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Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) Inhibitors

Preliminary Scan Report #2

March 2018

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Conflict of Interest Disclosures:
No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

Objective

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses on new randomized controlled trials and comparative effectiveness reviews as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Original Report: July 2015 (Searches through February 2015)

Date of Last Scan Report

Scan 1: March 2017

Expanded Scan, April 2017

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. What are the comparative benefits and harms of PCSK9 inhibitors in patients with heterozygous and homozygous familial hypercholesterolemia?

2. What are the comparative benefits and harms of PCSK9 inhibitors in patients with hypercholesterolemia who are unable to use statins due to intolerance or any other

reasons?

3. What are the comparative benefits and harms of PCSK9 inhibitors in patients with non-familial hypercholesterolemia who have not achieved LDL-C <100 mg/dL or <70 mg/dL with their current lipid lowering regimen (e.g., statin, with or without ezetimibe, etc.)?

4. Do the comparative benefits and harms of PCSK9 inhibitors differ when used in different patient subgroups based on demographics, socioeconomic status, other medications, or comorbidities?

Inclusion Criteria

Populations

- Patients with heterozygous and homozygous familial hypercholesterolemia.
- Patients with hypercholesterolemia who are unable to use statins due to intolerance or any other reasons.
    - Patients with non-familial hypercholesterolemia who have not achieved LDL-C <100 mg/dL or <70 mg/dL.

Interventions

Table 1. Included Interventions

Generic Name	Trade Name	FDA Approval	Dose and Form
Alirocumab	Praluent™	7/24/2015	75 mg/mL, 150 mg/mL injection
Evolocumab	Repatha™	8/27/2015	140 mg/mL injection

Abbreviations: BLA, biologics license application; FDA, U.S. Food & Drug Administration

Benefits Outcomes

- Survival and health events: reduction in nonfatal myocardial infarction (MI), coronary heart disease (CHD), mortality (CHD and all-cause), stroke, and need for revascularization (including coronary artery bypass grafting, angioplasty and coronary stents).
- LDL-C lowering ability.
- HDL-C raising ability.

Harms Outcomes

- Overall adverse events.
- Withdrawals due to adverse events.
- Serious adverse events.
- Specific adverse events (including, but not limited to, serious hypocholesterolemia, neurocognitive dysfunction, injection site reactions, nasopharyngitis, gastrointestinal disturbance, etc.). We accepted any classification criteria.

Comparisons

- Head-to-head comparisons of included interventions.
- Comparisons of an included intervention to other active pharmacologic treatments (e.g. statins and ezetimibe), including trials of add-on therapy that provide comparative data on an included drug versus another active treatment.

Methods for Scan

Literature Search

To identify relevant citations, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and the Cochrane Central Registry of Controlled Trials from March 2017 through February 2018 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan in addition to those included in Table 1. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, new populations, and new serious harms (e.g., boxed warnings). To identify new drugs, we conducted an internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X8) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

Results

New Drugs

Identified in this Preliminary Update Scan

None.

Note: Pfizer discontinued development of bococizumab in 2016

Note: Drugs with other mechanisms of action (Inclisiran, evinacumab) are in Phase I – III trials. Results for Phase III are not available at this time.

Identified in previous Preliminary Update Scans

None.

New Populations

Identified in this Preliminary Update Scan

None.

Identified in previous Preliminary Update Scans
None.

New Serious Harms (e.g., Boxed Warnings)

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scans
None.

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan
1 new review was found, a review from the Canadian Agency for Drugs, Technology and Health. However, the criteria were for only head to head studies (not limited to RCTs), and it included only 1 non-randomized study.

- *PCSK-9 inhibitors for hyperlipidemia: a review of comparative clinical effectiveness*. Ottawa: CADTH; 2017 Jun. (https://www.cadth.ca/pcsk-9-inhibitors-hyperlipidemia-comparative-clinical-effectiveness-0).

Identified in previous Preliminary Update Scans
One comparative effectiveness review from the Canadian Agency for Drugs, Technology and Health was identified, but did not include studies that were not included in the original DERP report.

Randomized Controlled Trials

Trials identified since the most recent Full Report
Since the original DERP report on PCSK9 Inhibitors, we have identified 18 new RCTs that are relevant to this report, 7 are new in this Scan. Characteristics of these trials are shown in Table 2, below. Abstracts are listed in the Appendix document. In addition, we have identified 6 secondary publications relating to previously identified RCTs. Characteristics of these trials are shown in Table 3, below. Abstracts are listed in the Appendix document.

The new RCTs in this scan continue to help to fill gaps identified in the original report. In patients with CV risk and elevated lipids, new studies evaluate patients with diabetes, Asian patients, and alternative dosing strategies with alirocumab and angiographic changes with evolocumab. Two other alirocumab studies evaluate use in patients receiving fibrates, ezetimibe or diet only and the effect on lipoprotein apheresis in patients with heterozygous familial hypercholesterolemia, and 1 additoinal trial evaluated and longer-term lipid outcomes with evolocumab in patients with heterozygous familial hypercholesterolemia.

These RCTs add to the studies reviewed in the expanded scan (April 2017). The Summary from that scan was that there were 9 fair-and good-quality RCTs (N=30,054) ranging in duration from 24 weeks to 26 months, included new evidence on cardiovascular outcomes, new evidence of lipid outcomes in populations not previously studied, and additional evidence supplementing lipid outcomes in patients with statin-intolerance.

- Evolocumab treatment significantly reduced the risk of a composite of major CV events and reduced the composite risk of cardiovascular death, myocardial infarction, or stroke. (1 trial, N=27,654, 26 months) in patients with CVD.
- Alirocumab is effective as monotherapy or add-on therapy compared to statin or ezetimibe therapy alone. (3 trials) in patients with moderate to very high risk of CVD.
- Alirocumab and evolocumab are effective in lowering LDL-C for patients with statin-intolerance. Definitions of statin-intolerance were more precise and trials included a statin re-challenge. (2 trials). This was the first study of alirocumab in statin intolerant patients, and the study of evolocumab confirms prior findings but with more accurately defined statin intolerance.
- New evidence in larger studies confirms findings of smaller studies that alirocumab significantly reduces LDL-C in patients with heterozygous familial hypercholesterolemia. (4 trials).

Table 2. New trials of PCSK9 inhibitors with Lipid and Other Intermediate Outcomes

Study	Comparison Duration	Population
Cardiovascular Outcomes		
Sabatine, 2017 FOURIER	Evolocumab vs Placebo 2 years	Atherosclerotic CVD and LDL-C≥ 70 mg/dL
Intermediate Outcomes (e.g. Lipids)		
Patients with Cardiovascular Risk and LDL-C ≥70 mg/dL		
Roth, 2014 Roth, 2015 ODYSSEY MONO	Alirocumab vs.Ezetimibe 24 weeks	LDL-C 100 to 190 mg/dL, 10-year risk of fatal CV events >1% to <5% (systemic coronary risk estimation)
Bays, 2015 ODYSSEY OPTIONS I	Alirocumab + atorvastatin vs. Ezetimibe + atorvastatin vs. Double atorvastatin dose vs. Switch to rosuvastatin 40 mg 24 weeks	Very high CVD risk and LDL-C ≥70 mg/dL or high CVD risk and LDL-C ≥100 mg/dL
Farnier, 2016 ODYSSEY	Alirocumab + rosuvastatin vs.	CVD and LDL-C >70 mg/dL or CVD risk factors and LDL-C >100 mg/dL

