

Review Article**Non-statin Treatments for Managing LDL Cholesterol and Their Outcomes**

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Purpose: Over the past 3 decades reducing LDL-C has proven to be the most reliable and easily achievable modifiable risk factor to decrease the rate of cardiovascular morbidity and mortality. Statins are effective, but problems with their side effects, adherence, or LDL-C efficacy in some patient groups remain. Most currently available alternative lipid-modifying therapies have limited efficacy or tolerability, and additional effective pharmacologic modalities to reduce LDL-C are needed.

Methods: Recent literature on new and evolving LDL-C-lowering modalities in preclinical and clinical development was reviewed.

Findings: Several new therapies targeting LDL-C are in development. Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), a recently elucidated key regulator of plasma LDL-C, is the most promising and effective, with a number of approaches aimed at this target. The most advanced are monoclonal antibodies, which have demonstrated LDL-C reductions of ~60%, whether given alone or added to statins. Other PCSK9-targeted therapies in clinical development include adnectins and gene silencing techniques. Preclinical approaches involve vaccines, whereas a search remains for small molecule inhibitors. Other new pharmacologic approaches in Phase III clinical trials include a refocusing of cholesterol ester transfer protein inhibitors from primarily agents to increase HDL-C to their off-target effect on LDL-C and adenosine triphosphate citrate lyase inhibition. In earlier clinical development is new delivery of nicotinic acid-containing compounds. Additional

agents are being developed as orphan indications expressly for patients with homozygous familial hypercholesterolemia, including peroxisome proliferator activated receptor- δ agonists, angiotensin-like protein 3 inhibitors, and gene therapy.

Implications: Monoclonal antibodies that inhibit PCSK9 were shown to be very effective reducers of LDL-C and well tolerated despite subcutaneous administration, and no significant safety issues have yet emerged during large Phase II and III trials. They have the potential to substantially impact further the risk of cardiovascular disease. A number of additional new, but less effective, oral LDL-C-lowering agents are also in various stages of development, including some which are targeted only to patients with homozygous familial hypercholesterolemia. (*Clin Ther.* 2015;37:2751–2769) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: CETP inhibitors, LDL cholesterol, PCSK9 inhibitors, Familial hypercholesterolemia.

INTRODUCTION

Reducing LDL-C concentrations was well established in large, prospective clinical trials as a primary modality for decreasing the risk of cardiovascular morbidity and mortality.^{1–3} Although hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, are the mainstay of LDL-C reduction, there are patient populations that either are intolerant or have contraindications to statins or are unable to achieve consensus

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based ‘optimal’ or ‘target’ LDL-C levels despite adequate response to statins and other currently available LDL-C reducing drugs.⁴ The recent, still controversial and even in the United States not widely accepted, American Heart Association/American College of Cardiology guidelines recommend consideration of non-statin therapies that have demonstrated favorable benefit, compared with adverse effects, for reduction of atherosclerotic cardiovascular disease (CVD).^{5,6} Currently available non-statin therapies for lowering LDL-C include bile acid sequestrants, cholesterol absorption transport inhibitors, niacin, and fibrates. However, with the exception of ezetimibe, these modalities are not well tolerated and often result in inadequate additional LDL-C reduction, and the benefit when added to statins has not shown to improve cardiovascular outcomes.⁷⁻¹⁰ More recently, in specific and rare populations with homozygous familial hypercholesterolemia (HoFH), agents that target apolipoprotein B (apoB)-containing lipoprotein formation, mipomersen and lomitapide, have gained limited approval and have encountered significant postmarketing adverse

side effects, further restricting their use even in these populations.¹¹ Thus, there remains an important need for efficacious agents to robustly and safely decrease LDL-C, and several compounds currently in clinical development are included in this review and are classified into those for widespread use in the general population and those specifically for patients with HoFH (Table I).

EVOLVING THERAPIES FOR REDUCING LDL-C IN THE GENERAL POPULATION

PCSK9 Inhibitors

Since its discovery in 2003 proprotein convertase subtilisin/kexin type 9 (PCSK9) was found to play a key role in the metabolism of LDL-C via its interaction with, and subsequent degradation of, the LDL receptor (LDLR).¹² The elucidation of the pathophysiologic role of PCSK9 via gain-of-function and loss-of-function (LOF) mutations has been extensively reviewed in the past few years and is not repeated here.¹³⁻¹⁵ However, it was mostly the studies documenting that LOF mutations resulted in small but lifelong reductions in LDL-C which were associated with a 40%

Table I. LDL cholesterol-lowering therapies: new drugs in development.

General or widespread use (non-FH, HeFH, and HoFH)

PCSK9 inhibitors

Monoclonal antibodies

Approved (alirocumab, evolocumab)

Phase III (bococizumab)

Phase II (LY3015014, RG7652)

Adnectins: Phase I (BMS-962476)

siRNA: Phase I (ALN-PCS)

CETP inhibitors: Phase III (anacetrapib, evacetrapib, TA-8995)

Adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase modulator:

Phase II (ETC-1002/ bempedoic acid)

New niacin-related agents: Phase I (CAT-2054); ARI-3037MO

Specific or orphan use (HoFH only)

PPAR- δ agonist (MBX-8025): Phase II

ACC inhibitor (gemcabene): Phase II

ANGPTL3 inhibition: monoclonal antibody (REGN1500) Phase I; antisense (ISIS-ANGPTL3Rx); siRNA (ALN-ANG)

ACC, acetyl coenzyme A carboxylase; ANGPTL3, angiopoietin-like protein 3; CETP, cholesterol ester transfer protein; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator-activated receptor; siRNA, small interfering RNA.

to 60% reduction in CVD risk that led to the search for, and development of, compounds that target PCSK9. The critical finding, by Legace et al¹⁶ in 2006, that circulating PCSK9 was responsible for interaction with the LDLR resulted in the rapid development of highly targeted therapy to inhibit PCSK9 with the use of monoclonal antibodies (mAbs). Alternative mechanisms that reduce intrahepatic PCSK9 production such as gene silencing techniques are also in development, whereas the search still continues for small molecules.

mAbs to PCSK9

The most promising and advanced current therapeutic approach to PCSK9 inhibition is mAbs. In 2009 to 2010, 2 mAbs targeting PCSK9, alirocumab and evolocumab, entered clinical trials in humans.^{17,18} Since that time, development has progressed rapidly (Figure 1), and both compounds were recently approved by the Food and Drug Administration by the Endocrinologic and Metabolic Drugs Advisory Committee and the European Medicines Agency with marketing having started in the United States in August 2015.^{19,20} Other mAbs in clinical development include bococizumab, currently in Phase III, and 2 agents, LY3015014

(Eli Lilly) and RG7652 (Genentech/Roche), reportedly awaiting a commercial decision to proceed after completing Phase II.^{21–23}

The first published study in humans with a PCSK9 mAb, alirocumab,¹⁷ clearly demonstrated PCSK9 inhibition to be a powerful modality for reducing LDL-C. Large and statistically significant dose response reductions in LDL-C, from 28% to 65%, were reported in 2 single ascending dose (SAD) trials conducted in healthy volunteers with baseline LDL-C concentrations >100 mg/dL. Although doses up to ~800 mg (12 mg/kg) were tested the study found a plateau of effect at a dose of ~150 mg. A multiple ascending dose (MAD) trial with alirocumab 50, 100, and 150 mg given at 2- and 4-week intervals was conducted in 3 cohorts (heterozygous familial hypercholesterolemia [HeFH] and non-familial hypercholesterolemia on stable dose atorvastatin, and subjects without FH on diet alone) assessed both safety and efficacy, confirming a moderate dose response that ranged from 39% to 61%. Maximum LDL-C lowering occurred rapidly and was stable for 2 weeks after dosing in all 3 cohorts. Single and multiple dose data were reported later in 2012 for evolocumab¹⁸

