LDL-C magnitude of effect was seen when alirocumab was added to atorvastatin 10mg. Co-administration of alirocumab and atorvastatin 80/10mg was generally well tolerated and 2weekly dosing of alirocumab appeared to maintain a steady state reduction in LDL-C.[11]

Evolocumab (RepathaTM): Evolocumab, another human monoclonal IgG2 antibody against PCSK9, had been tested in 4 phase II studies.

Laplace Timi 57 study: Laplace-Timi 57 study assessed the efficacy, safety, and tolerability of EVOLOCUMAB in stable patients with hypercholesterolemia on a statin. In this dose-ranging, multinational, blinded study in the USA, Canada, and Europe, 631 patients (18-80years) with LDL-C >85mg/dL on a stable dose of statin, with or without ezetimibe, were randomly assigned equally, to SC injections of EVOLOCUMAB 70mg, 105mg, or 140mg, or matching placebo every 2weeks; or subcutaneous injections of EVOLOCUMAB 280mg, 350mg, or 420mg, or matching placebo every 4weeks. At the end of the dosing interval at week 12, the primary end point of mean LDL-C reduction was 41·8% to 66·1% in 2weekly regime; p<0·0001 for each dose and 41·8% to 50·3%; in 4weekly regime; p<0·0001, without any treatment-related serious adverse events (Table 3).[12]

Mendel study: This multinational phase II study assessed the effects of EVOLOCUMAB in 406 patients (18-75 years) with hypercholesterolaemia (serum LDL-C 100-190mg/dL) in the absence of concurrent lipid-lowering treatment. Subjects were randomly assigned equally to SC EVOLOCUMAB 70 mg, 105mg, or 140mg, or placebo every 2weeks; SC EVOLOCUMAB 280mg, 350mg, or 420mg or placebo every 4weeks; or open label ezetimibe 10mg/day. The primary endpoint was percentage change from baseline in LDL-C concentration at week 12. EVOLOCUMAB significantly reduced LDL-C in all dose groups (mean baseline LDL-C 142mg/dl; changes from baseline with every 2weeks EVOLOCUMAB 70mg: −41·0% 105 mg −43·9%; 140mg −50·9%; every 4weeks EVOLOCUMAB 280mg −39·0%; 350mg −43·2%; 420mg −48·0%; placebo every 2weeks −3·7%; placebo every 4weeks 4·5%; and ezetimibe −14·7% (p<0·0001 for all doses *vs* placebo or ezetimibe). Treatment-emergent adverse events occurred in 136 (50%) of 271 patients in the EVOLOCUMAB groups, 41 (46%) of 90 patients in the placebo groups, and 26 (58%) of 45 patients in the ezetimibe group; no deaths or serious treatment-related adverse events were reported (Table 4).[13]

Rutherford study: Despite statin treatment, many patients with HeFH do not reach desired LDL-C targets. This phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-ranging study evaluated the efficacy and safety of EVOLOCUMAB in HeFH patients diagnosed by Simon Broome criteria with LDL-C >100mg/dL despite statin therapy with or without ezetimibe. The subjects (n=167) were randomized 1:1:1 to EVOLOCUMAB 350mg, 420mg, or placebo-administered SC every 4weeks. At week 12, the primary end point of mean percentage change from baseline in LDL-C was 43% and 55% with EVOLOCUMAB 350mg and 420 mg, respectively, compared with 1% increase with placebo (P<0.001 for both dose groups). Serious adverse events (not considered treatment-related) occurred in 2 patients on EVOLOCUMAB. Thus, EVOLOCUMAB administered every 4weeks yielded rapid and substantial reductions in LDL-C in HeFH patients despite intensive statin use, with or without ezetimibe, with minimal adverse events and good tolerability (Table 5).[14]

