



# Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: Rationale and design of the ODYSSEY Outcomes trial

Gregory G. Schwartz, MD, PhD,<sup>a,q</sup> Laurence Bessac, MD,<sup>b,c</sup> Lisa G. Berdan, PA, MHS,<sup>d</sup> Deepak L. Bhatt, MD, MPH,<sup>c</sup> Vera Bittner, MD,<sup>f</sup> Rafael Diaz, MD,<sup>g</sup> Shaun G. Goodman, MD, MSc,<sup>h</sup> Corinne Hanotin, MD,<sup>b,c</sup> Robert A. Harrington, MD,<sup>i</sup> J. Wouter Jukema, MD, PhD,<sup>j</sup> Kenneth W. Mahaffey, MD,<sup>i</sup> Angèle Moryusef, MD,<sup>b,c</sup> Robert Porcy, MD,<sup>k</sup> Matthew T. Roe, MD, MPH,<sup>d</sup> Tyrus Rorick, RN,<sup>d</sup> William J. Sasiela, PhD,<sup>k</sup> Cheerag Shirodaria, MBBS,<sup>l</sup> Michael Szarek, PhD,<sup>m</sup> Jean-François Tamby, MD,<sup>b,c</sup> Pierluigi Tricoci, MD,<sup>d</sup> Harvey White, MBBS, DSc,<sup>n</sup> Andreas Zeiher, MD,<sup>o</sup> and Philippe Gabriel Steg, MD<sup>p,q</sup> *Denver, CO; Paris, France; Bridgewater, NJ; Durham, NC; Boston, MA; Birmingham, AL; Rosario, Argentina; Toronto, Canada; Stanford, CA; Leiden, the Netherlands; Tarrytown, NY; Oxford, United Kingdom; Brooklyn, NY; Auckland, New Zealand; and Frankfurt, Germany*

**Background** Following acute coronary syndrome (ACS), the risk for future cardiovascular events is high and is related to levels of low-density lipoprotein cholesterol (LDL-C) even within the setting of intensive statin treatment. Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates LDL receptor expression and circulating levels of LDL-C. Antibodies to PCSK9 can produce substantial and sustained reductions of LDL-C. The ODYSSEY Outcomes trial tests the hypothesis that treatment with alirocumab, a fully human monoclonal antibody to PCSK9, improves cardiovascular outcomes after ACS.

**Design** This Phase 3 study will randomize approximately 18,000 patients to receive biweekly injections of alirocumab (75-150 mg) or matching placebo beginning 1 to 12 months after an index hospitalization for acute myocardial infarction or unstable angina. Qualifying patients are treated with atorvastatin 40 or 80 mg daily, rosuvastatin 20 or 40 mg daily, or the maximum tolerated and approved dose of one of these agents and fulfill one of the following criteria: LDL-C  $\geq$  70 mg/dL, non-high-density lipoprotein cholesterol  $\geq$  100 mg/dL, or apolipoprotein B  $\geq$  80 mg/dL. The primary efficacy measure is time to first occurrence of coronary heart disease death, acute myocardial infarction, hospitalization for unstable angina, or ischemic stroke. The trial is expected to continue until 1613 primary end point events have occurred with minimum follow-up of at least 2 years, providing 90% power to detect a 15% hazard reduction. Adverse events of special interest include allergic events and injection site reactions. Interim analyses are planned when approximately 50% and 75% of the targeted number of primary end points have occurred.

**Summary** ODYSSEY Outcomes will determine whether the addition of the PCSK9 antibody alirocumab to intensive statin therapy reduces cardiovascular morbidity and mortality after ACS. (Am Heart J 2014;168:682-689.e.1.)

Despite modern therapy including prompt coronary revascularization, dual antiplatelet therapy, and intensive statin treatment, cardiovascular events occur with high

frequency following an acute coronary syndrome (ACS).<sup>1-4</sup> Registry data indicate cardiovascular mortality as high as 13% at 5 years, with more than 4 out of 5 deaths