OPTIONS II	Ezetimibe + rosuvastatin vs. Double rosuvastatin dose 24 weeks	
Koh, 2017 ODYSSEY KT South Korea and Taiwan	Alirocumab vs. Placebo 24 weeks	Hypercholesterolemia at high CV risk on maximally tolerated statins
Leiter, 2017 Cairou, 2017 ODYSSEY DM-INSULIN	Alirocumab vs. Placebo 24 weeks	Type 1 or type 2 diabetes and high CV risk:
Roth, 2016 ODYSSEY CHOICE I	Alirocumab 300 mg Q 4W vs. 75 mg Q2W or Placebo (+/- statins) 48 weeks	Hypercholesterolemia at moderate-to-very-high CV risk
Nicholls, 2016 Puri, 2016 GLAGOV	Evolocumab vs. Placebo 76 weeks	Angiographic coronary disease
Statin Intolerance		
Stroes, 2016 ODYSSEY CHOICE II	Alirocumab 150 mg Q4W or 75 mg Q2W or placebo 24 Weeks	Inadequately controlled hypercholesterolemia receiving treatment with fenofibrate, ezetimibe, or diet
Moriarty, 2015 ODYSSEY ALTERNATIVE	Alirocumab vs. Ezetimibe vs. Atorvastatin rechallenge 24 weeks	Moderate to high CV risk with statin intolerance due to muscle symptoms
Nissen, 2016 GAUSS-3	Evolocumab 420 mg monthly vs. Ezetimibe 24 weeks	Adult patients with uncontrolled LDL-C and history of intolerance to ≥2 statins
Heterozygous Familial Hypercholesterolemia (heFH)		
Hovingh, 2017	Evolocumab vs Standard of Care	52-week extension trial in Heterozygous familial hypercholesterolemia
Kastelein, 2015 ODYSSEY FH I	Alirocumab add-on 24 weeks	History of heFH on max-tolerated statin ± other lipid-lowering therapy with History of CVD and LDL-C ≥ 70 mg/dL OR No history of CVD and LDL-C ≥ 100 mg/dL
Kastelein, 2015 ODYSSEY FH II	Alirocumab add-on 24 weeks	History of heFH on max-tolerated statin ± other lipid-lowering therapy with History of CVD and LDL-C ≥ 70 mg/dL OR No history of CVD and LDL-C ≥ 100 mg/dL
Ginsberg, 2016 ODYSSEY HIGH FH	Alirocumab vs. Placebo 24 weeks	Heterozygous familial hypercholesterolemia
Moriarty, 2016	Alirocumab vs. Placebo 18 weeks	Heterozygous familial hypercholesterolemia undergoing lipoprotein apheresis

ODYSSEY ESCAPE		
Mixed Patient Population		
Teramoto, 2016 ODYSSEY JAPAN	Alirocumab Vs Placebo 52 weeks	Japanese Patients With Heterozygous Familial Hypercholesterolemia or at High CV Risk
Teramoto, 2017 ODYSSEY NIPPON	Alirocumab 150 mg Q4W or 75 mg Q2W or placebo 24 Weeks	Japanese patients with hypercholesterolemia on the lowest-strength dose of atorvastatin (5 mg/day) or receiving a non-statin lipid-lowering therapy

Shading indicates new studies found in this scan. Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; Q2W = every 2 weeks

Table 2. Secondary Analyses

Study	Comparison Duration	Analysis	Primary Trial
Leiter, 2017	Alirocumab vs. Placebo 104 weeks	Lipids in Patients with and without DM High CV risk	ODYSSEY COMBO II
El Shahawy, 2017	Alirocumab vs. Placebo 104 weeks	Post hoc safety profile with longer versus shorter duration of alirocumab exposure	ODYSSEY COMBO II
Blom, 2017	Evolocumab vs placebo 52 weeks	Categorized by baseline glycemic status: type 2 diabetes, impaired fasting glucose (IFG), metabolic syndrome (MetS) or none of these	DESCARTES
Cho, 2016	Evolocumab vs placebo 12 weeks	Clinical Profile of Statin Intolerance	GAUSS-2
Giugliano, 2017	Evolocumab vs Placebo 2 years	Relationship between achieved LDL-cholesterol concentration at 4 weeks and subsequent cardiovascular outcomes	FOURIER
Sabatine, 2017	Evolocumab vs Placebo 2 years	Cardiovascular safety and efficacy in patients with and without diabetes, effect on glycaemia and risk of new-onset diabetes	FOURIER

Summary

Since the Original Report on this topic there are no newly approved drugs, new serious harms, or relevant comparative effectiveness reviews. Cumulatively, there are 18 new RCTs and 7 secondary analyses relevant to the PCSK9-Inhibitors DERP report. Six RCTs and 6 secondary analyses are new this scan. While the majority of new RCTs involve alirocumab, 1 RCT of

evolocumab reports on CV outcomes. The other new RCTs report intermediate outcomes such as lipids, with most addressing gaps in the previous evidence base.

Appendix A. New Trials of PCSK9 Inhibitors

Bays, H., et al. (2015). Alirocumab as Add-On to Atorvastatin Versus Other Lipid Treatment Strategies: ODYSSEY OPTIONS I Randomized Trial. Journal of Clinical Endocrinology & Metabolism. **100:** 3140-3148.

CONTEXT: Despite current standard of care, many patients at high risk of cardiovascular disease (CVD) still have elevated low-density lipoprotein cholesterol (LDL-C) levels. Alirocumab is a fully human monoclonal antibody inhibitor of proprotein convertase subtilisin/kexin type 9.

OBJECTIVE: The objective of the study was to compare the LDL-C-lowering efficacy of adding alirocumab vs other common lipid-lowering strategies.

DESIGN, PATIENTS, AND INTERVENTIONS: Patients (n = 355) with very high CVD risk and LDL-C levels of 70 mg/dL or greater or high CVD risk and LDL-C of 100 mg/dL or greater on baseline atorvastatin 20 or 40 mg were randomized to one of the following: 1) add-on alirocumab 75 mg every 2 weeks (Q2W) sc; 2) add-on ezetimibe 10 mg/d; 3) double atorvastatin dose; or 4) for atorvastatin 40 mg regimen only, switch to rosuvastatin 40 mg. For patients not achieving protocol-defined LDL-C goals, the alirocumab dose was increased (blinded) at week 12 to 150 mg Q2W.

MAIN OUTCOME MEASURE: The primary end point was percentage change in calculated LDL-C from baseline to 24 weeks (intent to treat).

RESULTS: Among atorvastatin 20 and 40 mg regimens, respectively, add-on alirocumab reduced LDL-C levels by 44.1% and 54.0% (P < .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. Most alirocumab-treated patients (86%) maintained their 75-mg Q2W regimen. Treatment-emergent adverse events occurred in 65.4% of alirocumab patients vs 64.4% ezetimibe and 63.8% double atorvastatin/switch to rosuvastatin (data were pooled).

CONCLUSIONS: Adding alirocumab to atorvastatin provided significantly greater LDL-C reductions vs adding ezetimibe, doubling atorvastatin dose, or switching to rosuvastatin and enabled greater LDL-C goal achievement.

Blom, D. J., et al. (2017). "Evaluation of the efficacy, safety and glycaemic effects of evolocumab (AMG 145) in hypercholesterolaemic patients stratified by glycaemic status and metabolic syndrome." Diabetes, obesity & metabolism **19**(1): 98-107.

Aim: To examine the lipid and glycaemic effects of 52 weeks of treatment with evolocumab. Materials and Methods: The Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES) was a 52-week placebo-controlled trial of evolocumab that randomized 905 patients from 88 study centres in 9 countries, with 901 receiving at least one dose of study drug. For this post-hoc analysis, DESCARTES patients were categorized by baseline glycaemic status: type 2 diabetes, impaired fasting glucose (IFG), metabolic syndrome (MetS) or none of these. Monthly subcutaneous evolocumab (420 mg) or placebo was administered. The main outcomes measured were percentage change in LDL-cholesterol (LDL-C) at week 52 and safety. Results: A total of 413 patients

had dysglycaemia (120, type 2 diabetes; 293, IFG), 289 had MetS (194 also had IFG) and 393 had none of these conditions. At week 52, evolocumab reduced LDL-C by >50% in all subgroups, with favourable effects on other lipids. No significant differences in fasting plasma glucose, HbA1c, insulin, C-peptide or HOMA indices were seen in any subgroup between evolocumab and placebo at week 52. The overall incidence of new-onset diabetes mellitus did not differ between placebo (6.6%) and evolocumab (5.6%); in those with baseline normoglycaemia, the incidences were 1.9% and 2.7%, respectively. Incidences of AEs were similar in evolocumab- and placebo-treated patients. Conclusions: Evolocumab showed encouraging safety and efficacy at 52 weeks in patients with or without dysglycaemia or MetS. Changes in glycaemic parameters did not differ between evolocumab- and placebo-treated patients within the glycaemic subgroups examined. Copyright (C) 2016 John Wiley & Sons Ltd

Cariou, B., et al. (2017). "Efficacy and safety of alirocumab in insulin-treated patients with type 1 or type 2 diabetes and high cardiovascular risk: rationale and design of the ODYSSEY DM-INSULIN trial." Diabetes and metabolism. **30**.