Gauss Study: In this study of 160 statin intolerant patients with a mean LDL-C of 193 mg/dl, EVOLOCUMAB 280, 350, 420mg once in 4 w or EVOLOCUMAB 420 + ezetemibe, or ezetemibe alone, the magnitude of LDL-C reduction at 12weeks was EVOLOCUMAB alone: 41% to 51%, EVOLOCUMAB + ezetemibe: 63%, and ezetemibe alone: 15%. The proportion of subjects achieving LDL-C <100 mg/dl was EVOLOCUMAB alone: 47% to 61%, EVOLOCUMAB + ezetemibe: 90%, and ezetemibe alone: 7%. Myalgia was reported by 3% on monotherapy, CK elevation >10 times was found in 2 patients and none developed significant elevation of hepatic transaminases (Table 6).[15]

Major findings in Phase II trials: Overall, subcutaneous (sc) administration of PCSK Mabs has been able to achieve 40% to 60% LDL-C reduction beyond what can be achieved by statins. In general, 2-weekly regimes have been more effective than 4-weekly dosing

intervals. The most common side effects have been injection site reactions and gastrointestinal symptoms. Myalgia was reported in 5% to 10%. Liver or renal dysfunction has not been reported with PCSK Mabs.

PCSK9 and Lp(a): In a pooled analysis of 1359 patients on background statin therapy in 4 phase II trials of 12weeks duration, evolocumab resulted in ~25% to ~30% reductions in Lp(a) compared to control ($p < 0.001$). While the mean percentage of reduction was significantly greater in those patients with baseline Lp(a) of ≤125nmol/l, the absolute reduction was substantially larger in those with levels >125nmol/l. Mean percentage reductions did not differ based on age or sex but the trend was greater in those patients taking statins.[16]

Table 1 Study Design and Methods of Phase I Studies with Alirocumab

Study	Overview
First in Human (FIH): R727-CL-0902 IV single dose Monotherapy NCT-01026597 N=40	Patient Population: Healthy Volunteers, men and women, age 18-65, not indicated for statin therapy LDL-C levels >100 mg/dL Objectives: Safety and tolerability Bio-effect on LDL-C and other serum lipids
First SC Study: R727-CL-0904 SC single dose, Monotherapy NCT-01074372 N=32	Patient Population: Healthy Volunteers, men and women, age 18-65, not indicated for statin therapy, LDL-C levels >100 mg/dL Objectives: Safety and tolerability Bio-effect on LDL-C and other serum lipids
Multiple SC Doses: R727-CL-1001 FH, non-FH With or without statin SC multiple doses NCT-01161082 N=62	Patient Population: heFH, non-FH, men and women, age 18-65, atorvastatin 10-40 mg OD (1 cohort mono-Rx); LDL-C levels >100 mg/dL (atorvastatin); 1 cohort monotherapy (no statin) LDL-C > 130 mg/dL Objectives: Safety and tolerability Pharmacodynamic effects on serum lipids and lipoproteins in combo Rx & mono-Rx in pts with hypercholesterolemia

Table 2 Study Design and Methods of Phase II Studies with Alirocumab

Design Parameter	Study 1003	Study 11565	Study 11566
Patient population	HeFH	Hypercholesterolemic	Hypercholesterolemic
Total N (n/arm)	77 (~15)	183 (~30)	92 (~30)
Baseline LDL-C	≥100 mg/dL	≥ 100 mg/dL	≥ 100 mg/dL
Background lipid lowering therapies	Any statin +/- ezetimibe (most patients on high doses of potent statins with ezetimibe)	Atorvastatin 10-40 mg	Atorvastatin 10mg or 80 mg
SAR236553 5 doses and 2 regimens studied	Q2W: 150 mg Q4W: 150, 200 and 300 mg	Q2W: 50, 100 and 150 mg Q4W: 200 and 300 mg	150 mg Q2W
Treatment Length	12 weeks (+ 8 week follow-up)	12 weeks (+ 8 week follow-up)	8 weeks (+8 week follow-up)

Table 3 LAPLACE-TIMI 57 Study

No. of Subjects	629
Profile	With or at risk for CVD
Baseline LDL-C	120 mg/dl
Background Therapy	Statin with or without Ezetemibe
Dosing	6 dosing regimes
LDL-C Reduction at 12 w once in 2 w regime	66% as compared to placebo
LDL-C Reduction at 12 w once in 4 w regime	50% as compared to placebo
% of Patients Achieving LDL-C <70 mg/dl	90% in highest dose group
Treatment-related SAE	Nil