From the <sup>a</sup>University of Colorado School of Medicine, Denver, CO, <sup>b</sup>Sanofi-Aventis Recherche et Développement S.A., Paris, France, <sup>c</sup>Sanofi-Aventis Recherche et Développement S.A., Bridgewater, NJ, <sup>d</sup>Duke Clinical Research Institute, Durham, NC, <sup>e</sup>Brigham and Women's Hospital and Harvard Medical School, Boston, MA, <sup>f</sup>University of Alabama at Birmingham, Birmingham, AL, <sup>g</sup>Estudios Cardiológicos Latinoamérica, Rosario, Argentina, <sup>h</sup>Canadian VIGOUR Centre, University of Alberta, Toronto, Canada, <sup>i</sup>Stanford University, Stanford, CA, <sup>j</sup>Leiden University Medical Center, Leiden, the Netherlands, <sup>k</sup>Regeneron Therapeutics, Tarrytown, NY, <sup>l</sup>Covance, Inc., Maidenhead, and Oxford University Hospitals NHS Trust, Oxford, United Kingdom, <sup>m</sup>State University of New York Downstate Medical Center, Brooklyn, NY, <sup>n</sup>Auckland City Hospital and University of Auckland, Auckland, New Zealand, <sup>o</sup>Johann Wolfgang Goethe University, Frankfurt, Germany, and <sup>p</sup>Assistance Publique-Hôpitaux de Paris,

INSERM U-1148, Université Paris Diderot, Paris, France.

<sup>q</sup>Drs. Schwartz and Steg contributed equally to this work.

RCT# NCT01663402

Submitted May 26, 2014; accepted July 31, 2014.

Reprint requests: Gregory G. Schwartz, MD, PhD, Cardiology Section, VA Medical Center (111B), 1055 Clermont St, Denver, CO 80220.

E-mail: [Gregory.Schwartz@va.gov](mailto:Gregory.Schwartz@va.gov)

0002-8703

© 2014 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>). <http://dx.doi.org/10.1016/j.ahj.2014.07.028>

**Table I.** Inclusion and principal exclusion criteria

**Inclusion criteria:**

- Hospitalization for ACS, defined by symptoms of myocardial ischemia with an unstable pattern, occurring at rest or with minimal exertion, within 72 h of an unscheduled hospital admission due to presumed or proven obstructive coronary disease and at least one of the following:
  - Elevated cardiac biomarkers
  - Resting ECG changes consistent with ischemia or infarction, plus additional evidence of obstructive coronary disease from regional wall motion or perfusion abnormality,  $\geq 70\%$  epicardial coronary stenosis by angiography, or need for coronary revascularization procedure.
- Lipid levels inadequately controlled by atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily or maximum tolerated dose of one of these agents, defined by at least one of the following:
  - LDL-C  $\geq 70$  mg/dL
  - Non-HDL-C  $\geq 100$  mg/dL
  - Apolipoprotein B  $\geq 80$  mg/dL

**Principal exclusion criteria:**

- Age  $< 40$  y
- Qualifying index ACS event  $< 4$  or  $> 52$  wk before randomization
- Not on stable lipid-modifying therapy for  $\geq 2$  wk before randomization
- Uncontrolled hypertension ( $> 180$  mm Hg systolic and/or  $> 110$  mm Hg diastolic at randomization visit)
- New York Heart Association class III or IV congestive heart failure persisting despite treatment or LVEF  $< 25\%$  if measured
- History of hemorrhagic stroke
- Fasting triglycerides  $> 400$  mg/dL (4.52 mmol/L) at qualifying laboratory visit
- Recurrent ACS event within 2 wk prior to randomization visit
- Coronary revascularization procedure performed within 2 wk prior to randomization visit or planned after randomization
- Liver transaminases  $> 3$  times upper limit of normal; laboratory evidence of current hepatitis B or C infection; creatine kinase  $> 3$  times upper limit of normal; estimated glomerular filtration rate  $< 30$  mL/(min 1.73 m<sup>2</sup>); positive urine or serum pregnancy test
- Use of fibrates other than fenofibrate or fenofibric acid

occurring after initial discharge from hospital.<sup>5</sup> Although intensive statin therapy can reduce levels of low-density lipoprotein cholesterol (LDL-C) by  $> 50\%$ , the relationship between serum cholesterol and cardiovascular risk does not have a clearly identified threshold.<sup>6</sup> In fact, among statin-treated patients, the risk of recurrent cardiovascular events after ACS or in chronic coronary heart disease remains related to LDL-C levels.<sup>1,7,8</sup> In addition, substantial numbers of patients either do not tolerate statins or have LDL-C levels that remain elevated despite statin treatment.<sup>9,10</sup> These observations raise the question of whether an intervention added to intensive statin therapy to further reduce LDL-C and other atherogenic lipoproteins would further reduce cardiovascular risk among these at-risk patients.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a regulator of LDL receptor expression on hepatocytes and as such plays an important role in determining circulating concentrations of LDL-C.<sup>11</sup> Observations drawn from subjects with genetic polymorphisms of PCSK9 support

its role in modulating susceptibility to atherosclerosis: Persons with loss-of-function mutations in this protein have both lower lifetime levels of LDL-C and lower incidence of coronary heart disease, whereas gain-of-function mutations are a cause of familial hypercholesterolemia and premature incidence of coronary heart disease.<sup>12,13</sup> Statins upregulate expression of PCSK9,<sup>14</sup> an effect that may limit the efficacy of statins to lower LDL-C.