Aims: The coadministration of alirocumab, a PCSK9 inhibitor for treatment of hypercholesterolaemia, and insulin in diabetes mellitus (DM) requires further study. Described here is the rationale behind a phase-IIIb study designed to characterize the efficacy and safety of alirocumab in insulin-treated patients with type 1 (T1) or type 2 (T2) DM with hypercholesterolaemia and high cardiovascular (CV) risk. Methods: ODYSSEY DM-INSULIN (NCT02585778) is a randomized, double-blind, placebo-controlled, multicentre study that planned to enrol around 400 T2 and up to 100 T1 insulin-treated DM patients. Participants had low-density lipoprotein cholesterol (LDL-C) levels at screening. >. 70. mg/dL (1.81. mmol/L) with stable maximum tolerated statin therapy or were statin-intolerant, and taking (or not) other lipid-lowering therapy; they also had established CV disease or at least one additional CV risk factor. Eligible patients were randomized 2:1 to 24. weeks of alirocumab 75. mg every 2. weeks (Q2W) or a placebo. Alirocumab-treated patients with LDL-C. >. 70. mg/dL at week 8 underwent a blinded dose increase to 150. mg Q2W at week 12. Primary endpoints were the difference between treatment arms in percentage change of calculated LDL-C from baseline to week 24, and alirocumab safety. Results: This is an ongoing clinical trial, with 76 T1 and 441 T2 DM patients enrolled; results are expected in mid-2017. Conclusion: The ODYSSEY DM-INSULIN study will provide information on the efficacy and safety of alirocumab in insulin-treated individuals with T1 or T2 DM who are at high CV risk and have hypercholesterolaemia not adequately controlled by the maximum tolerated statin therapy. Copyright (C) 2017 Elsevier Masson SAS.

Cho, L., et al. (2016). "Clinical Profile of Statin Intolerance in the Phase 3 GAUSS-2 Study." Cardiovascular Drugs & Therapy **30**(3): 297-304.

PURPOSE: Recent evidence suggests that statin intolerance may be more common than reported in randomized trials. However, the statin-intolerant population is not well characterized. The goal of this report is to characterize the population enrolled in the

phase 3 Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects Study (GAUSS-2; NCT 01763905).

METHODS: GAUSS-2 compared evolocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9) to ezetimibe in hypercholesterolemic patients who discontinued statin therapy due to statin-associated muscle symptoms (SAMS). GAUSS-2 was a 12-week, double-blind, placebo-controlled, randomized study that enrolled patients with elevated LDL-C who were either not on a statin or able to tolerate only a low-dose due to SAMS. Patients had received >=2 statins and were unable to tolerate any statin dose or increase in dose above a specified weekly dose due to SAMS.

RESULTS: Three hundred seven patients (mean [SD] age, 62 [10] years; 54 % males) were randomized 2:1 (evolocumab:ezetimibe). Mean (SD) LDL-C was 4.99 (1.51) mmol/L. Patients had used >=2 (100 %), >=3 (55 %), or >=4 (21 %) statins. Coronary artery disease was present in 29 % of patients. Statin-intolerant symptoms were myalgia in 80 % of patients, weakness in 39 %, and more serious complications in 20 %. In 98 % of patients, SAMS interfered with normal daily activity; in 52 %, symptoms precluded moderate exertion.

CONCLUSION: Evaluation of the GAUSS-2 trial population of statin-intolerant patients demonstrates that most patients were high risk with severely elevated LDL-C and many had statin-associated muscle symptoms that interfered with their quality of life.

El Shahawy, M., et al. (2017). "Efficacy and Safety of Alirocumab Versus Ezetimibe Over 2 Years (from ODYSSEY COMBO II)." American Journal of Cardiology **120**(6): 931-939.

The proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab has been shown to substantially reduce low-density lipoprotein cholesterol (LDL-C). Demonstrating whether efficacy and safety are maintained over a long duration of exposure is vital for clinical decision-making. The COMBO II trial compared the efficacy and safety of alirocumab versus ezetimibe over 2 years. A prespecified first analysis was reported at 52 weeks. Here we report the final end-of-study data (on-treatment) and evaluate post hoc the safety profile with longer versus shorter duration of alirocumab exposure. Patients (n=720) on maximally tolerated statin dose were treated with alirocumab (75/150mg every 2 weeks) or ezetimibe (10mg/day). Overall mean adherence for both treatment groups during the first and second year was >97%. At 2 years, LDL-C was reduced by 49% (alirocumab) versus 17% (ezetimibe; p<0.0001), and LDL-C <70mg/dl was achieved by 73% of alirocumab-treated versus 40% of ezetimibe-treated patients. Overall safety was similar in both treatment groups at 2 years and during the first versus the second year. Local injection-site reactions were reported by 2.5% (alirocumab) versus 0.8% (ezetimibe) during the first year, and 0.2% versus 0.5% during the second year, indicating early occurrence during prolonged alirocumab exposure. Two consecutive calculated LDL-C values <25mg/dl were observed in 28% of alirocumab-treated patients (vs 0.4% with ezetimibe). Persistent anti-drug antibody responses were observed in 1.3% (6 of 454) of alirocumab-treated versus 0.4% (1 of 231) of ezetimibe-treated patients. Neutralizing antibodies (that inhibit binding in vitro) were observed in 1.5% (7 of 454) of alirocumab-treated patients (0 with ezetimibe), mostly at isolated time points.

Alirocumab sustained substantial LDL-C reductions and was well tolerated up to 2 years in the COMBO II trial.

Farnier, M., et al. (2016). "Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial." Atherosclerosis **244**: 138-146.

OBJECTIVE: To compare lipid-lowering efficacy of adding alirocumab to rosuvastatin versus other treatment strategies (NCT01730053).

METHODS: Patients receiving baseline rosuvastatin regimens (10 or 20 mg) were randomized to: add-on alirocumab 75 mg every-2-weeks (Q2W) (1-mL subcutaneous injection via pre-filled pen); add-on ezetimibe 10 mg/day; or double-dose rosuvastatin. Patients had cardiovascular disease (CVD) and low-density lipoprotein cholesterol (LDL-C) >70 mg/dL (1.8 mmol/L) or CVD risk factors and LDL-C >100 mg/dL (2.6 mmol/L). In the alirocumab group, dose was blindly increased at Week 12 to 150 mg Q2W (also 1-mL volume) in patients not achieving their LDL-C target. Primary endpoint was percent change in calculated LDL-C from baseline to 24 weeks (intent-to-treat).

RESULTS: 305 patients were randomized. In the baseline rosuvastatin 10 mg group, significantly greater LDL-C reductions were observed with add-on alirocumab (-50.6%) versus ezetimibe (-14.4%; p < 0.0001) and double-dose rosuvastatin (-16.3%; p < 0.0001). In the baseline rosuvastatin 20 mg group, LDL-C reduction with add-on alirocumab was -36.3% compared with -11.0% with ezetimibe and -15.9% with double-dose rosuvastatin (p = 0.0136 and 0.0453, respectively; pre-specified threshold for significance p < 0.0125). Overall, ~80% alirocumab patients were maintained on 75 mg Q2W. Of alirocumab-treated patients, 84.9% and 66.7% in the baseline rosuvastatin 10 and 20 mg groups, respectively, achieved risk-based LDL-C targets. Treatment-emergent adverse events occurred in 56.3% of alirocumab patients versus 53.5% ezetimibe and 67.3% double-dose rosuvastatin (pooled data).

CONCLUSIONS: The addition of alirocumab to rosuvastatin provided incremental LDL-C lowering versus adding ezetimibe or doubling the rosuvastatin dose.

Ginsberg, H. N., et al. (2016). "Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dl or Higher." Cardiovascular Drugs & Therapy **30**(5): 473-483.