Table 4 MENDEL study

No. of Subjects	406
Profile	At low risk for CVD
Baseline LDL-C	>100 mg/dl
Background Therapy	Nil or Ezetemibe
Dosing	6 dosing regimes
LDL-C Reduction at 12 w	47% to 53% as compared to placebo with highest dose
LDL-C Reduction as compared to Ezetemibe	Significantly greater
Lp(a) reduction	30%
Safety	No signal of toxicity

Table 5 RUTHERFORD study

No. of Subjects	167
Profile	Heterozygous FH
Mean baseline LDL-C	158 mg/dl
Background Therapy	Statin with or without Ezetemibe
Dosing	350 or 420 mg once in 4 w
LDL-C Reduction	43% to 55% as compared to placebo
% Reaching LDL-C <100 mg/dl	EVOLOCUMAB 350 mg: 70%, 420 mg: 89%, Placebo: 2%
% Reaching LDL-C <70 mg/dl	EVOLOCUMAB 350 mg: 44%, 420 mg: 65%, Placebo: 0%

Table 6 Gauss study

No. of Subjects	160
Profile	Statin intolerance due to myalgia
Mean LDL-C at Baseline	193 mg/dl
Treatment Arms	EVOLOCUMAB 280, 350, 420 mg once in 4 w
	EVOLOCUMAB 420 + Ezetemibe
	Ezetemibe alone
LDL-C Reduction at 12 w	EVOLOCUMAB alone: 41% to 51%
	EVOLOCUMAB + Ezetemibe: 63%
	Ezetemibe alone: 15%
Patients reaching LDL-C goal <100 mg/dl	EVOLOCUMAB alone: 47% to 61%
	EVOLOCUMAB + Ezetemibe: 90%
	Ezetemibe alone: 7%
Patients reaching LDL-C goal <70 mg/dl	EVOLOCUMAB alone: 9% to 29%
	EVOLOCUMAB + Ezetemibe: 62%
	Ezetemibe alone: 0%
Side Effects	Myalgia: 3% on monotherapy, CK >10 times: 2 patients, Abnormal LFT: O

Phase III Studies with Alirocumab

Odyssey combo I: The ODYSSEY COMBO I study evaluated the efficacy and safety of alirocumab as add-on therapy to stable maximally tolerated daily statin with or without other lipid-lowering therapy in high cardiovascular risk patients with suboptimally controlled hypercholesterolemia. This multicenter, phase 3, randomized, double-blind, 52-week trial enrolled 316 patients with established coronary heart disease or coronary heart disease risk equivalents and hypercholesterolemia. The primary efficacy end point of percent change in LDL-C from baseline to week 24 was -48.2% and -2.3% for alirocumab and placebo, respectively (P < .0001). Treatment-emergent adverse events were comparable between groups (Table 7).[17,18]

Odyssey combo II: The 720-patient, double-blind ODYSSEY COMBO II trial evaluated the long-term safety and efficacy of alirocumab vs. ezetimibe in combination with a maximally tolerated statin dose. Results showed greater decrease in LDL-C with alirocumab versus ezetimibe at week 24 (51% vs. 21%, *P*<0.0001). In addition, 77 percent of alirocumab patients achieved LDL-C <70 mg/dL at week 24.[19]

Odyssey long-term: Odyssey Long-term was a randomized trial involving 2341 patients at high risk for cardiovascular events who had LDL cholesterol levels of >70mg/dL and were receiving treatment with statins at the maximum tolerated dose with or without other lipid-lowering therapy. Patients were randomly assigned in a 2:1 ratio to receive alirocumab (150mg) or placebo every 2weeks for 78weeks. At week 24, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL-C was −62% points (P<0.001); the treatment effect remained consistent over a period of 78weeks. In a post-hoc analysis, the rate of major adverse cardiovascular events was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52, nominal P = 0.02).[20]

Odyssey mono: In this study, the efficacy and safety of alirocumab were compared with ezetimibe in hypercholesterolemic patients at moderate cardiovascular risk not receiving statins or other lipid-lowering therapy. The primary endpoint of mean LDL-C percentage change from baseline to 24weeks was 47% with alirocumab versus 16% with ezetimibe.[21]