Alirocumab is a fully human monoclonal antibody to PCSK9. As monotherapy, alirocumab can reduce LDL-C as much as intensive statin treatment<sup>15</sup>; and in conjunction with statin, alirocumab greatly enhances LDL-C lowering.<sup>16,17</sup> For example, among patients with baseline LDL-C  $\geq 100$  mg/dL on atorvastatin 10 mg daily, an increase in atorvastatin to 80 mg daily resulted in a further 17% decrease in LDL-C, whereas an increase in atorvastatin to 80 mg daily along with alirocumab 150 mg every 2 weeks resulted in a further 73% decrease.<sup>18</sup> To date, treatment with alirocumab has been generally well tolerated, with occasional, mild local injection site reactions.

The ODYSSEY Outcomes trial tests the hypothesis that alirocumab, compared with placebo, reduces cardiovascular morbidity and mortality in patients with recent ACS and levels of atherogenic lipoproteins that remain above specified concentrations despite intensive atorvastatin or rosuvastatin therapy or the maximally tolerated dose of either of these statins.

## Methods

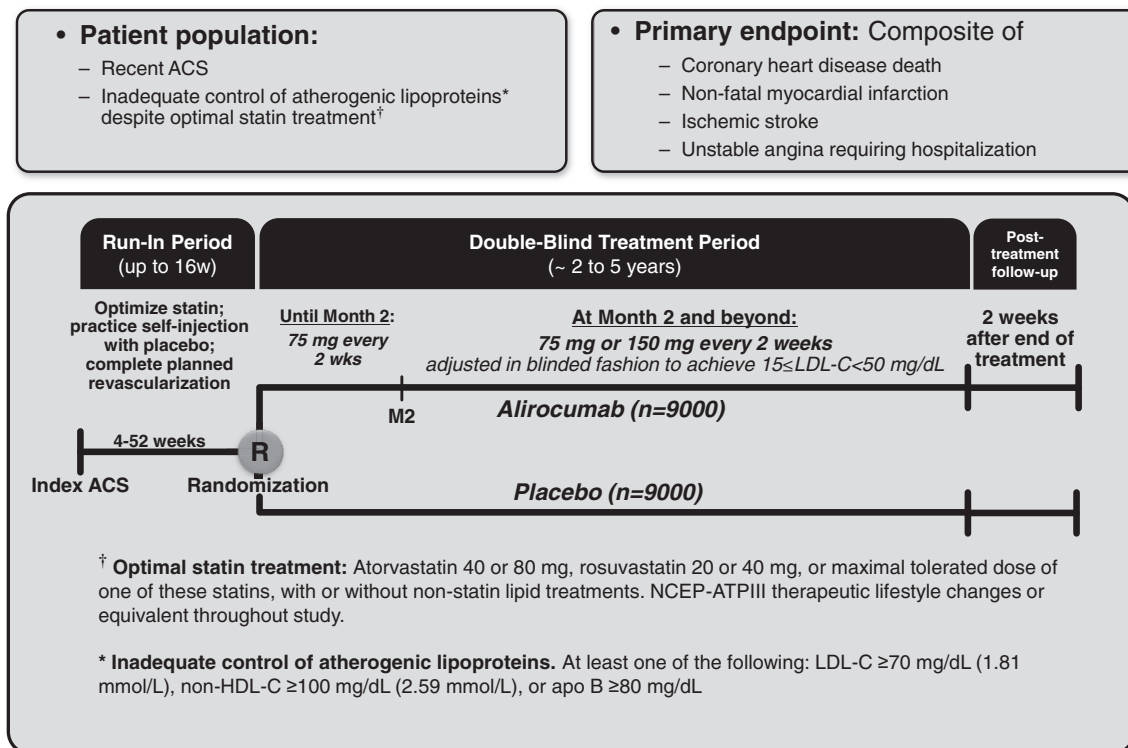
### Study objective

ODYSSEY Outcomes ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT01663402) is an international, multicenter, randomized, double-blind, placebo-controlled study in approximately 18,000 patients with a recent ACS, conducted at  $> 1,000$  sites worldwide, and approved in each participating center by the responsible Institutional Review Board or Ethics Committee. The protocol was developed by an independent academic Executive Committee (online Appendix) in conjunction with the sponsors. The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of this paper, and its final contents. Funding for the study is provided by Sanofi-Aventis SA and by Regeneron Pharmaceuticals. The primary objective is to evaluate whether alirocumab (75 or 150 mg by subcutaneous injection every 2 weeks), initiated 1 to 12 months after an index ACS event, reduces the incidence of the composite outcome of coronary heart disease death, major nonfatal coronary events (myocardial infarction or hospitalization for unstable angina), or ischemic stroke.