PURPOSE: Even with statins and other lipid-lowering therapy (LLT), many patients with heterozygous familial hypercholesterolemia (heFH) continue to have elevated low-density lipoprotein cholesterol (LDL-C) levels. ODYSSEY HIGH FH (NCT01617655) assessed the efficacy and safety of alirocumab, a proprotein convertase subtilisin/kexin type 9 monoclonal antibody, versus placebo in patients with heFH and LDL-C >= 160 mg/dl despite maximally tolerated statin +/- other LLT.

METHODS: Patients were randomized to subcutaneous alirocumab 150 mg or placebo every 2 weeks (Q2W) for 78 weeks. The primary endpoint was percent change in LDL-C from baseline to week 24.

RESULTS: Mean baseline LDL-C levels were 196.3 mg/dl in the alirocumab (n = 71) and 201.0 mg/dl in the placebo groups (n = 35). Significant mean (standard error [SE]) reductions in LDL-C from baseline to week 24 were observed with alirocumab (-45.7 [3.5] %) versus placebo (-6.6 [4.9] %), a difference of -39.1 (6.0) % (P < 0.0001). Absolute mean (SE) LDL-C levels were reduced from baseline by 90.8 (6.7) mg/dl with alirocumab at week 24, with reductions maintained to week 78. Treatment-emergent adverse events were generally comparable between groups. Injection-site reactions were more frequent in the alirocumab group (8.3 %) versus placebo (5.7 %); most were mild in severity and did not result in study medication discontinuation.

CONCLUSIONS: In patients with heFH and very high LDL-C baseline levels despite maximally tolerated statin +/- other LLT, alirocumab 150 mg Q2W demonstrated significant reductions in LDL-C levels with 41 % of patients achieving predefined LDL-C goals. Alirocumab was generally well tolerated.

Giugliano, R. P., et al. (2017). "Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial." Lancet(pagination).

Background: LDL cholesterol is a well established risk factor for atherosclerotic cardiovascular disease. How much one should or safely can lower this risk factor remains debated. We aimed to explore the relationship between progressively lower LDL-cholesterol concentrations achieved at 4 weeks and clinical efficacy and safety in the FOURIER trial of evolocumab, a monoclonal antibody to proprotein convertase subtilisin-kexin type 9 (PCSK9). Methods: In this prespecified secondary analysis of 25 982 patients from the randomised FOURIER trial, the relationship between achieved LDL-cholesterol concentration at 4 weeks and subsequent cardiovascular outcomes (primary endpoint was the composite of cardiovascular death, myocardial infarction, stroke, coronary revascularisation, or unstable angina; key secondary endpoint was the composite of cardiovascular death, myocardial infarction, or stroke) and ten prespecified safety events of interest was examined over a median of 2.2 years of follow-up. We used multivariable modelling to adjust for baseline factors associated with achieved LDL cholesterol. This trial is registered with ClinicalTrials.gov, number NCT01764633. Findings: Between Feb 8, 2013, and June 5, 2015, 27 564 patients were randomly assigned a treatment in the FOURIER study. 1025 (4%) patients did not have an LDL cholesterol measured at 4 weeks and 557 (2%) had already had a primary endpoint event or one of the ten prespecified safety events before the week-4 visit. From the remaining 25 982 patients (94% of those randomly assigned) 13 013 were assigned evolocumab and 12 969 were assigned placebo. 2669 (10%) of 25 982 patients achieved LDL-cholesterol concentrations of less than 0.5 mmol/L, 8003 (31%) patients achieved concentrations between 0.5 and less than 1.3 mmol/L, 3444 (13%) patients achieved concentrations between 1.3 and less than 1.8 mmol/L, 7471 (29%) patients achieved concentrations between 1.8 to less than 2.6 mmol/L, and 4395 (17%) patients achieved concentrations of 2.6 mmol/L or higher. There was a highly significant monotonic relationship between low LDL-cholesterol concentrations and lower risk of the primary and secondary efficacy composite endpoints extending to the bottom first percentile (LDL-cholesterol concentrations of

less than 0.2 mmol/L; p=0.0012 for the primary endpoint, p=0.0001 for the secondary endpoint). Conversely, no significant association was observed between achieved LDL cholesterol and safety outcomes, either for all serious adverse events or any of the other nine prespecified safety events. Interpretation: There was a monotonic relationship between achieved LDL cholesterol and major cardiovascular outcomes down to LDL-cholesterol concentrations of less than 0.2 mmol/L. Conversely, there were no safety concerns with very low LDL-cholesterol concentrations over a median of 2.2 years. These data support further LDL-cholesterol lowering in patients with cardiovascular disease to well below current recommendations. Funding: Amgen. Copyright (C) 2017 Elsevier Ltd.

Hovingh, G. K., et al. (2017). "Long-term safety, tolerability, and efficacy of evolocumab in patients with heterozygous familial hypercholesterolemia." Journal of clinical lipidology **11**(6): 1448-1457.

Background Evolocumab, a fully human monoclonal antibody against proprotein convertase subtilisin/kexin type 9, is safe and effective when dosed biweekly (Q2W) or monthly (QM) in patients with heterozygous familial hypercholesterolemia (HeFH) as demonstrated in two 12-week trials: Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD; phase 2) and RUTHERFORD-2 (phase 3). Objective The objective of the study was to evaluate long-term efficacy, safety, and tolerability of evolocumab during open-label extension trials. Methods Patients completing parent trials were re-randomized 2:1 to evolocumab plus standard of care (SOC) or SOC alone for 52 weeks (Open-Label Study of Long-term Evaluation Against LDL-C [OSLER-1]) or 48 weeks (OSLER-2). Evolocumab dosing was 420 mg QM (OSLER-1) and 140 mg Q2W or 420 mg QM (OSLER-2). A pooled analysis of OSLER data was performed from this subset of HeFH patients. Results Four hundred forty HeFH patients from RUTHERFORD (n = 147) and RUTHERFORD-2 (n = 293) (mean [standard deviation] age 51 [12] years, 58% male, 90% White) were randomized to evolocumab plus SOC (n = 289) or SOC (n = 151). The 48-week period was completed by 425 patients (96.6%). Eight patients discontinued evolocumab plus SOC (2.8%) and 7 discontinued SOC (4.6%). Compared to parent study baseline, patients receiving evolocumab plus SOC experienced a mean 53.6% reduction in low-density lipoprotein cholesterol after 48 weeks. No patient experienced an adverse event leading to permanent evolocumab discontinuation during the 1-year SOC-controlled period. Serious adverse event rates were similar between groups (evolocumab plus SOC, 7.3%; SOC, 8.6%). Conclusion Continued use of evolocumab added to SOC in patients with HeFH yields persistent and marked low-density lipoprotein cholesterol reductions during 48 weeks of follow-up. Long-term dosing of evolocumab with SOC was safe and well tolerated. Copyright (C) 2017 National Lipid Association

Kastelein, J. J., et al. (2015). "ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia." European heart journal **36**(43): 2996-3003.

AIMS: To assess long-term (78 weeks) alirocumab treatment in patients with heterozygous familial hypercholesterolaemia (HeFH) and inadequate LDL-C control on maximally tolerated lipid-lowering therapy (LLT).

METHODS AND RESULTS: In two randomized, double-blind studies (ODYSSEY FH I, n = 486; FH II, n = 249), patients were randomized 2 : 1 to alirocumab 75 mg or placebo every 2 weeks (Q2W). Alirocumab dose was increased at Week 12 to 150 mg Q2W if Week 8 LDL-C was >1.8 mmol/L (70 mg/dL). Primary endpoint (both studies) was percentage change in calculated LDL-C from baseline to Week 24. Mean LDL-C levels decreased from 3.7 mmol/L (144.7 mg/dL) at baseline to 1.8 mmol/L (71.3 mg/dL; -57.9% vs. placebo) at Week 24 in patients randomized to alirocumab in FH I and from 3.5 mmol/L (134.6 mg/dL) to 1.8 mmol/L (67.7 mg/dL; -51.4% vs. placebo) in FH II (P < 0.0001). These reductions were maintained through Week 78. LDL-C <1.8 mmol/L (regardless of cardiovascular risk) was achieved at Week 24 by 59.8 and 68.2% of alirocumab-treated patients in FH I and FH II, respectively. Adverse events resulted in discontinuation in 3.4% of alirocumab-treated patients in FH I (vs. 6.1% placebo) and 3.6% (vs. 1.2%) in FH II. Rate of injection site reactions in alirocumab-treated patients was 12.4% in FH I and 11.4% in FH II (vs. 11.0 and 7.4% with placebo).