Odyssey alternative: Odyssey alternative compared alirocumab with ezetimibe in patients at moderate to high cardiovascular risk with statin intolerance. Patients (n=361) received single-blind (sc) and oral placebo for 4weeks during placebo run-in. Patients reporting muscle-related symptoms during the run-in were to be withdrawn. Continuing patients were randomized to double-blind alirocumab, ezetimibe, or atorvastatin 20 mg/d for 24weeks. Primary end point was percent change in LDL-C from baseline to week 24 for alirocumab vs ezetimibe. Alirocumab reduced mean LDL-C by 45.0% vs 14.6% with ezetimibe (P=0.0001). Skeletal muscle-related events were less frequent with alirocumab vs atorvastatin (hazard ratio 0.6, P=0.042).[22]

Odyssey FH I and FH II: Odyssey FH I (n=486) and FH II (n=249) assessed the long-term (78weeks) effects of alirocumab treatment in patients with HeFH, inadequately controlled on maximally tolerated lipid-lowering therapy. Mean LDL-C levels decreased by 57.9% vs. placebo at week 24 in FH I and by 51.4% vs. placebo in FH II (P < 0.0001). These reductions were maintained through Week 78. LDL-C <70 mg/dl was achieved at week 24 by 59.8% and 68.2% of alirocumab-treated patients in FH I and FH II, respectively.[23]

Odyssey option I: To compare the LDL-C-lowering efficacy of adding alirocumab with other lipid-lowering strategies, 355 patients with very high CVD risk and LDL-C >70 or high CVD risk and LDL-C >100mg/dL on baseline atorvastatin 20 or 40mg were randomized to: 1) add-on alirocumab, 2) add-on ezetimibe, 3) double atorvastatin dose, or 4) for atorvastatin 40mg regimen only, switch to rosuvastatin 40 mg. The primary end point was percentage change in calculated LDL-C from baseline to 24weeks. Among atorvastatin 20 and 40mg regimens, respectively, add-on alirocumab reduced LDL-C levels by 44.1% and 54.0% (P=0.001 vs all comparators); add-on ezetimibe, 20.5% and 22.6%; doubling of atorvastatin dose, 5.0% and 4.8%; and switching atorvastatin 40 mg to rosuvastatin 40 mg, 21.4%. Most alirocumab-treated patients (87.2% and 84.6%) achieved their LDL-C goals. Treatment-emergent adverse events occurred in 65.4% of alirocumab patients vs 64.4% ezetimibe and 63.8% double atorvastatin/switch to rosuvastatin.[24,25]

Phase III Trials with Evolocumab

Mendel-2: Mendel-2 compared evolocumab with placebo and oral ezetimibe in 614 adult patients with fasting LDL-C between 100 m/dl and <190 mg/dl and Framingham risk scores ≤10%. Evolocumab reduced LDL-C from baseline by ~55% more than placebo and 38% more than ezetimibe (p < 0.001 for both). Adverse events and muscle-related symptoms were comparable across treatment groups (Table 8).[26]

Table 7 Ongoing/Completed Odyssey Trials with Alirocumab[18]