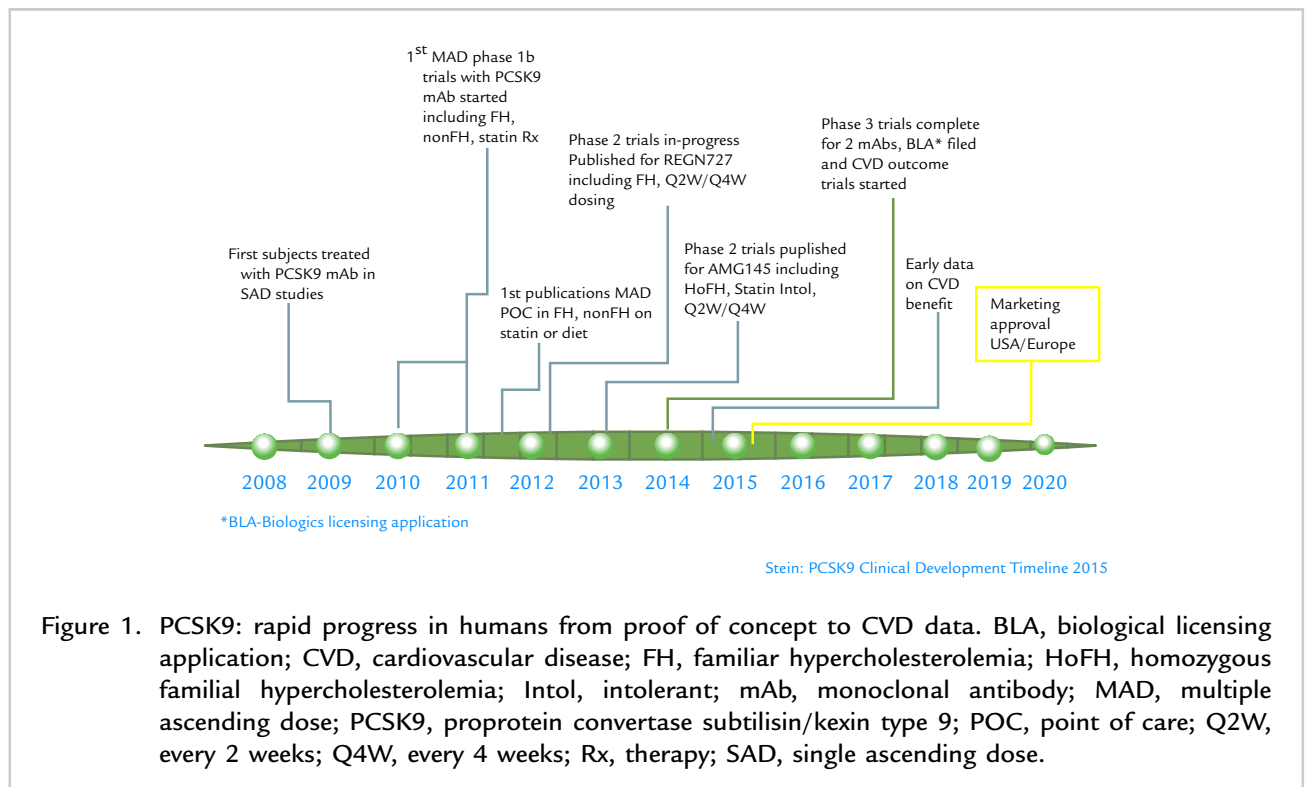


Figure 1. PCSK9: rapid progress in humans from proof of concept to CVD data. BLA, biological licensing application; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; Intol, intolerant; mAb, monoclonal antibody; MAD, multiple ascending dose; PCSK9, proprotein convertase subtilisin/kexin type 9; POC, point of care; Q2W, every 2 weeks; Q4W, every 4 weeks; Rx, therapy; SAD, single ascending dose.

Table II. Key clinical information from Phase II and III trials of alirocumab and evolocumab.

Pharmacokinetic and pharmacodynamic properties
LDL-C efficacy in various phenotypes and genotypes
Non-familial hypercholesterolemia
Monotherapy
Combination with statins
Long-term adherence
Statin adverse patients
Heterozygous familial hypercholesterolemia
Homozygous familial hypercholesterolemia
Effect on Lp(a) and other lipids and lipoproteins
Safety and tolerability
Emerging CVD data and Outcomes trials

CVD, cardiovascular disease.

with similar patient populations and results. The safety and tolerability profile of both alirocumab and evolocumab in these early short-term trials were similar to that of placebo, and development of both drugs progressed rapidly to Phase II.

Over the past 3 years a large number of randomized, mostly double-blind, placebo-controlled, Phase II and III trials with alirocumab²⁴⁻²⁶ and evolocumab,²⁷⁻³⁴ have been published involving over 8000 patients with various lipid phenotypes and genotypes and on a variety of background therapies. This review focuses on what we have learned from these trials, particularly trials that address specific clinical questions listed in Table II.

PK and Pharmacodynamic Properties of mAbs to PCSK9

As the concentration of the mAb, total and free PCSK9, and LDL-C are measurable in plasma/serum, it provides a unique opportunity to be able to study both the pharmacokinetic (PK) and pharmacodynamic parameters of this therapy. As shown in Figure 2, using evolocumab as the example, the mAb is rapidly absorbed after subcutaneous injection, peaks within a few hours in the circulation, and after binding to its target, PCSK9, is gradually cleared via the reticular endothelial system over the ensuing weeks.¹⁸ Although total PCSK9 in plasma increases because of binding by the mAb, free PCSK9 rapidly decreases and at effective doses of mAb within a few hours is reduced by >99% (Figure 2). This is followed within days by a reduction in LDL-C which plateaus at roughly 60% and remains