CONCLUSION: In patients with HeFH and inadequate LDL-C control at baseline despite maximally tolerated statin +/- other LLT, alirocumab treatment resulted in significant LDL-C lowering and greater achievement of LDL-C target levels and was well tolerated.

CLINICAL TRIAL REGISTRATION: Cinicaltrials.gov (identifiers: NCT01623115; NCT01709500).

Koh, K. K., et al. (2017). "A randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan (ODYSSEY KT)." Journal of clinical lipidology(pagination).

Background: Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, has been shown to provide significant reductions in low-density lipoprotein cholesterol (LDL-C). Data about its efficacy and safety in patients from South Korea and Taiwan are limited. Objective: ODYSSEY KT assessed the efficacy and safety of alirocumab in patients from South Korea and Taiwan. Methods: Patients with hypercholesterolemia at high cardiovascular risk who were on maximally tolerated statin were randomized (1:1) to alirocumab (75 mg every 2 weeks, with dose increase to 150 mg every 2 weeks at week 12 if LDL-C >=70 mg/dL at week 8) or placebo for 24 weeks. The primary efficacy endpoint was percentage change in LDL-C from baseline to week 24. Safety was assessed throughout. Results: At week 24, alirocumab changed LDL-C levels by -57.1% (placebo: +6.3%). In the alirocumab group, 9 patients (9.5%) received dose increase at week 12. At week 24, 85.8% of patients in the alirocumab group reached LDL-C <70 mg/dL (placebo: 14.2%; P <= .0001 vs placebo). Alirocumab significantly improved non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B, total cholesterol, lipoprotein (a), and HDL-C vs placebo (P <= .05). Two consecutive calculated LDL-C values <25 mg/dL were recorded in 27.8% of alirocumab-treated patients. Overall, 58.8% (alirocumab) and 61.8% (placebo) of patients experienced treatment-emergent adverse events; 2.1% and 1.0% discontinued treatment due to treatment-emergent

adverse events, respectively. Conclusion: Alirocumab significantly improved LDL-C, apolipoprotein B, non-HDL-C, lipoprotein (a), HDL-C, and total cholesterol in Asian patients. Alirocumab was generally well tolerated. These findings are consistent with ODYSSEY findings to date. Copyright (C) 2017 National Lipid Association.

Leiter, L. A., et al. (2017). "Efficacy and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: the ODYSSEY DM-INSULIN randomized trial." Diabetes, obesity & metabolism(pagination).

Aims: To investigate the efficacy and safety of alirocumab in participants with type 2 (T2D) or type 1 diabetes (T1D) treated with insulin who have elevated LDL cholesterol levels despite maximally tolerated statin therapy. Methods: Participants at high cardiovascular risk with T2D (n=441) or T1D (n=76) and LDL cholesterol levels >=1.8mmol/L (>=70mg/dL) were randomized 2:1 to alirocumab:placebo administered subcutaneously every 2weeks, for 24weeks' double-blind treatment. Alirocumab-treated participants received 75mg every 2weeks, with blinded dose increase to 150mg every 2weeks at week 12 if week 8 LDL cholesterol levels were >=1.8mmol/L. Primary endpoints were percentage change in calculated LDL cholesterol from baseline to week 24, and safety assessments. Results: Alirocumab reduced LDL cholesterol from baseline to week 24 by a mean+/-standard error of 49.0%+/-2.7% and 47.8%+/-6.5% vs placebo (both P<.0001) in participants with T2D and T1D, respectively. Significant reductions were observed in non-HDL cholesterol (P<.0001), apolipoprotein B (P<.0001) and lipoprotein (a) (P<=.0039). At week 24, 76.4% and 70.2% of the alirocumab group achieved LDL cholesterol <1.8mmol/L in the T2D and T1D populations (P<.0001), respectively. Glycated haemoglobin and fasting plasma glucose levels remained stable for the study duration. Treatment-emergent adverse events were observed in 64.5% of alirocumab- vs 64.1% of placebo-treated individuals (overall population). Conclusions: Alirocumab produced significant LDL cholesterol reductions in participants with insulin-treated diabetes regardless of diabetes type, and was generally well tolerated. Concomitant administration of alirocumab and insulin did not raise any safety concerns (NCT02585778). Copyright (C) 2017 John Wiley & Sons Ltd.

Leiter, L. A., et al. (2017). "Lipid-lowering efficacy and safety of alirocumab in patients with or without diabetes: a sub-analysis of ODYSSEY COMBO II." Diabetes, obesity & metabolism(pagination).

Aim: This sub-analysis of the ODYSSEY COMBO II study compared the effects of alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, in high cardiovascular risk patients with or without diabetes mellitus (DM) receiving maximally tolerated statin therapy. Methods: COMBO II was a 104-week, double-blind study (n=720) enrolling patients with documented atherosclerotic cardiovascular disease (ASCVD) and baseline LDL-C >70mg/dL (1.8mmol/L), and patients without documented ASCVD at high cardiovascular risk with LDL-C >100mg/dL (2.6mmol/L). Patients receiving maximally tolerated statin therapy were randomized (2:1) to alirocumab 75mg every 2weeks (Q2W; 1mL subcutaneous injection) or oral ezetimibe 10mg daily. Alirocumab dose was increased to 150mg Q2W (also 1mL) at Week 12 if Week 8 LDL-C was

>70mg/dL. Results: History of DM was reported in 31% (n=148) of patients on alirocumab and 32% (n=77) of patients on ezetimibe. At Week 24, alirocumab consistently reduced LDL-C from baseline in patients with (-49.1%) or without DM (-51.2%) to a significantly greater extent than ezetimibe (-18.4% and -21.8%, respectively). Occurrence of treatment-emergent adverse events was similar between groups. Efficacy results at 104weeks were similar to those at 24weeks. Conclusions: Over a 104-week double-blind study period, alirocumab provided consistently greater LDL-C reductions than ezetimibe, with similar LDL-C results in patients with or without DM. Safety of alirocumab was similar regardless of baseline DM status. Copyright (C) 2017 John Wiley & Sons Ltd.

Moriarty, P. M., et al. (2016). "Alirocumab in patients with heterozygous familial hypercholesterolemia undergoing lipoprotein apheresis: Rationale and design of the ODYSSEY ESCAPE trial." Journal of clinical lipidology **10**(3): 627-634.

BACKGROUND: Many patients with heterozygous familial hypercholesterolemia (HeFH) fail to reach optimal low-density lipoprotein cholesterol (LDL-C) levels with available lipid-lowering medications, including statins, and require treatment using alternative methods such as lipoprotein apheresis.

OBJECTIVE: To evaluate the efficacy of alirocumab 150 mg every 2 weeks (Q2W) compared with placebo in reducing the frequency of lipoprotein apheresis treatments in patients with HeFH.

METHODS: ODYSSEY ESCAPE is a randomized, double-blind, placebo-controlled, parallel-group, 18-week, phase 3 study being conducted in the United States and Germany. ODYSSEY ESCAPE will evaluate the efficacy and safety of alirocumab in approximately 63 adults with HeFH undergoing regular weekly (QW; for >=4 weeks) or Q2W (for >=8 weeks) lipoprotein apheresis. Patients will be randomly assigned (2:1, respectively) to receive alirocumab 150 mg subcutaneously Q2W or placebo subcutaneously Q2W (both in 1-mL injections) for 18 weeks. From day 1 to week 6, the apheresis frequency will be fixed to the individual patient's established schedule (QW or Q2W); thereafter, apheresis will be performed according to the LDL-C value at that visit: apheresis will not be performed when the LDL-C value is >=30% lower than the baseline pre-apheresis LDL-C value. The primary end point is the frequency of apheresis treatments over a 12-week period starting at week 7.

DISCUSSION: The ODYSSEY ESCAPE trial will determine whether alirocumab reduces the frequency of lipoprotein apheresis in patients with HeFH.