### Study population

Principal inclusion and exclusion criteria are shown in Table I. The trial will enroll male and female patients  $\geq 40$  years of age who are hospitalized for an ACS. Criteria for a

Figure 1



Schematic of study design.

qualifying ACS event include symptoms of myocardial ischemia occurring at rest or minimal exertion within 72 hours of an unscheduled hospital admission due to presumed or proven obstructive coronary disease. In addition, at least one of the following criteria must be fulfilled: elevated cardiac biomarkers consistent with acute myocardial infarction, or new or presumed new resting electrocardiographic (ECG) changes consistent with ischemia or infarction plus evidence of obstructive coronary disease from imaging studies and/or need for coronary revascularization related to the event.

Qualifying patients must demonstrate inadequate control of atherogenic lipoproteins despite treatment with atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg daily, or the maximum tolerated or advisable dose of one of these statins. Inadequate control of atherogenic lipoproteins is defined by at least one of the following: LDL-C ≥ 70 mg/dL (1.81 mmol/L), non-high-density lipoprotein cholesterol (non-HDL-C) ≥ 100 mg/dL (2.59 mmol/L), or apolipoprotein B ≥ 80 mg/dL (0.8 mmol/L).

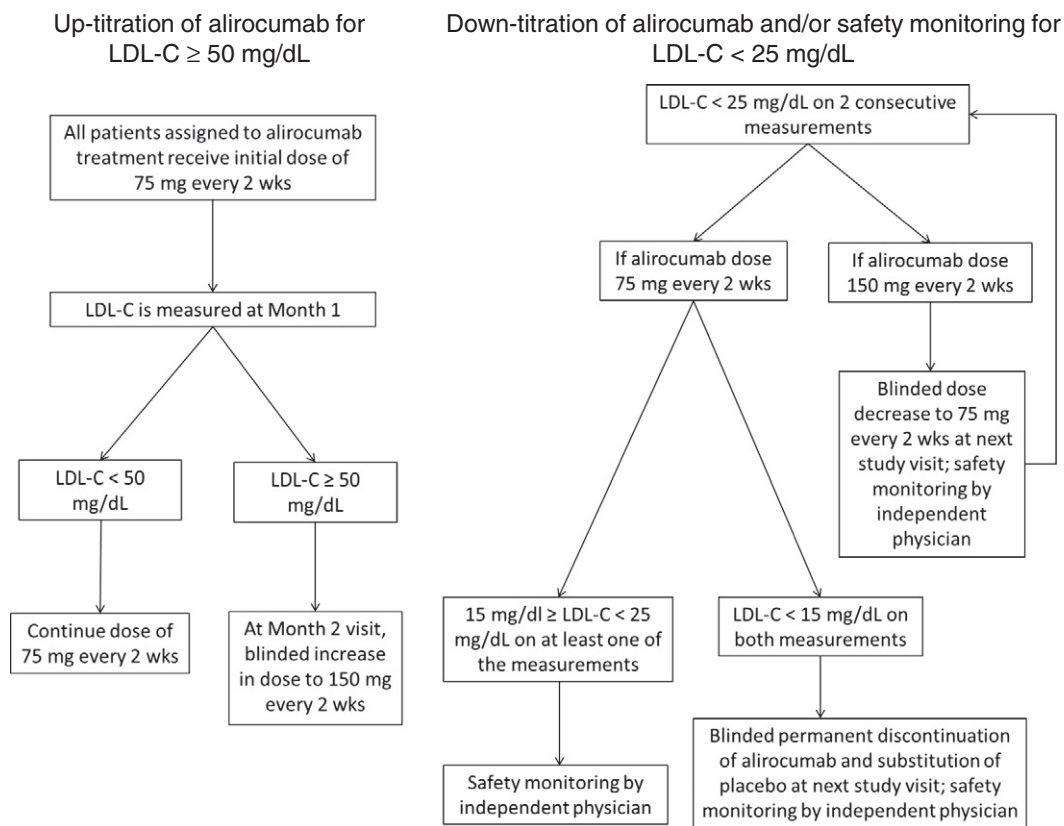
### Study procedures

Figure 1 illustrates the key phases of the trial. Patients providing informed consent enter a run-in period of

duration 2 to 16 weeks. During this period, patients are instructed in the technique of self-injection using a 1-mL prefilled pen. The run-in period also allows metabolic steady state after ACS and pharmacologic steady state on lipid-modifying drug treatment to be achieved prior to randomization. Atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg daily is initiated and/or adjusted as necessary to determine the maximum tolerated dose. A lower dose of one of these statins (or even no statin) is allowed in cases of documented statin intolerance or when prescribing guidance advises a lower dose (eg, advanced age, low body mass, or potential drug-drug interactions). Other nonexcluded lipid-modifying therapies may also be initiated during the run-in period at the investigator's discretion. After at least 2 weeks of stable lipid-modifying therapy, a fasting blood sample is obtained to determine if at least one of the qualifying lipoprotein criteria is met.