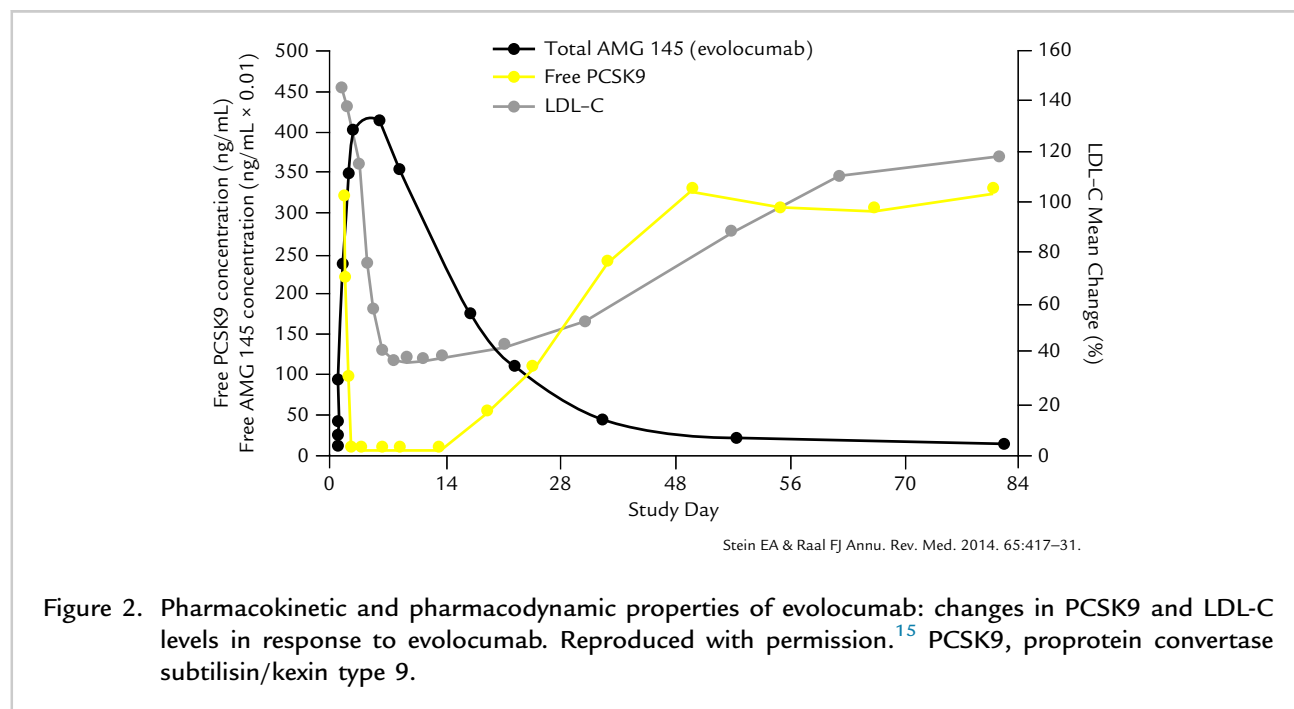


Figure 2. Pharmacokinetic and pharmacodynamic properties of evolocumab: changes in PCSK9 and LDL-C levels in response to evolocumab. Reproduced with permission.¹⁵ PCSK9, proprotein convertase subtilisin/kexin type 9.

stable as long as there is sufficient mAb to keep free PCSK9 suppressed. It became apparent from the early SAD and MAD trials that the LDL-C dose response tailed off soon after a dose of ~140 to 150 mg and that the duration of effect on LDL-C appeared related to the dose of mAb administered. In the SAD trial of alirocumab at a dose of 12 mg/kg, ~800 mg in a 70-kg human, reduced LDL-C to no greater extent than doses of 3 or 6 mg/kg; however, the duration of LDL-C reduction was extended to nearly 60 days.¹⁷ To robustly confirm these 2 aspects further, larger numbers of patients in various dose groups were required, and is thus best assessed by the pooled Phase II data published on evolocumab which compared placebo, 70, 105, 140, 280, 350, and 420 mg in cohorts of 125 to 210 per group.²⁷ To assess maximal reduction in LDL-C for any dose a time point 2 weeks after mAb administration is optimal, and it can be seen from this pooled analysis that a maximal decrease of ~60% was achieved with the 140-mg dose and despite a 3-fold increase to 420 mg essentially no additional LDL-C reduction occurred. This is consistent with the biology of PCSK9 in that once all free PCSK9 is bound no additional upregulation of LDLR will be attained. To assess the duration of effect it can also be seen from the pooled data that the larger the dose of mAb the greater the duration of LDL-C reduction, and when the drug is administered at 420 mg every 4 weeks, almost identical LDL-C reductions occur compared with the 140-mg dose given every 2 weeks. This rule of thumb that it takes 3 times the every-2-weeks dose to achieve the same results as an every-2-weeks dose is consistent with nonlinear PK properties for evolocumab and may reflect non-target mediated clearance of unbound mAb and/or reduced clearance of free PCSK9 because it no longer binds to and is cleared by the LDLR. Although reduced frequency of administration is desirable, it does require larger injection volumes, and the current physical limitation of ~150 mg mAb in 1 mL, an optimal volume for an autoinjector, means that 3 mL is required for a 420-mg every-4-week dose. This entails 3 × 1 mL autoinjectors or more optimally the use of a slow subcutaneous infusion device.

LDL-C Efficacy in Patients without FH

Influences of Background Therapy; Diet Alone, Low- or High-Dose Statin Therapy, or Statin with Ezetimibe

A number of trials were done in patients on diet alone and others in patients on existing statin therapy or randomized to various doses of statins, and

all have shown a consistent response irrespective of the background treatment. Perhaps the Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES) best exemplifies the effect of various background therapy in a single trial because patients with hyperlipidemia were stratified according to risk categories from the National Cholesterol Education Program Adult Treatment Panel III.³⁴ They were then started on background lipid-lowering therapy with diet alone or diet plus atorvastatin 10 mg daily, atorvastatin 80 mg daily, or atorvastatin 80 mg plus 10 mg ezetimibe for a run-in period of 4 to 12 weeks. Patients with an LDL-C ≥75 mg/dL were then randomized in a 2:1 ratio to receive either evolocumab (420 mg) or placebo every 4 weeks for 52 weeks. The overall LDL-C reduction with evolocumab compared with placebo was 57% with the reductions in each of the different background groups, diet alone, atorvastatin 10 mg, atorvastatin 80 mg, and atorvastatin 80 mg plus ezetimibe 56%, 62%, 57%, and 49%, respectively. Thus, there appears to be little impact of background therapy with the addition of mAb to reduce LDL-C an additional 55% to 60%. These results were also consistent with LDL-C reductions of ~60% found with every-2-week treatment with 150 mg alirocumab or 140 mg evolocumab in trials in which patients were on various background therapies.^{30,31,35}

Long-Term Tolerability and Adherence

Alirocumab and evolocumab were well tolerated in the Phase II trials that were of 8 to 12 weeks in duration, and concern remained as to longer term adherence, given that this was the first mainstream subcutaneous therapy for LDL-C. A number of trials in Phase III of ≥52 weeks were thus considered pivotal for this reason alone. DESCARTES, the Open Label Study of Long-Term Evaluation against LDL-C Trial (OSLER), and the ODYSSEY trials FH I, FH II^{36,37} and LONGTERM all demonstrated adherence as good as trials of similar duration with statins, ezetimibe, and other oral lipid-altering agents, with 88% of patients in DESCARTES and 93% in the open label OSLER trial completing the 52-week trial and 72% completing the 78-week ODYSSEY LONG TERM study.^{38,39}

Addition to Statin; Synergy or Additive?

Two issues related to statins were addressed. First, if inhibition of PCSK9 would be synergistic, additive,

or less than additive, and second, if patients who could not tolerate statins, or effective doses of statins, would respond to and tolerate mAbs. The first question related to an initial hypothesis after the finding that statins caused upregulation of PCSK9 synthesis, in addition to synthesis of LDLRs.³⁴ It was postulated that this may be the reason for the log linear dose response curve with statins, also known as the rule of 6 or 7.⁴⁰ On the basis of this it was suggested that inhibition of PCSK9 would therefore be synergistic and lead to enhanced LDL-C reduction with statins, especially higher doses of statins. Although no trial addressed this specifically, the trial by Roth et al²⁴ comes closest. In this trial patients were on stable treatment with atorvastatin 10 mg daily before being randomized to receive either continued atorvastatin 10 mg plus alirocumab 150 mg every 2 weeks or increased to 80 mg plus alirocumab 150 mg every 2 weeks or placebo injections. The increase from 10 to 80 mg atorvastatin resulted in the expected additional ~17% reduction in LDL-C, whereas continuing on atorvastatin 10 mg and adding alirocumab decreased LDL-C 66%. Thus, if PCSK9 inhibition was additive, increasing atorvastatin to 80 mg and adding alirocumab would be expected to reduce LDL-C by 66% + 17% or 83% and even more if the inhibition of PCSK9 was synergistic. However, the LDL-C reduction in the atorvastatin 80 mg + alirocumab group was 73%, only 7% more than in the atorvastatin 10 mg + alirocumab arm. This study clearly showed no synergy exists and suggested that at the highest doses of statins there may be a limit to the upregulation of LDLR activity.