Moriarty, P. M., et al. (2015). "Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial." Journal of Clinical Lipidology **9**(6): 758-769.

BACKGROUND: Statin intolerance limits many patients from achieving optimal low-density lipoprotein cholesterol (LDL-C) concentrations. Current options for such patients include using a lower but tolerated dose of a statin and adding or switching to ezetimibe or other non-statin therapies.

METHODS: ODYSSEY ALTERNATIVE (NCT01709513) compared alirocumab with ezetimibe in patients at moderate to high cardiovascular risk with statin intolerance (unable to tolerate >2 statins, including one at the lowest approved starting dose) due to muscle symptoms. A placebo run-in and statin rechallenge arm were included in an attempt to confirm intolerance. Patients (n = 361) received single-blind subcutaneous (SC) and oral placebo for 4 weeks during placebo run-in. Patients reporting muscle-related symptoms during the run-in were to be withdrawn. Continuing patients were randomized (2:2:1) to double-blind alirocumab 75 mg SC every 2 weeks (Q2W; plus oral placebo), ezetimibe 10 mg/d (plus SC placebo Q2W), or atorvastatin 20 mg/d (rechallenge; plus SC placebo Q2W) for 24 weeks. Alirocumab dose was increased to 150 mg Q2W at week 12 depending on week 8 LDL-C values. Primary end point was percent change in LDL-C from baseline to week 24 (intent-to-treat) for alirocumab vs ezetimibe.

RESULTS: Baseline mean (standard deviation) LDL-C was 191.3 (69.3) mg/dL (5.0 [1.8] mmol/L). Alirocumab reduced mean (standard error) LDL-C by 45.0% (2.2%) vs 14.6% (2.2%) with ezetimibe (mean difference 30.4% [3.1%], P < .0001). Skeletal muscle-related events were less frequent with alirocumab vs atorvastatin (hazard ratio 0.61, 95% confidence interval 0.38-0.99, P = .042).

CONCLUSIONS: Alirocumab produced greater LDL-C reductions than ezetimibe in statin-intolerant patients, with fewer skeletal-muscle adverse events vs atorvastatin.

Nicholls, S. J., et al. (2016). "Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial." JAMA **316**(22): 2373-2384.

Importance: Reducing levels of low-density lipoprotein cholesterol (LDL-C) with intensive statin therapy reduces progression of coronary atherosclerosis in proportion to achieved LDL-C levels. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors produce incremental LDL-C lowering in statin-treated patients; however, the effects of these drugs on coronary atherosclerosis have not been evaluated.

Objective: To determine the effects of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients.

Design, Setting, and Participants: The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment May 3, 2013, to January 12, 2015) conducted at 197 academic and community hospitals in North America, Europe, South America, Asia, Australia, and South Africa and enrolling 968 patients presenting for coronary angiography.

Interventions: Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420 mg) (n=484) or placebo (n=484) via subcutaneous injection for 76 weeks, in addition to statins.

Main Outcomes and Measures: The primary efficacy measure was the nominal change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasonography (IVUS) imaging. Secondary efficacy measures were nominal change in normalized total atheroma volume (TAV) and percentage of patients demonstrating plaque regression. Safety and tolerability were also evaluated.

Results: Among the 968 treated patients (mean age, 59.8 years [SD, 9.2]; 269 [27.8%] women; mean LDL-C level, 92.5 mg/dL [SD, 27.2]), 846 had evaluable imaging at follow-up. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL-C levels (93.0 vs 36.6 mg/dL; difference, -56.5 mg/dL [95% CI, -59.7 to -53.4]; P<.001). The primary efficacy parameter, PAV, increased 0.05% with placebo and decreased 0.95% with evolocumab (difference, -1.0% [95% CI, -1.8% to -0.64%]; P<.001). The secondary efficacy parameter, normalized TAV, decreased 0.9 mm3 with placebo and 5.8 mm3 with evolocumab (difference, -4.9 mm3 [95% CI, -7.3 to -2.5]; P<.001). Evolocumab induced plaque regression in a greater percentage of patients than placebo (64.3% vs 47.3%; difference, 17.0% [95% CI, 10.4% to 23.6%]; P<.001 for PAV and 61.5% vs 48.9%; difference, 12.5% [95% CI, 5.9% to 19.2%]; P<.001 for TAV).

Conclusions and Relevance: Among patients with angiographic coronary disease treated with statins, addition of evolocumab, compared with placebo, resulted in a greater decrease in PAV after 76 weeks of treatment. Further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.

Trial Registration: clinicaltrials.gov Identifier: NCT01813422.

Nissen, S. E., et al. (2016). "Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial." JAMA **315**(15): 1580-1590.

IMPORTANCE: Muscle-related statin intolerance is reported by 5% to 20% of patients.

OBJECTIVE: To identify patients with muscle symptoms confirmed by statin rechallenge and compare lipid-lowering efficacy for 2 nonstatin therapies, ezetimibe and evolocumab.

DESIGN, SETTING, AND PARTICIPANTS: Two-stage randomized clinical trial including 511 adult patients with uncontrolled low-density lipoprotein cholesterol (LDL-C) levels and history of intolerance to 2 or more statins enrolled in 2013 and 2014 globally. Phase A used a 24-week crossover procedure with atorvastatin or placebo to identify patients having symptoms only with atorvastatin but not placebo. In phase B, after a 2-week washout, patients were randomized to ezetimibe or evolocumab for 24 weeks.

INTERVENTIONS: Phase A: atorvastatin (20 mg) vs placebo. Phase B: randomization 2:1 to subcutaneous evolocumab (420 mg monthly) or oral ezetimibe (10 mg daily).

MAIN OUTCOME AND MEASURES: Coprimary end points were the mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels.

RESULTS: Of the 491 patients who entered phase A (mean age, 60.7 [SD, 10.2] years; 246 women [50.1%]; 170 with coronary heart disease [34.6%]; entry mean LDL-C level, 212.3 [SD, 67.9] mg/dL), muscle symptoms occurred in 209 of 491 (42.6%) while taking atorvastatin but not while taking placebo. Of these, 199 entered phase B, along with 19 who proceeded directly to phase B for elevated creatine kinase (N=218, with 73 randomized to ezetimibe and 145 to evolocumab; entry mean LDL-C level, 219.9 [SD, 72] mg/dL). For the mean of weeks 22 and 24, LDL-C level with ezetimibe was 183.0 mg/dL; mean percent LDL-C change, -16.7% (95% CI, -20.5% to -12.9%), absolute change, -31.0 mg/dL and with evolocumab was 103.6 mg/dL; mean percent change, -54.5% (95% CI, -57.2% to -51.8%); absolute change, -106.8 mg/dL (P<.001). LDL-C level at week 24 with ezetimibe was

181.5 mg/dL; mean percent change, -16.7% (95% CI, -20.8% to -12.5%); absolute change, -31.2 mg/dL and with evolocumab was 104.1 mg/dL; mean percent change, -52.8% (95% CI, -55.8% to -49.8%); absolute change, -102.9 mg/dL (P<.001). For the mean of weeks 22 and 24, between-group difference in LDL-C was -37.8%; absolute difference, -75.8 mg/dL. For week 24, between-group difference in LDL-C was -36.1%; absolute difference, -71.7 mg/dL. Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients (log-rank P=.17). Active study drug was stopped for muscle symptoms in 5 of 73 ezetimibe-treated patients (6.8%) and 1 of 145 evolocumab-treated patients (0.7%).

CONCLUSIONS AND RELEVANCE: Among patients with statin intolerance related to muscle-related adverse effects, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks. Further studies are needed to assess long-term efficacy and safety.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01984424.

Puri, R., et al. (2016). "Impact of PCSK9 inhibition on coronary atheroma progression: Rationale and design of Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV)." American Heart Journal **176**: 83-92.

BACKGROUND: Statin-mediated low-density lipoprotein cholesterol (LDL-C) lowering fails to prevent more than half of cardiovascular events in clinical trials. Serial plaque imaging studies have highlighted the benefits of aggressive LDL-C lowering, with plaque regression evident in up to two-thirds of patients with achieved LDL-C levels <70 mg/dL. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors permit LDL-C-lowering by a further 54% to 75% in statin-treated patients. The impact of achieving very low LDL-C levels with PCSK9 inhibitors on coronary atherosclerosis has not been investigated.