Trial	Aim	Comparator	Status
ODYSSEY COMBO I	To evaluate the efficacy and safety of Alirocumab as add on therapy to stable, maximally tolerated daily statin therapy, with or without other lipid modifying therapy, in patients with hypercholesterolemia at high cardiovascular risk.	Placebo	Study completed
ODYSSEY COMBO II	To evaluate the efficacy and safety of Alirocumab as add on therapy to stable, maximally tolerated daily statin therapy in comparison with ezetimibe in patients with hypercholesterolemia at high cardiovascular risk. Study.	Ezetimibe	Recruitment completed, study ongoing
ODYSSEY LONG TERM	To evaluate the long-term safety and tolerability of Alirocumab for the treatment of high cardiovascular risk patients with hypercholesterolemia who are not adequately controlled by their current lipid-modifying therapy.	Placebo	Recruitment completed, study ongoing
ODYSSEY MONO	To evaluate the efficacy and safety of Alirocumab as monotherapy in comparison with ezetimibe in patients with primary hypercholesterolemia.	Ezetimibe	Study completed
ODYSSEY ALTERNATIVE	To evaluate the efficacy and safety of Alirocumab in comparison with ezetimibe in patients with hypercholesterolemia who are intolerant to statins.	Ezetimibe	Recruitment completed, study ongoing
ODYSSEY FH I	To evaluate the efficacy and safety of Alrocumab as add-on therapy to stable maximally tolerated daily statin therapy, with or without other lipid modifying therapy, in comparison with placebo in patients with heterozygous familial hypercholesterolemia.	Placebo	Recruitment completed, study ongoing
ODYSSEY FH II	To evaluate the efficacy and safety of Alirocumab as add-on therapy to stable maximally tolerated daily statin therapy, with or without other lipid modifying therapy, in comparison with placebo in patients with HeFH.	Placebo	Recruitment completed, study ongoing
ODYSSEY OPTIONS I	To evaluate the efficacy and safety of Alrocumab as add-on therapy to atorvastatin in comparison with ezetimibe as add-on therapy to atorvastatin, the doubling of the atorvastatin dose, or a switch from atorvastatin to rosuvastatin in high cardiovascular risk patients with hypercholesterolemia who are not adequately controlled on nonmaximal doses of atorvastatin.	Ezetimibe AND Atorvastatin at double originial dose AND Patients switching from the statin Atorvastatin to Rosuvastatin.	Study completed
ODYSSEY CHOICE I	To evaluate the efficacy, long term safety, and tolerability of 300 mg alirocumab every 4 weeks in patients who have hypercholesterolemia not adequately controlled and who are at moderate, high, or very high CVD risk.	Placebo	Recruitment Completed, study ongoing
ODYSSEY CHOICE II	To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by a regimen including an alirocumab starting dose of 150 mg Q4W as add-on to non-statin lipid modifying background therapy or as monotherapy in comparison with placebo in patients with primary hypercholesterolemia not treated with a statin including those who are statin intolerant.	Placebo	Recruitment Completed, study ongoing
ODYSSEY OLE	To assess the long-term safety of Alirocumab when added to currently available lipid lowering drug therapy in patients with HeFH who have successfully completed one of the earlier studies	Open label	Actively recruiting
ODYSSEY HIGH FH	To evaluate the efficacy and safety of Alirocumab as add-on therapy to stable maximally tolerated daily statin therapy, with or without other lipid modifying therapy, in comparison with placebo in patients with HeFH.	Placebo	Recruitment completed, study ongoing
ODYSSEY OPTIONS II	To evaluate the efficacy and safety of Alirocumab as add-on therapy to atorvastatin in comparison with ezetimibe as add-on therapy to atorvastatin, the doubling of the atorvastatin dose, or a switch from atorvastatin to rosuvastatin in high cardiovascular risk patients with hypercholesterolemia who are not adequately controlled on nonmaximal doses of atorvastatin	Ezetimibe AND Atorvastatin at double original dose	Study completed
ODYSSEY OUTCOMES	To evaluate the effect of Alirocumab on the occurrence of cardiovascular events in patients who have recently experienced an acute coronary event.	Placebo	Recruiting

Table 8 Ongoing/Completed Phase III Trials with Evolocumab[26]