Patients who meet all inclusion and no exclusion criteria at the end of the run-in period are randomly assigned to initial treatment with alirocumab 75 mg subcutaneously every 2 weeks or matching placebo. Follow-up visits occur 1, 2, 4, 8, 12, 16, 20, and 24 months after randomization and then at 6-month intervals until the common study end date. At randomization and at

**Figure 2**



Blinded dose titration algorithms for alirocumab.

multiple time points after randomization, patients are assessed for study end points and adverse events. Blood and urine samples are collected for measurements including lipoproteins and apolipoproteins, hematology studies, liver, muscle, and kidney function tests, hemoglobin A1c, high-sensitivity C-reactive protein, anti-alirocumab antibodies, and pregnancy testing in women of child-bearing potential. Low-density lipoprotein cholesterol is calculated using the Friedewald formula, except that calculated values <15 mg/dL or LDL-C in hypertriglyceridemic specimens (triglycerides > 400 mg/dL or 4.52 mmol/L) are confirmed by direct measurement.<sup>19</sup> Samples are also collected for measurement of PCSK9 levels, lipoprotein subfractions, and mediators of inflammation and cardiovascular risk. Because optimal, evidence-based lipid-modifying therapy has been initiated during the run-in period, lipoprotein levels remain blinded to patients and investigators during the randomized treatment period; and treating physicians are instructed to refrain from usual clinical lipoprotein testing.

The ODYSSEY Outcomes trial seeks to determine whether clinical outcomes are improved by lowering

levels of LDL-C and other atherogenic lipoproteins below those achieved on optimal statin therapy alone. The trial is not designed to explore the safety of sustained, very low LDL-C levels. Accordingly, blinded dose adjustment and monitoring procedures are incorporated in the protocol, as indicated in Figure 2. Among patients assigned to treatment with alirocumab, if LDL-C measured 1 month after randomization (ie, after 2 doses of alirocumab 75 mg every 2 weeks) remains  $\geq 50$  mg/dL, the dose of alirocumab is increased in a blinded fashion to 150 mg every 2 weeks (also 1-mL injection volume). If LDL-C measured 1 month after randomization is <50 mg/dL, the dose of alirocumab is maintained at 75 mg. If LDL-C is <25 mg/dL on any 2 consecutive measurements on alirocumab 150 mg, the dose is reduced to 75 mg. If LDL-C is <25 mg/dL but  $\geq 15$  mg/dL on 2 consecutive measurements on alirocumab 75 mg, that dose is continued; but the patient is monitored for potentially related adverse events by an independent safety physician who reports individual and aggregate findings to the Data Safety Monitoring Board (DSMB) and recommends blinded discontinuation of treatment if data suggest that an adverse event is causally related to treatment. If LDL-C is <15 mg/dL on 2 consecutive measurements during

**Table II.** Definitions of components of the primary efficacy measure*Coronary heart disease death*

- Any death with a clear relationship to underlying coronary heart disease, including death secondary to acute myocardial infarction, sudden death, heart failure, complication of a coronary revascularization procedure where the cause of death is clearly related to the procedure, unobserved and unexpected death, and other death that cannot definitely be attributed to a nonvascular cause.

*Acute nonfatal myocardial infarction*

- Defined and subclassified in accordance with ACC/AHA/ESC universal definition of myocardial infarction<sup>27</sup>
- Silent myocardial infarction is not considered part of the primary end point

*Ischemic stroke*

- An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction, defined by at least one of the following:
  - Pathological, imaging, or other objective evidence of acute, focal cerebral, spinal, or retinal ischemic injury in a defined vascular distribution
  - Symptoms of acute cerebral, spinal, or retinal ischemic injury persisting  $\geq 24$  h or until death, with other etiologies excluded
- Hemorrhagic infarction is considered an ischemic stroke, but stroke caused by intracerebral or subarachnoid hemorrhage is not.
- Strokes not otherwise subclassified are considered part of the primary end point.