Statin-adverse Patients

For PCSK9 mAbs in patients with statin-associated muscle side effects (SAMSs),⁴ three trials were published or presented, 2 with evolocumab (GAUSS [Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects] and GAUSS-2)^{29,32} and 1 with alirocumab (ODYSSEY ALTERNATIVE).^{41,42} GAUSS and GAUSS-2 required patients have documented intolerance to at least 1 and 2 statins, respectively, and both studies showed that physicians and patients in fact attempt different statins more frequently than previously thought. For example, in GAUSS-2 75% to 80% of patients in the trial had been treated with 3 statins and 20% to 25% had been exposed to a fourth statin. In addition in

GAUSS-2 nearly 20% of the patients had more severe and objective adverse effects, including myositis or rhabdomyolysis. In both GAUSS trials most patients were at high or very high risk of CVD, and the baseline LDL-C was >190 mg/dL, concentrations not seen in such patients since before the advent of statins. The ODYSSEY ALTERNATIVE trial had a different design with patients enrolled only if they consented to the potential of being exposed to atorvastatin 20 mg in the double-blind phase. This in essence likely excluded patients with the most significant and serious SAMSs especially myositis and rhabdomyolysis and patients previously exposed to multiple statins.⁴¹ There was also a single-blind double placebo (oral medication and subcutaneous injection) lead-in during which time ~6% of patients were excluded from the randomized phase. The trial excluded patients in the atorvastatin arm from the efficacy analysis a priori because the purpose was to compare statin re-exposure for tolerability. In the efficacy arm ezetimibe was used as in the GAUSS trials. The patient population in terms of CVD risk and baseline LDL-C was similar to that in the GAUSS trials, emphasizing the significant unmet need for additional effective LDL-C lowering in this population. In the first GAUSS trial,²⁹ dose-dependent reductions in LDL-C concentrations of 41% to 63% in patients on evolocumab, compared with 15% in the ezetimibe group, were observed. There was no significant difference in tolerability seen between evolocumab- and ezetimibe-treated patients. GAUSS-2³² showed LDL-C reductions of up to 56%, and >75% achieved LDL-C concentrations of <100 mg/dL. Based on a questionnaire, muscle adverse events (AEs) were reported in 12% of evolocumab-treated patients and 23% of ezetimibe-treated patients. In ODYSSEY ALTERNATIVE⁴¹ LDL-C was reduced 45% from baseline compared with 15% in the ezetimibe group. Tolerability was better and discontinuations fewer in the alirocumab group, followed by the ezetimibe arm with nearly 50% of patients exposed to atorvastatin reporting SAMSs.

Patients with HeFH

The Phase I MAD studies for both alirocumab and evolocumab included cohorts of patients with HeFH who demonstrated LDL-C reductions similar to that seen in patients without FH. However, most of these patients were from a single clinical site and thus likely carried similar genetic mutations. It is known that

there are >1600 mutations in the LDLR alone that cause FH, so it was important to assess the response in large and global trials in which patients with greater diversity of LDLR, apoB, and potentially PCSK9 gain-of-function mutations would be found. In addition, it was of potential clinical importance to assess if the LDL-C response would be related to the underlying defect because this could lead to more tailored use of what are likely to be expensive medications. To address the first issue the HeFH population was expanded in Phase II trial to patients from North America in a 77-patient alirocumab trial that also assessed higher doses of 200 and 300 mg every 4 weeks compared with 150 mg given both every 2 weeks and every 4 weeks in patients with LDL-C >100 mg/dL on stable maximal statin therapy and many with ezetimibe.²⁵ The evolocumab trial, RUTHERFORD (Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder),²⁸ was global with 168 patients, 90% of whom were on intensive statin therapy, randomized to receive evolocumab 350 mg or 420 mg subcutaneously every 4 weeks or placebo for 12 weeks. Maximal reductions in LDL-C of $60\% \pm 5\%$ were seen in both the alirocumab 150-mg every-2-week dose group and the evolocumab 420 mg dose group with lesser reductions in the lower dose every-4-week arms, again confirming that the response in HeFH even on maximal statin, with or without ezetimibe, was no different from patients without FH. Even larger numbers and greater global diversity of patients with HeFH along with longer duration of therapy were achieved in the Phase III trials for alirocumab and evolocumab. Alirocumab enrolled 1150 patients in the ODYSSEY FH1, FH2, and LONG TERM trials, all of which lasted >52 weeks and with a 2:1 randomization to alirocumab or placebo, resulted in >750 receiving the PCSK9 mAb.³⁶⁻³⁸ The reductions in LDL-C were different because of the incorporation of a lower starting dose of 75 mg every 2 weeks in FH1 and FH2, which was increased to the full 150-mg dose if LDL-C goal was not achieved after 12 weeks of therapy. This resulted in LDL-C reductions that ranged from 51% to 61% compared with placebo. The evolocumab RUTHERFORD-2⁴³ trial enrolled 331 patients with HeFH on maximal statin with or without ezetimibe and randomized assigned them 2:1 to 140 mg every 2 weeks, 420 mg every 4 weeks, or placebo for 24

weeks. The LDL-C reductions in both evolocumab groups were virtually identical at 59% and 61%, respectively, versus placebo. The unique aspect of RUTHERFORD-2 was that in the 80% of patients who consented to genetic analysis of their mutation that caused FH it was unequivocally demonstrated the LDL-C reduction was not related to underlying defect with equal reductions seen in those with LDLR defective and negative mutations.

Patients with HoFH

Some initial skepticism that PCSK9 inhibition would not be effective in lowering LDL-C in patients with HoFH was dispelled by a small pilot proof-of-concept trial with evolocumab (TESLA part A).⁴⁴ Eight LDLR-negative or -defective patients with HoFH on maximal stable drug therapy were treated with evolocumab 420 mg every 4 weeks for ≥ 12 weeks, followed by 420 mg every 2 weeks for an additional 12 weeks. No reduction was seen in the 2 LDLR-negative patients but in the 6 with LDLR-defective mutations reductions of 19.3% and 26.3% were found with 4- and 2-week dosing, respectively, and ranged from 4% to 48%. On the basis of these results a larger more definitive randomized placebo-controlled, double-blind trial, TESLA part B, was undertaken. Forty-nine patients, including patients aged ≥ 12 years on maximal statin \pm ezetimibe but not apheresis with mean baseline LDL-C of 348 mg/dL were randomized 2:1 to receive evolocumab 420 mg every 4 weeks or placebo for 12 weeks.³³ Compared to placebo, LDL-C was reduced by 31%, and the absolute decrease in LDL-C was 93 mg/dL. The trial also assessed response based on the underlying genetic mutation, and, although few patients had defects associated with no receptor activity, it confirmed they did not respond. However, in the majority of patients, who had at least 1 LDLR defective mutation, the LDL-C reduction was 41% and in patients with 2 LDLR defective genes it was 46%.

Effect on Lp(a) and Other Lipid and Lipoproteins

Similar to statins that upregulate LDLR synthesis and activity, PCSK9 mAbs reduce apoB and related lipids and lipoproteins such as total cholesterol, non-HDL-C, and VLDL in parallel to LDL-C. In addition, mild-to-moderate reductions in triglycerides (TGs) were reported. Small increases in HDL-C and its associated apoA1 were seen in most trials, which is,

again, consistent with the effect seen with statins whereby clearance of atherogenic lipoproteins is enhanced. However, a completely unexpected effect was the robust and consistent reductions in Lp(a) which was first noted in the MAD trials.^{17,18} The reduction was confirmed in the larger Phase II and III trials, and, while dose dependent, at the doses most frequently used and likely to be marketed of 150 mg every 2 weeks for alirocumab and 140 mg every 2 weeks and 420 mg every 4 weeks for evolocumab, respectively, Lp(a) is reduced 25% to 30%.^{45,46} Although a number of theories exist for the reduction, which is not seen with other drugs that lower LDL-C by increased clearance, the mechanism is yet to be elucidated.