AIMS: To test the hypothesis that incremental LDL-C lowering with the PCSK9 inhibitor, evolocumab, will result in a significantly greater change from baseline in coronary atheroma volume than placebo in subjects receiving maximally tolerated statin therapy.

METHODS: A phase 3, multicenter, double-blind, randomized, placebo-controlled trial evaluating the impact of evolocumab on coronary atheroma volume as assessed by serial coronary intravascular ultrasound at baseline in patients undergoing a clinically indicated coronary angiogram with angiographic evidence of coronary atheroma, and after 78 weeks of treatment. Subjects (n = 968) were randomized 1:1 into 2 groups to receive monthly either evolocumab 420 mg or placebo subcutaneous injections.

CONCLUSIONS: The GLAGOV trial will explore whether greater degrees of plaque regression are achievable with ultrahigh-intensity LDL-C lowering after combination statin-PCSK9 inhibitor therapy. GLAGOV will provide important mechanistic, safety, and efficacy data prior to the eagerly anticipated clinical outcomes trials testing the PCSK9 inhibitor hypothesis (www.clinicaltrials.gov identifier NCT01813422).

Roth, E. M., et al. (2016). "A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I." Atherosclerosis **254**: 254-262.

BACKGROUND AND AIMS: In previous phase III studies, the PCSK9 monoclonal antibody alirocumab was administered at doses of 75 or 150 mg every 2 weeks (Q2W). CHOICE I

(NCT01926782) evaluated 300 mg every 4 weeks (Q4W) in patients on either maximally tolerated statin or no statin, both +/- other lipid-lowering therapies.
METHODS: CHOICE I included patients with hypercholesterolemia at moderate-to-very-high cardiovascular risk. Patients were randomized to alirocumab 300 mg Q4W, 75 mg Q2W (calibrator arm), or placebo for 48 weeks, with dose adjustment for either alirocumab arm to 150 mg Q2W at Week (W) 12 if at W8 LDL-C levels were >70/100 mg/dL (1.8/2.6 mmol/L) depending on cardiovascular risk or LDL-C reduction was <30% from baseline. Co-primary endpoints were percent LDL-C change from baseline to W24, and to time-averaged LDL-C over W21-24.
RESULTS: Approximately two-thirds of randomized patients were receiving statins. At W12, 14.7% (no statin) and 19.3% (statin) of patients receiving alirocumab 300 mg Q4W required dose adjustment. At W24, significant LDL-C reductions from baseline were observed with alirocumab 300 mg Q4W: mean differences were -52.7% (no statin; placebo: -0.3%) and -58.8% (statin; placebo: -0.1%). Average LDL-C reductions from baseline to W21-24 were also significantly greater with alirocumab 300 mg Q4W vs. placebo in patients not receiving (-56.9% vs. -1.6%) and receiving statin (-65.8% vs. -0.8%). Treatment-emergent adverse event rates ranged from 61.1 to 75.0% (placebo) and 71.5 to 78.1% (alirocumab 300 mg Q4W).
CONCLUSIONS: Alirocumab 300 mg Q4W is a viable additional treatment option in patients requiring LDL-C-lowering.

Roth, E. M. and J. M. McKenney (2015). "ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks." Future Cardiology **11**(1): 27-37.

ABSTRACT Alirocumab is a fully human monoclonal antibody to PCSK9. The ODYSSEY MONO study was the first alirocumab Phase III study to test a previously unused dose of 75 mg subcutaneously every 2 weeks in a population on no lipid-lowering therapy. A total of 103 patients were randomly assigned to alirocumab starting at 75 mg subcutaneously every 2 weeks or ezetimibe 10 mg per os every day with alirocumab dose uptitration at 12 weeks based on achieved LDL-cholesterol level at week 8 and followed to week 24. At the week-24 primary end point, the alirocumab intent-to-treat group showed a 47.2% (least square [LS] mean) reduction in LDL-cholesterol compared with a 15.6% (LS mean) reduction with ezetimibe (LS mean difference of 31.6%; p < 0.0001). Safety parameters and adverse events were similar between the two groups.

Roth, E. M., et al. (2014). "Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial." International Journal of Cardiology **176**(1): 55-61.

BACKGROUND: Efficacy and safety of alirocumab were compared with ezetimibe in hypercholesterolemic patients at moderate cardiovascular risk not receiving statins or other lipid-lowering therapy.
METHODS: In a Phase 3, randomized, double-blind, double-dummy study (NCT01644474), patients (low-density lipoprotein cholesterol [LDL-C] 100-190 mg/dL, 10-year risk of fatal cardiovascular events > 1%-<5% [systemic coronary risk estimation]) were randomized

to ezetimibe 10mg/day (n=51) or alirocumab 75 mg subcutaneously (via 1-mL autoinjector) every 2 weeks (Q2W) (n=52), with dose up-titrated to 150 mg Q2W (also 1 mL) at week 12 if week 8 LDL-C was > 70 mg/dL. Primary endpoint was mean LDL-C % change from baseline to 24 weeks, analyzed using all available data (intent-to-treat approach, ITT). Analyses using on-treatment LDL-C values were also conducted.

RESULTS: Mean (SD) baseline LDL-C levels were 141.1 (27.1) mg/dL (alirocumab) and 138.3 (24.5) mg/dL (ezetimibe). The 24-week treatment period was completed by 85% of alirocumab and 86% of ezetimibe patients. Least squares mean (SE) LDL-C reductions were 47 (3)% with alirocumab versus 16 (3)% with ezetimibe (ITT; p<0.0001) and 54 (2)% versus 17 (2)% (on-treatment; p<0.0001). At week 12, before up-titration, alirocumab 75 mg Q2W reduced LDL-C by 53 (2)% (on-treatment). Injection site reactions were infrequent (<2% and <4% of alirocumab and ezetimibe patients, respectively).

CONCLUSIONS: Alirocumab demonstrated significantly greater LDL-C lowering versus ezetimibe after 24 weeks with the lower 75 mg Q2W dose sufficient to provide > 50% LDL-C reduction in the majority of the patients. Adverse events were comparable between groups.

Sabatine, M. S., et al. (2017). "Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease." New England Journal of Medicine **376**(18): 1713-1722.

METHODS: We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years. RESULTS: At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) (P<0.001). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; P<0.001) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol per liter]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%). CONCLUSIONS: In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that

patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633 .). BACKGROUND: Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

Sabatine, M. S., et al. (2017). "Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial." The lancet diabetes and endocrinology(pagination).

Background: The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab reduced LDL cholesterol and cardiovascular events in the FOURIER trial. In this prespecified analysis of FOURIER, we investigated the efficacy and safety of evolocumab by diabetes status and the effect of evolocumab on glycaemia and risk of developing diabetes. Methods: FOURIER was a randomised trial of evolocumab (140 mg every 2 weeks or 420 mg once per month) versus placebo in 27 564 patients with atherosclerotic disease who were on statin therapy, followed up for a median of 2.2 years. In this prespecified analysis, we investigated the effect of evolocumab on cardiovascular events by diabetes status at baseline, defined on the basis of patient history, clinical events committee review of medical records, or baseline HbA<inf>1c</inf> of 6.5% (48 mmol/mol) or greater or fasting plasma glucose (FPG) of 7.0 mmol/L or greater. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularisation. The key secondary endpoint was a composite of cardiovascular death, myocardial infarction, or stroke. We also assessed the effect of evolocumab on glycaemia, and on the risk of new-onset diabetes among patients without diabetes at baseline. HbA<inf>1c</inf> was measured at baseline then every 24 weeks and FPG was measured at baseline, week 12, week 24, and every 24 weeks thereafter, and potential cases of new-onset diabetes were adjudicated centrally. In a post-hoc analysis, we also investigated the effects on glycaemia and diabetes risk in patients with prediabetes (HbA<inf>1c</inf> 5.7-6.4% [39-46 mmol/mol] or FPG 5.6-6.9 mmol/L) at baseline. FOURIER is registered with ClinicalTrials.gov, number NCT01764633. Findings: At study baseline, 11 031 patients (40%) had diabetes and 16 533 (60%) did not have diabetes (of whom 10 344 had prediabetes and 6189 had normoglycaemia). Evolocumab significantly reduced cardiovascular outcomes consistently in patients with and without diabetes at baseline. For the primary composite endpoint, the hazard ratios (HRs) were 0.83 (95% CI 0.75-0.93; p=0.0008) for patients with diabetes and 0.87 (0.79-0.96; p=0.0052) for patients without diabetes (p<inf>interaction</inf>=0.60). For the key secondary endpoint, the HRs were 0.82 (0.72-0.93; p=0.0021) for those with diabetes and 0.78 (0.69-0.89; p=0.0002) for those without diabetes (p<inf>interaction</inf>=0.65). Evolocumab did not increase the risk of new-onset diabetes in patients without diabetes at baseline (HR 1.05, 0.94-1.17), including in those with prediabetes (HR 1.00, 0.89-1.13). Levels of HbA<inf>1c</inf> and FPG were similar between the evolocumab and placebo