*Hospitalization for unstable angina*

- Admission to hospital or emergency department with symptoms of myocardial ischemia with an accelerating tempo in the prior 48 h and/or rest chest discomfort  $\geq 20$  min, requiring in addition both of the following:
  - New or presumed new ischemic ECG changes, defined by ST depression  $>0.5$  mm in 2 contiguous leads; T-wave inversion  $>1$  mm in 2 contiguous leads with prominent R-wave or R/S  $> 1$ ; ST elevation in  $>2$  contiguous leads  $>0.2$  mV in V2 or V3 in men,  $>0.15$  mV in V2 or V3 in women, or  $>0.1$  mV in other leads; or LBBB.
  - Definite contemporary evidence of coronary obstruction by need for coronary revascularization procedure or at least one epicardial stenosis  $\geq 70\%$ . Procedures or stenoses due only to restenosis at prior PCI site are excluded.

ACC/AHA/ESC, American College of Cardiology/American Heart Association/European Society of Cardiology; LBBB, left bundle-branch block; PCI, percutaneous coronary intervention.

treatment with alirocumab 75 mg, active treatment is discontinued at the next study visit; and placebo injections are substituted in a blinded manner for the remainder of the study. In composite, these blinded dose adjustments are intended to maximize the number of patients in the alirocumab group with LDL-C  $< 50$  mg/dL while minimizing the number of patients with sustained levels of LDL-C  $< 15$  mg/dL.

**Study outcomes**

The primary efficacy measure is the time to first occurrence of coronary heart disease death, major nonfatal coronary event (myocardial infarction or hospitalization for unstable angina), or ischemic stroke. Criteria and definitions for each type of ischemic event are provided in [Table II](#). Together, coronary heart disease death and fatal stroke are expected to encompass a large majority of cardiovascular deaths that are likely to be modified by lipid-lowering therapy. Secondary end points include ischemia-driven coronary revascularization procedures, hospitalization for congestive heart failure, and all-cause mortality. Prespecified secondary efficacy measures are listed in [Table III](#). Laboratory end points include change from baseline in calculated LDL-C, apolipoprotein B, non-HDL-C, hemoglobin A1c, and high-sensitivity C-reactive protein. Health-related quality of life is assessed with the Euroqol 5-dimensions questionnaire.<sup>20</sup> In a subset of patients who provide specific, additional informed consent, a blood sample is obtained for pharmacogenomic analysis to determine associations with hyperlipidemia, cardiovascular disease, and response to alirocumab. Safety of alirocumab treatment is assessed by reporting of adverse events and laboratory tests. Adverse events of special interest include allergic events and injection site reactions.

In addition, other categories of adverse events that might theoretically be related to low LDL-C, including hemolytic anemia and neurocognitive abnormalities, will be systematically ascertained. Anti-alirocumab antibodies are measured at randomization; months 2, 4, and 12; and then annually until the common end of trial date and at the time of any premature discontinuation of study medication.

**Statistical considerations**

The primary efficacy end point will be analyzed on an intent-to-treat basis. The projected Kaplan-Meier incidence of a primary end point event in the placebo group is 3.8% at 12 months, 6.4% at 24 months, 9.0% at 36 months, and 11.4% at 48 months.<sup>1,21</sup> Other assumptions include 1% of patients lost to follow-up through 24 months, a median LDL-C at baseline of 90 mg/dL,<sup>8</sup> and a 50% reduction of LDL-C from baseline with alirocumab treatment,<sup>18</sup> resulting in an expected 15% hazard reduction. Based on the assumptions above and specifying a log-rank test at an overall 1-sided 2.5% significance level (0.01% at second interim analysis and 2.49% at final analysis), the trial will have 90% power with 1,613 primary end point events. To achieve these 1,613 events, 18,000 patients (9,000 per group) will be randomized over an expected 40-month period. If not halted following an interim analysis, the trial is expected to continue until 1,613 primary end point events have occurred and all evaluable patients have been followed for  $\geq 2$  years. The primary outcome will be analyzed with the log-rank test procedure stratified by geographical region. For the primary outcome, treatment effects will be examined across subgroups prespecified in the statistical analysis plan and categorized according to gender, age, race, and geographical region. In addition,



**Table III.** Efficacy and safety measures

Primary efficacy measure:

- Time to first occurrence of coronary heart disease death, nonfatal acute myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

Main secondary efficacy measures (in hierarchical order):