Safety Profile

Despite exposure to >8000 patients for durations up to 2 years no specific or serious clinical or laboratory AEs have emerged so far.²⁴⁻³⁴ The subcutaneous injections have been well tolerated with few injection site reactions, and, because both alirocumab and evolocumab are fully human mAbs, few and low titer anti-mAb antibodies were seen. It thus appears fortuitous that circulating PCSK9 has no other role other than to bind to and regulate LDLR recycling; thus, removal of PCSK9 via binding to mAbs results in no off target effects. This is also supported by the

human genetic studies in populations with LOF mutations in which no adverse effects have been reported and even in the rare patient with dual PCSK9 LOF where no plasma PCSK9 is detectable, LDL-C concentrations are <20 mg/dL, but no physical, psychological, endocrine, or reproductive abnormalities are found.⁴⁷⁻⁵⁰

The other area of potential concern has been the very low LDL-C levels attained in many patients, especially those in whom pre-PCSK9 mAb treatment LDL-C is just above 70 mg/dL, and the large treatment-associated decreases result in LDL-C <25 or even 15 mg/dL. However, recently reported results from both the ODYSSEY LONG TERM trial and OSLER extension trials examined the incidence of clinical and laboratory AEs in these patient subgroups and found no differences in mAb-treated patients with higher LDL-C or those in the placebo or standard of care (SOC) alone groups (Tables III and IV).^{38,39} One potential area that requires additional monitoring and assessment is neurocognitive events that in both OSLER and ODYSSEY LONG TERM trials showed slight excess in the groups treated with mAbs. These events were not assessed or adjudicated in a systematic manner in either study and appeared to vary in the same patient from visit to visit. However, to address the issue in greater detail and more systematically a substudy, EBBINGHAUS (Evaluating PCSK9 Binding

Table III. OSLER: adverse events by achieved LDL-C.³⁹

	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n = 2976)	SOC Alone (n = 1489)
	<25 mg/dL (n = 773)	25 to <40 mg/dL (n = 759)	<40 mg/dL (n = 1532)	≥40 mg/dL (n = 1426)		
Adverse events (%)						
Any	70.0	68.1	69.1	70.1	69.2	64.8
Serious	7.6	6.9	7.2	7.8	7.5	7.5
Muscle related	4.9	7.1	6.0	6.9	6.4	6.0
Neurocognitive	0.5	1.2	0.8	1.0	0.9	0.3
Laboratory results (%)						
ALT/AST > 3× ULN	0.9	0.8	0.8	1.3	1.0	1.2
CK > 5× ULN	0.4	0.9	0.7	0.5	0.6	1.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; EvoMab, evolocumab; OSLER, Open Label Study of Long-Term Evaluation against LDL-C Trial; ULN, upper limit of normal; SOC, standard of care.

Table IV. ODYSSEY outcomes: summary of adverse events (AEs) by achieved LDL-C.³⁸

	Alirocumab (n = 1550)	Alirocumab with 2 consecutive LDL-C <25 mg/dL (n = 575)	Placebo (n = 788)
Any AE	1255 (81.0)	435 (75.7)	650 (82.5)
Serious AE	290 (18.7)	98 (17.0)	154 (19.5)
AE leading to death	8 (0.5)	4 (0.7)	10 (1.3)
AE leading to study drug discontinuation	111 (7.2)	26 (4.5)	46 (5.8)

AE, adverse event.
Values are n (%).

Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects; ClinicalTrials.gov identifier NCT02207634) was incorporated in the evolocumab, CVD outcome trial FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk).

However, just as with statins, decades of therapy with these agents in many hundreds of thousands of patients may be necessary to detect more subtle side effects not readily apparent in short-term trials.

Cardiovascular Events and Outcome Trials

Unlike the development of statins 3 decades ago when no impact on CVD events were discernable before regulatory approval and marketing, and it took nearly a decade after initial approval until the results of the 4S trial were reported,³ 2 Phase III trials with both alirocumab and evolocumab showing a reduction in CVD have been published.^{38,39} In the OSLER trial, evolocumab was studied in 4465 patients who enrolled into an open-label trial after completing 1 of the Phase II or III parent trials. Patients were re-randomized 2:1 to receive standard of care (SOC) plus evolocumab 140 mg every 2 weeks or 420 mg every 4 weeks for 12 months or SOC alone. A prespecified exploratory analysis included CVD events, which were adjudicated blinded without knowledge of treatment group. LDL-C was reduced with evolocumab, 61%, to a median LDL-C of 48 mg/dL from a baseline median of 120 mg/dL, and at 11 months CVD event estimates by Kaplan-Meier analysis were 0.95% and 2.18%, with SOC + evolocumab and SOC alone, respectively (hazard ratio, 0.47; 95% CI, 0.28–0.78; $P = 0.003$). A blinded post hoc analysis of CVD events in the 2341 high-risk patient

double-blind ODYSSEY LONG TERM trial, where LDL-C was decreased 62% with alirocumab 150 mg every 2 weeks, showed a 48% reduction in CVD events at 78 weeks (1.7% with alirocumab vs 3.3% with placebo; hazard ratio, 0.52; 95% CI, 0.31–0.90; $P = 0.02$). Although CVD events were not the primary or even secondary end points for these 2 trials and the number of events was relatively small in both trials, both were statistically significant and demonstrated almost identical reductions of nearly 50% relative to either placebo or SOC. These studies are encouraging and also in direct contrast to smaller short-term trials for example, with torcetrapib. In Rating Atherosclerotic Disease by Imaging with a new CETP inhibitor (RADIANCE) I and II, in which the primary end point was carotid intimal media change, CVD events in both trials showed an increase with torcetrapib added to atorvastatin, reaching statistical significance ($P < 0.05$) in RADIANCE I.⁵¹

The definitive CVD outcome trials for evolocumab, alirocumab, and bococizumab are already under way (Table V) and should also address the long-term safety profile of the drugs and low and very low LDL-C levels. The FOURIER (NCT01764633) trial that compares evolocumab 150 mg every 2 weeks or 420 mg every 4 weeks added to statin versus statin alone is already fully enrolled with 27,500 patients with results expected no later than 2017.⁵² The ODYSSEY OUTCOMES trial is projected to complete planned enrollment of 18,000 patients by the end of 2015 and will compare addition to statin of alirocumab 75 mg every 2 weeks, with up titration to 150 mg every 2 weeks if LDL-C <70 mg is not achieved, to statin alone, and results are anticipated by late 2017 or early 2018.⁵³

Table V. PCSK9 inhibitor CVD outcomes trials in progress.

	Evolocumab (AMG 145)	Alirocumab (SAR236553/ REGN727)	Bococizumab (RN 3160)	
Sponsor	Amgen	Sanofi/Regeneron	Pfizer	
Trial	FOURIER	ODYSSEY Outcomes	SPIRE I	SPIRE II
Sample size	27,500	18,000	17,000	9000
Patients	MI, stroke, or PAD	4–25 wk after ACS	High risk or CV event	
Statin	Atorva ≥ 20 mg or equiv	Evidence-based medical Rx	Lipid-lowering Rx	
LDL-C mg/dL (mmol/L)	≥ 70 (≥ 1.8)	≥ 70 (≥ 1.8)	70–99 (1.8–2.6) ≥ 100 (≥ 2.6)	
PCSK9i dosing	Q2W or Q4W	Q2W	Q2W	
End point	1°: CV death, MI, stroke, revasc or hosp for UA Key 2°: CV death, MI, or stroke	CHD death, MI, ischemic stroke, or hosp for UA	CV death, MI, stroke, or urgent revasc	
Recruitment status	Completed June 2015	Projected for December 2015 ?		
Completion	December 2017	January 2015	August 2017	

ACS, acute coronary syndrome; Atorva, atorvastatin; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; equiv, equivalent; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; hosp, hospital; MI, myocardial infarction; PAD, peripheral artery disease; Q2W, every 2 weeks; Q4W, every 4 weeks; revasc, revascularization; Rx, therapy; SPIRE, Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects; UA, unstable angina.