groups over time in patients with diabetes, prediabetes, or normoglycaemia. Among patients with diabetes at baseline, the proportions of patients with adverse events were 78.5% (4327 of 5513 patients) in the evolocumab group and 78.3% (4307 of 5502 patients) in the placebo group; among patients without diabetes at baseline, the proportions with adverse events were 76.8% (6337 of 8256 patients) in the evolocumab group and 76.8% (6337 of 8254 patients) in the placebo group. Interpretation: PCSK9 inhibition with evolocumab significantly reduced cardiovascular risk in patients with and without diabetes. Evolocumab did not increase the risk of new-onset diabetes, nor did it worsen glycaemia. These data suggest evolocumab use in patients with atherosclerotic disease is efficacious and safe in patients with and without diabetes. Funding: Amgen. Copyright (C) 2017 Elsevier Ltd.

Stroes, E., et al. (2016). "Efficacy and Safety of Alirocumab 150 mg Every 4 Weeks in Patients With Hypercholesterolemia Not on Statin Therapy: The ODYSSEY CHOICE II Study." Journal of the American Heart Association **5**(9): 13.

BACKGROUND: The PCSK9 antibody alirocumab (75 mg every 2 weeks; Q2W) as monotherapy reduced low-density lipoprotein-cholesterol (LDL-C) levels by 47%. Because the option of a monthly dosing regimen is convenient, ODYSSEY CHOICE II evaluated alirocumab 150 mg Q4W in patients with inadequately controlled hypercholesterolemia and not on statin (majority with statin-associated muscle symptoms), receiving treatment with fenofibrate, ezetimibe, or diet alone.

METHODS AND RESULTS: Patients were randomly assigned to placebo, alirocumab 150 mg Q4W or 75 mg Q2W (calibrator arm), with dose adjustment to 150 mg Q2W at week (W) 12 if W8 predefined LDL-C target levels were not met. The primary efficacy endpoint was LDL-C percentage change from baseline to W24. Mean baseline LDL-C levels were 163.9 mg/dL (alirocumab 150 mg Q4W, n=59), 154.5 mg/dL (alirocumab 75 mg Q2W, n=116), and 158.5 mg/dL (placebo, n=58). In the alirocumab 150 mg Q4W and 75 mg Q2W groups (49.1% and 36.0% of patients received dose adjustment, respectively), least-squares mean LDL-C changes from baseline to W24 were -51.7% and -53.5%, respectively (placebo [+4.7%]; both groups P<0.0001 versus placebo). In total, 63.9% and 70.3% of alirocumab-treated patients achieved their LDL-C targets at W24. Treatment-emergent adverse events occurred in 77.6% (alirocumab 150 mg Q4W), 73.0% (alirocumab 75 mg Q2W), and 63.8% (placebo) of patients, with injection-site reactions among the most common treatment-emergent adverse events.

CONCLUSIONS: Alirocumab 150 mg Q4W can be considered in patients not on statin with inadequately controlled hypercholesterolemia as a convenient option for lowering LDL-C.

CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02023879.

Teramoto, T., et al. (2016). "Efficacy and Safety of Alirocumab in Japanese Patients With Heterozygous Familial Hypercholesterolemia or at High Cardiovascular Risk With Hypercholesterolemia Not Adequately Controlled With Statins- ODYSSEY JAPAN Randomized Controlled Trial.[Erratum appears in Circ J. 2016;80(11):2414; PMID: 27784878]." Circulation Journal **80**(9): 1980-1987.

BACKGROUND: The ODYSSEY Japan study was designed to demonstrate the reduction in low-density lipoprotein cholesterol (LDL-C) by alirocumab as add-on to existing lipid-lowering therapy in Japanese patients with heterozygous familial hypercholesterolemia (heFH) or non-FH at high cardiovascular risk who require additional pharmacological management to achieve their LDL-C treatment goal (<2.6 or <3.1 mmol/L, depending on risk category).

METHODS AND RESULTS: This randomized, double-blind, parallel-group, 52-week study was conducted in Japan. Patients (n=216) with heFH, non-FH at high cardiovascular risk with coronary disease, or classified as category III were enrolled. The prespecified safety analysis was done after the last patient completed 52 weeks. Patients were randomized (2:1, alirocumab:placebo) with stratification for heFH to s.c. alirocumab (75 mg every 2 weeks [Q2 W] with increase to 150 mg if week 8 LDL-C >=2.6/3.1 mmol/L) or placebo for 52 weeks plus stable statin therapy. At week 24, mean+/-SE change in LDL-C from baseline was -62.5+/-1.3% in the alirocumab group and 1.6+/-1.8% in the placebo group (difference, -64.1+/-2.2%; P<0.0001); the reduction was sustained to week 52 (alirocumab, -62.5+/-1.4%; placebo, -3.6+/-1.9%). No patterns were evident between treatment groups for adverse events at 52 weeks.

CONCLUSIONS: In high-risk Japanese patients with hypercholesterolemia on stable statin therapy, alirocumab markedly reduced LDL-C vs. placebo and was well tolerated over 52 weeks. (Circ J 2016; 80: 1980-1987).

Teramoto, T., et al. (2017). "Efficacy and safety of alirocumab in patients with hypercholesterolemia not adequately controlled with non-statin lipid-lowering therapy or the lowest strength of statin: ODYSSEY NIPPON study design and rationale." Lipids in health and disease **16**(1).

Background Statins are generally well-tolerated and serious side effects are infrequent, but some patients experience adverse events and reduce their statin dose or discontinue treatment altogether. Alirocumab is a highly specific, fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), which can produce substantial and sustained reductions of low-density lipoprotein cholesterol (LDL-C). Methods The randomized, double-blind, placebo-controlled, parallel-group, phase 3 ODYSSEY NIPPON study will explore alirocumab 150 mg every 4 weeks (Q4W) in 163 Japanese patients with hypercholesterolemia who are on the lowest-strength dose of atorvastatin (5 mg/day) or are receiving a non-statin lipid-lowering therapy (LLT) (fenofibrate, bezafibrate, ezetimibe, or diet therapy alone). Hypercholesterolemia is defined as LDL-C >= 100 mg/dL (2.6 mmol/L) in patients with heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia with a history of documented coronary heart disease, or >=120 mg/dL (3.1 mmol/L) in patients with non-familial hypercholesterolemia classified as primary prevention category III (i.e. high-risk patients). During the 12-week double-blind treatment period, patients will be randomized (1:1:1) to receive alirocumab subcutaneously (SC) 150 mg Q4W alternating with placebo for alirocumab Q4W, or alirocumab 150 mg SC every 2 weeks (Q2W), or SC placebo Q2W. The primary efficacy endpoint is the percentage change in calculated LDL-C from baseline to week 12. The long-term safety and tolerability of alirocumab will also be

investigated. Discussion The ODYSSEY NIPPON study will provide insights into the efficacy and safety of alirocumab 150 mg Q4W or 150 mg Q2W among Japanese patients with hypercholesterolemia who are on the lowest-strength dose of atorvastatin, or are receiving a non-statin LLT (including diet therapy alone). Trial registration ClinicalTrials.gov number: NCT02584504