MENDEL-2	Framingham Risk Score ≤10% and LDL-C level ≥100 mg/dl (no specification regarding statin therapy)	To evaluate the safety and efficacy of evolocumab every 2 or 4 weeks versus ezetimibe and versus placebo, at 10 and 12 weeks	Completed
GAUSS-3	Statin intolerance; hypercholesterolaemia (no statin or low-dose statin)	To evaluate the safety and efficacy of evolocumab every 2 or 4 weeks versus ezetimibe, at 10 and 12 weeks	Completed
DESCARTES	LDL-C level ≥85 mg/dl and either at ATP III target with background lipid therapy or taking maximum background lipid therapy (no specification regarding statin therapy)	To evaluate the efficacy, safety, and tolerability of evolocumab every 4 weeks versus placebo, at 52 weeks, when added to assigned background lipid-lowering therapy	Completed
LAPLACE-2	Primary hypercholesterolaemia or mixed dyslipidaemia (taking statin therapy with or without ezetimibe)	To evaluate the safety, tolerability, and efficacy of evolocumab every 2 or 4 weeks plus a statin versus a statin plus ezetimibe, at 10 and 12 weeks	Completed
RUTHERFORD-2	Heterozygous FH and LDL-C level ≥100 mg/dl with statin therapy (no specification regarding statin therapy)	To evaluate the safety, tolerability, and efficacy of evolocumab every 2 or 4 weeks versus placebo, at 10 and 12 weeks	Completed
OSLER-2	Hypercholesterolaemia or mixed dyslipidaemia; completion of previous evolocumab study (no specification regarding statin therapy)	To evaluate the long-term safety, tolerability, and efficacy of evolocumab versus usual care, at 104 weeks	Completed
TESLA	Homozygous FH and LDL-C level >130 mg/dl with stable lipid therapy (no specification regarding statin therapy)	To determine the safety, tolerability, and efficacy of evolocumab in patients with homozygous FH, at 12 weeks	Completed
TAUSSIG	Homozygous FH or PCSK9 mutations; LDL-C level above ATP III target or receiving apheresis; and completion of previous evolocumab study (no specification regarding statin therapy)	To assess the long-term safety and efficacy of evolocumab every 2 or 4 weeks on LDL-C level in patients with severe FH, at 5 years	Completed
FOURIER	Clinical CVD, high risk of recurrent CVD event, and LDL-C level ≥70 mg/dl or non-HDL-C ≥100 mg/dl (no specification regarding statin therapy)	To assess the effect of evolocumab every 2 or 4 weeks plus a statin versus placebo plus a statin on major CVD events (CVD death, nonfatal myocardial infarction, unstable angina requiring hospitalization, stroke, or coronary revascularization), at 5 years	Ongoing

Gauss-3: GAUSS-3 trial evaluated evolocumab in patients with high cholesterol who cannot tolerate statins. It met its co-primary endpoints of mean percent reductions from baseline in LDL-C at weeks 22 and 24, and the percent reduction from baseline in LDL-C at week.[27]

Descartes: Descartes was a phase 3 placebo-controlled trial to evaluate the safety and efficacy of 52weeks of treatment with evolocumab 420mg every 4weeks or placebo in 901 patients with an LDL-C of >75mg/dL despite a background diet or diet plus atorvastatin (10/80 mg daily), or atorvastatin 80 + ezetimibe 10mg. The primary end point of the change from baseline in LDL-C at week 52 was 57% in evolocumab group as compared to placebo (P<0.001).[28]

Laplace-2: To evaluate the efficacy and tolerability of evolocumab when used in combination with a moderate- vs high-intensity statin, this Phase 3, 12-week, randomized, double-blind, placebo- and ezetimibe-controlled study in patients with primary hypercholesterolemia and mixed dyslipidemia (n = 2067) were randomized to 1 of 24 treatment groups in 2 steps. After a 4-week lipid-stabilization period, patients (n = 1899) were randomized to compare evolocumab (140mg every 2 weeks or 420mg monthly) with placebo or ezetimibe or placebo. 63% to 75%. Adverse events 0were reported in 36%, 40%, and 39%of evolocumab, ezetimibe-, and placebo-treated patients, respectively. The most common adverse events in evolocumab-treated patients were back pain, arthralgia, headache, muscle spasms, and pain in extremity (all <2%).[29]

Rutherford-2: Rutherford-2 investigated the effect of evolocumab on LDL-C in patients with heterozygous familial hypercholesterolaemia (HeFH). This multicentre, randomised, double-blind, placebo-controlled trial was undertaken with 331 adult patients with HeFH on stable lipid-lowering therapy with a fasting LDL-C of 2·6 mmol/L or higher, were randomly allocated to receive sc evolocumab every 2 weeks (n=111), 4weeks (n=110), or placebo (n=110) for 12weeks. Compared with placebo, evolocumab at both dosing schedules led to a significant ~60% reduction in mean LDL-C at week 12 (both p<0·0001). The most common adverse events were nasopharyngitis (9%) and muscle-related adverse events (5%).[30]