Regulatory Status, Marketing Approval, and Annual Cost

The development progress from first in human trials through to completion of Phase III, filing biological licensing application, regulatory review, and final marketing approval for alirocumab and evolocumab was remarkably rapid (Figure 1) in both Europe and the United States.^{19,20} Alirocumab became available in the United States in early August 2015, with a recommended starting dose of 75 mg every 2 weeks, for use as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic CVD, who require additional lowering of LDL-C. Evolocumab became available in early September with similar indications plus the additional indication for patients with HoFH aged 13 or older. The list price for alirocumab, 75 mg or 150 mg doses, was recently announced by the manufacturers at \$14,600 per year, although it is likely that actual costs to health insurance payers will be less. The price of evolocumab is approximately \$500 per year less. However, even

though these drugs are by far the most efficacious LDL-C agents yet developed and have excellent tolerability and early safety profiles, it is important that they be used only when appropriate and always only after maximal tolerable doses of the most efficacious statins, atorvastatin and rosuvastatin, plus ezetimibe have been fully implemented.

ADNECTINS: BINDING PROTEINS TO PCSK9

Although mAbs to PCSK9 have shown to be effective and well tolerated, they are expensive to manufacture because they require production in mammalian cell lines and have physical limitations in terms of injection volumes as previously described. Alternative smaller binding proteins that like mAbs bind circulating PCSK9 may therefore offer potential advantages. Adnectins are proprietary fusion proteins derived from the tenth type III domain of human fibronectin, designed to bind with high affinity and specificity to a therapeutic target, analogous to mAbs, and are produced via an *Escherichia coli*-based manufacturing process.⁵⁴ BMS-962476 is an ~11-kDa polypeptide

first-generation PCSK9-targeted adnectin conjugated to polyethylene glycol to provide extended circulating time and to extend its PK properties. In a phase I SAD study⁵⁵ of 64 otherwise healthy patients with elevated LDL-C treated with statins or diet alone, SC doses of BMS-962476 showed a dose-related effect with 0.3 mg/kg, reducing free PCSK9 >90% and LDL-C 48% from baseline. While an attractive alternative to mAbs, given the lower potential cost of production and smaller injection volumes, it remains to be seen if adnectins provide the same tolerability, safety profile, and reductions in LDL-C as mAbs.

Gene Silencing Approaches to PCSK9 Inhibition: RNA Interference and Antisense Oligonucleotides

Gene-silencing techniques, such as RNA interference and antisense oligonucleotides impede the intracellular production of target proteins through nucleic acid-based therapies that interfere with RNA function. RNA interference occurs at the post-transcriptional level and is a mechanism by which double-stranded RNA is processed by an endonuclease to small interfering RNA (siRNA), 15 to 30 nucleotides in length, which is then bound to a nuclease complex that triggers unwinding of the siRNA, the antisense siRNA strand is then directed to a complementary target mRNA, resulting in degradation of mRNA, preventing translation of the target protein, potentially silencing gene expression.⁵⁶ ALN-PCS (Alnylam Pharmaceuticals, Cambridge, Mass), a siRNA inhibitor of PCSK9 administered intravenously, was studied in a Phase I SAD study in 32 healthy subjects with LDL-C >115 mg/dL and reduced mean PCSK9 protein and LDL-C concentrations by 70% and 40% 3 days after infusion, respectively, in the highest dosed, 0.400 mg/kg, cohort. Treatment-emergent AEs were similar in the ALN-PCS and placebo groups; however, subjects required premedication with dexamethasone and antihistamines to mitigate the potential for infusion-related reactions that can occur with lipid-formulated drugs.⁵⁷ Subsequently, siRNA paired with triantennary N-acetylgalactosamine (GalNAc) resulted in a GalNAc-siRNA conjugate, comprised of a sugar moiety that acts as a ligand to the asialoglycoprotein receptor, resulting in a 5-fold improvement in efficacy and enabling targeted delivery directly to the liver, inducing marked gene silencing with subcutaneous administration.⁵⁸ In a preclinical study of ALN-PCS conjugate given as a single dose in cynomolgous monkeys, PCSK9 protein was lowered by

95% and mean LDL-C decreased 69% at the highest dose, with effective reductions maintained >50 days after the last dose, raising the possibility of monthly or longer dosing intervals. ALN-PCS is currently in Phase I clinical development (clinicaltrials.gov identifier NCT02314442) in a SAD/MAD trial in healthy volunteers with LDL-C \geq 100 mg/dL; ALN-PCS combined with statins will be assessed in the multiple dose phase. It is anticipated this agent will enter Phase II in late 2015 or early 2016.

Vaccines Targeting PCSK9

Peptide-based anti-PCSK9 vaccines being developed by AffiRis AG (Vienna, Austria) have shown LDL-C reduction up to 55% for 1 year in preclinical studies. Generated PCSK9-specific antibodies efficiently blocked PCSK9 protein in animals, upregulated LDLRs, and also recognized human PCSK9.⁵⁹ Pfizer has announced a vaccine to PCSK9 will begin clinical development in 2016.

CETP Inhibitors

Cholesterol ester transfer protein (CETP) inhibition may be anticipated to reduce the risk of CVD, supported by epidemiologic studies showing genetic mutations that result in CETP deficiency and associated increases in HDL-C.^{60,61} The background on the epidemiology, physiology, and pharmacology of CETP inhibitors (CETPis) was recently reviewed.^{62,63}

Over the past decade several CETPis have entered clinical development with the primary goal of reducing CVD events through their ability to increase HDL-C concentrations and enhance reverse cholesterol transport. The effect on HDL-C has ranged from 35% with dalcetrapib to >150% with TA-8995, whereas reductions in LDL-C concentrations have varied from minimal with dalcetrapib to 45% with TA-8995. Because there is no regulatory pathway for approval on the basis of HDL-C as a surrogate biomarker, trials demonstrating reduction in CVD are required. Two agents, torcetrapib and dalcetrapib, were terminated during large CVD outcome trials after an increase in CVD events of 25% in patients taking torcetrapib,⁶⁴ whereas the trial with dalcetrapib was terminated because of futility as dalcetrapib did not improve CVD events compared to placebo at a planned interim analysis.⁶⁵

Three CETPis remain in clinical development, anacetrapib, evacetrapib, and TA-8995. Anacetrapib 100 mg daily has been evaluated in patients with

HeFH and without FH, with reported increases in HDL-C of ~100% and LDL-C reductions when measured accurately of 25% to 35%. Adverse events appear similar in the anacetrapib and placebo groups; however, the drug has an extremely long half-life, measured in months, because it accumulates in adipose tissue, which is a concern.⁶⁶ Prespecified CVD end points in two 1- to 2-year trials with patients with HeFH and without FH have not shown significant increased or decreased events compared with placebo.^{67,68} The large CVD outcome trial with anacetrapib, REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid-Modification; clinicaltrials.gov identifier NCT01252953), which is recruiting 30,000 patients with established CVD, is expected to complete in 2017.