- Time from randomization to first occurrence of major coronary heart disease event (coronary heart disease death or nonfatal myocardial infarction), unstable angina requiring hospitalization, or ischemia-driven coronary revascularization procedure (PCI or CABG, excluding procedures performed solely for restenosis at prior PCI site). Ischemia-driven coronary revascularization must be driven by one of the following:
  - Acute ischemia (ACS)
  - New or progressive symptoms (angina or equivalent) or new or progressive functional testing abnormalities (eg, stress testing or imaging)
- Time from randomization to first occurrence of a major coronary heart disease event
- Time from randomization to first occurrence of any cardiovascular event (any cardiovascular death, any nonfatal coronary heart disease event, or nonfatal ischemic stroke)
- Time from randomization to first occurrence of all-cause mortality, nonfatal myocardial infarction, or nonfatal ischemic stroke
- Time from randomization to death (all-cause mortality)

Other secondary efficacy measures:

- Time from randomization to coronary heart disease death
- Time from randomization to first occurrence of nonfatal myocardial infarction
- Time from randomization to first occurrence of ischemic stroke
- Time from randomization to first occurrence of unstable angina requiring hospitalization
- Time from randomization to first occurrence of ischemia-driven coronary revascularization procedure
- Time from randomization to first occurrence of congestive heart failure requiring hospitalization

Safety measures:

- All adverse events, heart rate and blood pressure, hematology, and biochemistry assessments

Other:

- Anti-alirocumab antibodies assessed throughout the study
- Percent change from baseline to month 4, month 24, and the common study end date in calculated LDL-C, apolipoprotein B, and non-HDL-C
- Percent change from baseline to the common study end date in hemoglobin A1c and high-sensitivity C-reactive protein
- Change from baseline to end of treatment in health-related quality of life (Euroqol 5-dimensions score)
- Incidence of clinically significant complications or procedures related to peripheral arterial disease (not planned at time of randomization)
- Incidence of venous thromboembolic events

CABG, coronary artery bypass graft.

the effect of the time from ACS event to randomization will be assessed using a Cox proportional hazards model including the time from ACS event as a covariate, the treatment group, and the interaction. Time-to-event secondary outcomes will be analyzed using the same methodology as for the primary end point. For main secondary outcomes, the overall type 1 error will be controlled by use of a sequential inferential approach. Safety results will be presented by treatment group without formal inferential testing. The percent change from baseline in lipids parameters at month 4, at month 24, and at the common study end date will be analyzed in the intent-to-treat population.

The independent Data Safety Monitoring Board (DSMB), composed of 3 cardiologists, 1 lipidologist, and 1 statistician, reviews data at regular intervals to assess safety and efficacy. When approximately 50% of events have occurred, the DSMB will conduct an interim analysis for futility (nonbinding boundary corresponding to hazard ratio > 1.008). When approximately 75% of events have occurred, the DSMB will conduct a second interim analysis for futility (nonbinding boundary corresponding to hazard ratio > 0.951) and overwhelming efficacy (hazard ratio < 0.802 corresponding to  $P < .0001$  for the primary end point with consistency across subgroups and regions, positive trends for secondary end points including all-cause mortality, and no excess noncardiovascular mortality).

## Study organization

The ODYSSEY Outcomes trial was conceived by the co-principal investigators and developed in conjunction with the independent academic Executive Committee and the sponsors. The Executive Committee, composed of 10 academic cardiologists, 1 academic statistician, and nonvoting sponsor representatives, is responsible for oversight and guidance of the study. The independent academic statistician will perform or confirm all statistical analyses of the final data. A National Leaders Committee, composed of lead investigators from each participating country, works in tandem with the Executive Committee. Site and data management is coordinated by the Duke Clinical Research Institute, an academic research organization, and Covance, Inc. The Clinical Events Committee composed of cardiologists and neurologists reviews and adjudicates in blinded fashion each component of the primary composite end point, ischemia-driven coronary revascularization, and hospitalization for congestive heart failure.

## Discussion

Statins have been approved for clinical use since 1987. Since that time, no lipid-modifying therapy has been shown to improve cardiovascular outcomes on a background of statin treatment. However, most of the treatments

tested to date, including niacin, fenofibrate, ezetimibe, pioglitazone, and dalcetrapib, have modest or negligible effects on LDL-C.<sup>1,22-25</sup>