Osler-2: To examine long-term efficacy of evolocumab, 1104 (81%) of 1359 randomized patients in the 4 evolocumab phase 2 parent studies who elected to enroll in OSLER study were included in this open-label study. Regardless of their treatment assignment in the parent study, patients were randomized 2:1 to receive either open-label sc evolocumab every 4weeks with standard of care (SOC) (n=736) or SOC alone (n=368). Around 90% of patients in both groups completed 52weeks of follow-up. Patients who had first received evolocumab in OSLER experienced a mean 52.3% reduction in LDL-C at week 52 (P<0.0001). Patients who received 1 of 6 dosing regimens of evolocumab in the parent studies and received evolocumab+SOC in OSLER had persistent mean LDL-C reduction of 50% (P=0.31). In patients who discontinued evolocumab on entry, LDL-C levels returned to near baseline levels.[31]

Tesla part B: Tesla Part B was a randomised, double-blind, placebo-controlled phase 3 trial involving 49 patients above 12years with homozygous familial hypercholesterolaemia (HoFH) on stable lipid

therapy and not receiving lipoprotein apheresis. The subjects were randomly allocated to receive sc evolocumab or placebo every 4weeks for 12weeks. The primary endpoint was percentage change in LDL-C. Compared with placebo, evolocumab significantly reduced LDL-C at 12weeks by 31% (p<0·0001). No serious clinical or laboratory adverse events occurred, and no anti-evolocumab antibody development was detected during the study.[32]

Taussig: Taussigstudy presented recently in the European Atherosclerosis Society 2016 Congress showed a 23% reduction in LDL-C over 48weeks with open-label treatment with evolocumab in 106 patients >12years with HoFH, ~a third of whom were also on lipoprotein apheresis. Though statistically underpowered to assess clinical events, investigators also estimated an annualized cardiac event rate of 2.14% for patients taking evolocumab, which compares favourably with an annualized mortality of 3.5% and a cardiovascular event rate of about 11% per year in other studies of HoFH patients on a statin plus ezetimibe combination.[33,34]

PCSK9 inhibition and cardiovascular outcomes

The ultimate utility of PCSK9 inhibitors shall be determined by their effect on clinical outcomes. Preliminary evidence of cardiovascular benefit with evolocumab was suggested in OSLER-1 and OSLER-2 studies and in post hoc analysis of the ODYSSEY LONG TERM trial conducetd with alirocumab. Statistically powered cardiovascular outcome trials are underway with evolocumab (FOURIER; NCT01764633), alirocumab (ODYSSEY OUTCOMES; NCT01663402), and bococizumab (SPIRE-1; NCT01975376 and SPIRE-2; NCT01975389).

Approved clinical indications of PCSK9 inhibitors

Based on the results of RUTHERFORD-2 and TESLA Part B, evolocumab has recently been approved in several countries including US and EU. In the US, it is indicated in adults as an adjunct to other therapies for treatment of adults with HeFH, HoFH or clinical atherosclerotic cardiovascular disease (ASCVD). Alirocumab is also approved as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH ASCVD, who require additional lowering of LDL-C. It is noteworthy that at the time of writing, the effect of both evolocumab and alirocumab on cardiovascular morbidity and mortality has not been determined.

Conclusion

Monoclonal antibodies have demonstrated LDL-C lowering of up to 60% as monotherapy and up to 70% when added to statins. Lipoprotein (a) levels may also be significantly lowered. LDL-C lowering is the primary target for ASCVD risk reduction as well as mortality reduction. However, 70% of events occur even on statin therapy. This residual risk may be attenuated with additional LDL-C reduction, though this is not yet proved. Statin intolerance is common, occurring in about 10%. There is also a significant inter-individual variation LDL-C response to statins. Treating to targets is also often an elusive goal in familial hypercholesterolemia. PCSK9 inhibition holds promise in management of all of these conditions.

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Conflicts of interest

Author declares there is no conflicts opf interest.

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