Evacetrapib has been shown to increase HDL-C by ~120% and reduce LDL-C 20% to 25% when added to statin therapy and is currently undergoing a large CVD outcome trial, ACCELERATE (A Study of Evacetrapib in High-Risk Vascular Disease; clinicaltrials.gov Identifier NCT01687998), which will evaluate an estimated 11,000 patients to determine whether evacetrapib added to statins provides additional risk reduction in major adverse cardiovascular events compared with statins alone in patients with CVD; results are expected in 2016. The sponsors recently announced that after an interim analysis for futility the data safety and monitoring committee had recommended continuation of the trial.⁶⁹

Recently, TULIP (TA-8995: Its Use in Patients with Mild Dyslipidaemia), reported a Phase II dose-ranging study of the CETPi TA-8995 in patients with LDL-C between 100 and 175 mg/dL, HDL-C between 30 and 70 mg/dL, doses of 1, 2.5, 5, or 10 mg daily as monotherapy, 10 mg TA-8995 plus 20 mg atorvastatin or 10 mg rosuvastatin, or placebo. LDL-C reductions after 12 weeks were significant at all TA-8995 doses, with a decrease of 45.3% in the 10-mg dose monotherapy group and 50.2% reduction in LDL-C when combined with statin compared with statin alone.⁷⁰

Dual Adenosine Triphosphate Citrate Lyase Inhibitor/Adenosine Monophosphate-Activated Protein Kinase Activator

Bempezoic acid, ETC-1002 (Esperion Therapeutics Inc, Ann Arbor, Mich), is a novel, oral, once daily therapeutic agent in development to reduce LDL-C

concentrations and to target dyslipidemia and other cardiometabolic risk factors associated with the metabolic syndrome and atherosclerosis.⁷¹ A dual mechanism of action has been demonstrated in preclinical studies, consisting of adenosine monophosphate-activated protein kinase activation and direct inhibition of the enzyme adenosine triphosphate citrate lyase by bempezoic acid-coenzyme A, a thioester coenzyme rapidly formed in the liver. This was linked to beneficial effects on lipid and carbohydrate metabolism, including inhibition of both sterol and fatty acid synthesis, improved glycemic control, and increased fatty acid oxidation.⁷²

In completed Phase I and II clinical trials nearly 1000 patients were studied, two-thirds were treated with ETC-1002 at doses of 60, 120, 180, and 240 mg daily, either as monotherapy or in combination with ezetimibe or low-dose statins. Dose-dependent reductions in LDL-C were seen and the percentage of decreases with monotherapy versus placebo or baseline have varied from the low 20s to as high as 45% in a trial in diabetic patients.⁷¹ The occurrence of treatment emergent AEs was similar in patients receiving ETC-1002 and placebo, and there were no discontinuations of ETC-1002 because of muscle-related complaints.^{73,74}

In the initial exploratory 6-week study LDL-C was reduced 24% compared with placebo with ETC-1002 180 mg in patients on diet-only therapy. A subsequent 12-week trial, 008, in which patients on diet only were treated with ETC-1002 120 mg or 180 mg as monotherapy had reductions in LDL-C from baseline of 27% and 30%, respectively. In study 009, treatment with 120 and 180 mg daily of ETC-1002 added to stable statin background therapy resulted in a 17% and 24% reduction in LDL-cholesterol, respectively, compared with patients on statin therapy alone.⁷¹

ETC-1002 has also shown a consistent reduction of 25% to 40% in high-sensitivity C-reactive protein and a neutral effect on blood pressure, with good safety profile and tolerability even in patient subgroups with prior SAMs.⁷¹

No increased muscle-related AEs or elevated liver function test results relative to placebo were reported in these trials. Thus, ETC-1002 appears to offer an oral agent with promising, if moderate, additional LDL-C reduction with good tolerability and is proceeding into large Phase III trials that are primarily to assess long-term safety.

NEW NIACIN (NICOTINIC ACID)-RELATED COMPOUNDS

Niacin (nicotinic acid) is one of the oldest lipid-altering drugs in use, having been used therapeutically since the mid-1950s. It has well-documented favorable effect on lipid parameters, including TG and LDL-C reductions of 20% to 50% and 10% to 25%, respectively, and HDL-C increases of 15% to 35%.^{75,76} Reduced rates of cardiovascular morbidity and mortality with monotherapy were seen in the Coronary Drug Project,^{77,78} where doses of immediate release nicotinic acid >2 g/d in patients with prior myocardial infarction were associated with a 27% reduction in nonfatal recurrent myocardial infarctions ($P < 0.004$) and long-term 15-year follow up showed 11% fewer deaths in the treatment group than in the placebo group. Side effects with niacin treatment, in part because of niacin-mediated GPR109A receptor agonist activity, have resulted in difficulty with tolerability, mainly because of flushing, consisting of skin symptoms that include warmth, redness, itching, or tingling, and increased insulin resistance.⁷⁹ However, 2 large CVD outcome trials, both with the use of extended release niacin formulations added to statins, AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcome)^{8,9} and HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events),⁸ failed to show clinical benefit. Despite these setbacks, research into niacin and its derivatives continues.

With the use of a proprietary technology, SMART linker, approach to target and deliver niacin in higher concentrations directly to the liver CAT-2054 (Catabasis Pharmaceuticals Inc, Cambridge, Mass) is an oral novel small molecule compound designed to reduce sterol regulatory-element binding protein, a family of membrane-bound transcription factors that activate genes encoding enzymes involved in cholesterol and fatty acid synthetic pathways, the LDLR, and PCSK9.⁸⁰ CAT-2054, consisting of eicosapentaenoic acid conjugated to niacin, does not activate the GPR109A receptor, thus mitigating the potential for flushing and via the eicosapentaenoic acid ensures direct delivery to the hepatocyte. Preclinical studies have shown reductions in both LDL-C and PCSK9 concentrations, and in a Phase I SAD trial in healthy volunteers, CAT-2054 was well tolerated, and AEs were similar at doses ≤ 500 mg/dL, flushing was not

reported by study patients.⁸¹ The results of a recently completed MAD trial showed that tolerability remained good, LDL-C reductions of up to 20% were seen, and the drug is planned to enter Phase II.⁸²

ARI-3037MO (Arisaph Pharmaceuticals, Boston, Mass) is a new, synthetic derivative of nicotinic acid⁸³ that does not interact with the GPR109A receptor, and a healthy volunteer SAD trial of 0.5 to 6 g daily found statistically significant mean decreases in TGs of 56.7% and increases in HDL-C of 7.7% in the 6-g cohort. A MAD trial, dose range 0.5 to 3.5 g daily, demonstrated significant reductions in TG concentrations, and a trend toward reduction in LDL-C in the 2-g cohort. In both trials, at all dosing regimens, ARI-3037MO was well tolerated without flushing, itching, or other skin changes; in addition, no liver enzyme or glucose abnormalities were observed. Future trials will determine whether the trends toward LDL-C reduction seen in early studies will be efficacious in a dyslipidemic population.

EVOLVING THERAPIES FOR REDUCING LDL-C IN SPECIFIC OR ORPHAN HOFH POPULATIONS

Two orphan drugs were approved in the past 2 years only for use for HoFH and under stringent requirements because of the significant potential toxicity associated with both drugs.¹¹ The 2 agents have similar mechanism of action in that they decrease formation of apoB-containing lipoproteins and thus entry of VLDL and LDL into the circulation. Lomitapide inhibits the enzyme microsomal TG transfer protein which is present in both the intestine and liver and is essential for the addition of lipid to apoB (B₄₈ in the gut and B₁₀₀ in the liver) to allow chylomicron and VLDL formation, respectively. Mipomersen is an apoB antisense agent that works in the liver to downregulate synthesis of apoB, the apolipoprotein essential for VLDL production and its subsequent down-stream product LDL.¹¹ Although effective at reducing plasma LDL-C, especially because no LDLR activity is involved, both drugs result in hepatic fat accumulation with unknown long-term consequences, in addition to significant and limiting side effects such as diarrhea and fat-soluble vitamin reductions with lomitapide and injection site reactions and flu-like symptoms with mipomersen. Both drugs are also extremely expensive with list price in the United States of \sim \$300,000 per year for lomitapide and close to

\$200,000 for mipomersen. Excellent recent reviews on the pharmacology, lipid altering, side effects and restrictions for use are available; thus, this review focuses on novel agents in development for this difficult to treat severe disease.¹¹

PPAR Agonists

Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors that are comprised of 3 receptors PPAR- α , PPAR- δ , and PPAR- γ , and function as ligand-activated transcription factors to regulate multiple metabolic processes such as glucose and lipid metabolism, fatty acid oxidation, adipogenesis, and insulin sensitivity. Drugs with PPAR- α activity, such as clofibrate, gemfibrozil, and fenofibrate, have been used for decades to treat lipid disorders, predominantly to reduce TGs and to increase HDL-C. PPAR- δ activation affects lipid transport, storage, and metabolism in liver and muscle, resulting in decreased concentrations of TGs and LDL-C, decreased HDL-C concentrations, and improved insulin sensitivity, and has been identified as a therapeutic target.⁸⁴

MBX-8025 (Cymabay Therapeutics, Newark, Calif), a novel, potent PPAR- δ agonist with >750-fold and >2500-fold activity compared with PPAR- α or PPAR- γ receptors, respectively, was previously evaluated in a double-blind, placebo-controlled, proof-of-concept study of 181 patients with mixed dyslipidemia who were randomized to receive MBX-8025 50 or 100 mg daily with or without atorvastatin 20 mg daily, atorvastatin alone, or placebo and reduced apoB^{85,86} compared with baseline, 20% to 38% ($P < 0.0001$). In addition, LDL-C decreased 18% to 43%. No differences were reported in AEs between treatment groups, and the drug was well tolerated.

The drug has been repositioned, and MBX-8025 has received an orphan drug designation for HoFH whereby clinical development is being undertaken. Part of the premise for efficacy in HoFH is that in Watanabe-heritable hyperlipidemic rabbits, with low (<5%) hepatic LDLR activity and markedly elevated LDL-C concentrations (360–592 mg/dL) characteristic of HoFH, subcutaneous administration of MBX-8025 30 mg/kg daily for 3 weeks resulted in mean LDL-C reduction from baseline of 42%.⁸⁷ A Phase II open-label, dose-escalation, proof of concept trial in HoFH (clinicaltrials.gov identifier NCT02472535) has commenced, and, if successful, a larger phase 3 trial will follow.

Acetyl Coenzyme A Carboxylase Inhibitors

Gemcabene, a dialkyl ether (dicarboxylic acid), part of a class of lipid-modifying compounds that possess a gem-dimethyl carboxylate moiety, has been shown in preclinical studies to act as a PPAR ligand.⁸⁸ Originally discovered in the 1990s it entered clinical development as a drug for broad use in all patients to reduce LDL-C, and thus was studied in nearly 1000 patients in Phase I and II trials.⁸⁹ Moderate LDL-C lowering of 15% to 25% was demonstrated along with good safety. The drug has recently been licensed to a start-up biotech company, orphan designation for use in HoFH obtained, and gemcabene is now being developed for HoFH, and a Phase II proof-of-concept trial is planned.

ANGPTL3 Inhibitors

Angiopoietin-like protein 3 (ANGPTL3) is a glycoprotein, secreted by the liver, with modulating effects on lipoprotein and glucose metabolism, mainly through inhibition of lipoprotein lipase activity. Genome-wide association studies have linked the ANGPTL3 gene to levels of circulating lipids; multiple single-nucleotide polymorphisms have been associated with decreased TGs. A unique lipid phenotype related to LOF mutations in the ANGPTL3 gene, familial combined hypolipidemia (FHBL2), comprised of low concentrations of all plasma lipoproteins (VLDL, LDL, and HDL), was initially described in 4 siblings subsequently found to be compound heterozygotes with 2 inactivating mutations in ANGPTL3 (p.E129X/p.S17X). To date, 9 distinct mutations in ANGPTL3-producing FHBL2 have been identified, with LDL-C concentrations as low as 35 mg/dL reported.⁹⁰ These findings suggest that inhibiting ANGPTL3 may be an attractive target to treat hyperlipidemia.

REGN1500 (Regeneron Pharmaceuticals, Tarrytown, New York) is a fully humanized mAb with high-binding affinity to ANGPTL3. In preclinical studies in dyslipidemic mice, administration of REGN1500 was associated with 2.5-fold increased concentrations of post-heparin LPL activity, and statistically significant reductions in TGs, total cholesterol, and LDL-C levels up to 53%, 35%, and 45%, respectively, were observed after 8 weeks of treatment with REGN1500 compared to controls. Subsequent studies in dyslipidemic monkeys given either 3 or 10 mg/kg in a single dose again showed robust reductions in TG

concentrations of 89% at days 1 and 2 with sustained reductions in TGs maintained for 33 days before returning to baseline concentrations; LDL-C levels did not change, possibly because of a low mean baseline level of 58 mg/dL.⁹¹ Currently, REGN1500 is in clinical development with 3 active trials, 2 Phase I SAD and MAD studies, and a proof-of-concept trial to evaluate the safety and efficacy of both single and multiple doses of REGN1500 in patients with HoFH (clinicaltrials.gov identifiers NCT01749878, NCT02107872, and NCT02265952, respectively).

Isis Pharmaceuticals (Carlsbad, Calif) and its subsidiary, Akcea Therapeutics, are pursuing clinical development of an antisense oligonucleotide, ISIS-ANGPTL3Rx, and recently reported results from a Phase I SAD/MAD study in healthy volunteers. In this study, ISIS-ANGPTL3Rx was generally well tolerated and demonstrated reductions of up to 93% in ANGPTL3 from baseline ($P < 0.001$). In addition, statistically significant reductions from baseline in lipid markers were observed, with mean TG and total cholesterol concentrations decreased by 49% and 28%, respectively.⁹² ALN-ANG is a novel GalNAc-RNA interference conjugate in preclinical development by Alynham Pharmaceuticals (Cambridge, Mass). In an ob/ob mouse model of hyperlipidemia, ALN-ANG 3 mg/kg given subcutaneously daily for 5 weeks reduced ANGPTL3 protein concentrations by >95%; TG, total cholesterol, and LDL-C concentrations were decreased by >95%, >60%, and >85%, respectively.⁹³

CONCLUSION

It has been 30 years since the first statins entered general use, and, despite development of slightly more efficacious statins during this period, the only additional safe and well-tolerated LDL-C-reducing drug has been ezetimibe which provided an additional 18% decrease in LDL-C. In fact, interest in developing new LDL-C-lowering agents had waned within the pharmaceutical industry along with reduced research as focus moved to what was felt to be more interesting and presumably more profitable targets such as CETPis for HDL-C and ω 3 fatty acids for TGs.

However, the development of apoB antisense and microsomal triglyceride transfer protein inhibitors, both initially in development for general use, as orphan drugs for HoFH and the discovery of PCSK9

has rapidly changed the climate within academia and industry so that LDL-C is once again a major focus. The encouraging results with PCSK9 mAbs, including the early but promising impact on CVD events, have created an environment in the clinical and cardiovascular community which is likely to surpass even the statin era as the large-scale CVD outcome trials come to fruition in the next 2 years.

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CONFLICTS OF INTEREST

Dr Turner has no personal conflicts; her institution has received funds related to clinical trials and central laboratory analysis from Amgen, Regeneron, Sanofi, Genentech, Roche, ISIS, Genzyme, Catabasis and BMS. Dr Stein has received consulting fees from Amgen, Regeneron, Sanofi, Genentech, Roche, ISIS, Catabasis, AstraZeneca, CymaBay, and BMS.

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