Recent guidelines of the American Heart Association and American College of Cardiology for the reduction of blood cholesterol levels<sup>26</sup> recommend *intensive statin treatment* (defined as atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily) in patients with established coronary heart disease and do not espouse titration of statin to specific LDL-C targets in such patients. These recommendations are based on previous randomized controlled trials that demonstrated that the maximal doses of these statins provide the greatest clinical efficacy in high-risk patients. The guidelines do not dispute the well-established relation between LDL-C and coronary risk. In ODYSSEY Outcomes, stipulated background statin therapy is concordant with new guideline recommendations. On this background, the trial will determine whether further reduction in cardiovascular risk can be achieved by addition of the monoclonal PCSK9 antibody, alirocumab, resulting in further reduction of LDL-C and other atherogenic lipoproteins. Patients with recent ACS were chosen as the study population because they face a higher risk of recurrent events than patients with stable cardiovascular disease and therefore might derive a larger absolute benefit from an effective new treatment. The study population was further defined by threshold levels of LDL-C, non-HDL-C, or apolipoprotein B to target those whose residual cardiovascular risk is most likely to be modified by further reduction of these lipoproteins. Recruitment of patients began in 2012 and is projected to be complete in 2016. With an expected median duration of treatment of approximately 3 years, the trial will also provide substantial information regarding the safety of PCSK9 inhibition.

## Acknowledgements

The ODYSSEY Outcomes trial is funded by Sanofi-Aventis SA and Regeneron Pharmaceuticals.

## References

- Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;367(22):2089-99.
- Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361(11):1045-57.
- Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285(13):1711-8.
- Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350(15):1495-504.
- Fox KA, Carruthers KF, Dunbar DR, et al. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J* 2010;31(22):2755-64.
- Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256(20):2823-8.
- Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376(9753):1670-81.
- Wiviott SD, Cannon CP, Morrow DA, et al. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. *J Am Coll Cardiol* 2005;46(8):1411-6.
- Karalis DG, Victor B, Ahedor L, et al. Use of lipid-lowering medications and the likelihood of achieving optimal LDL-cholesterol goals in coronary artery disease patients. *Cholesterol* 2012;2012:861924.
- Kotseva K, Wood D, De Backer BG, et al. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Cardiovasc Prev Rehabil* 2009;16(2):121-37.
- Do RQ, Vogel RA, Schwartz GG. PCSK9 inhibitors: potential in cardiovascular therapeutics. *Curr Cardiol Rep* 2013;15(3):345.
- Cohen JC, Boerwinkle E, Mosley Jr TH, et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;354(12):1264-72.
- Naoumova RP, Tosi I, Patel D, et al. Severe hypercholesterolemia in four British families with the D374Y mutation in the PCSK9 gene: long-term follow-up and treatment response. *Arterioscler Thromb Vasc Biol* 2005;25(12):2654-60.
- Welder G, Zineh I, Pacanowski MA, et al. High-dose atorvastatin causes a rapid sustained increase in human serum PCSK9 and disrupts its correlation with LDL cholesterol. *J Lipid Res* 2010;51(9):2714-21.
- Stein EA, Mellis S, Yancopoulos GD, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. *N Engl J Med* 2012;366(12):1108-18.
- McKenney JM, Koren MJ, Kereiakes DJ, et al. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J Am Coll Cardiol* 2012;59(25):2344-53.
- Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. *Lancet* 2012;380(9836):29-36.
- Roth EM, McKenney JM, Hanotin C, et al. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med* 2012;367(20):1891-900.
- Martin SS, Blaha MJ, Elshazly MB, et al. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. *J Am Coll Cardiol* 2013;62(8):732-9.
- Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35(11):1095-108.
- Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344(25):1879-87.
- Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365(24):2255-67.

23. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366(9493):1279-89.
24. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362(17):1563-74.
25. Cannon CP, Giugliano RP, Blazing MA, et al. Rationale and design of IMPROVE-IT (IMproved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J* 2008;156(5):826-32.
26. Stone NJ, Robinson J, Lichtenstein AH, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(25 Suppl 2):S1-S45.
27. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J* 2012;33(20):2551-67.



## Appendix. Committees

*Executive Steering Committee:* Gregory G. Schwartz and Philippe Gabriel Steg, Co-Chairs; Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Shaun G. Goodman, Robert A. Harrington, J. Wouter Jukema, Michael Szarek, Harvey White, Andreas Zeiher. Nonvoting members: Pierluigi Tricoci and Kenneth Mahaffey (ex officio); Corinne Hanotin, Angèle Moryusef, Robert Pordy, Jean-François Tamby (sponsor representatives).

*National Leaders Committee:* Argentina: Rafael Diaz; Australia: Philip Aylward; Austria: Heinz Drexel; Belgium: Peter Sinnaeve; Bosnia and Herzegovina: Mirza Dilic; Brazil: Renato Lopes; Bulgaria: Nina Gotcheva; Canada: Shaun Goodman; Chile: Juan-Carlos Prieto; China: Huo Yong; Colombia: Patricio Lopez-Jaramillo; Croatia: Zeljko Reiner; Czech Republic: Petr Ostadal; Denmark: Steen Poulsen; Estonia: Margus Vigimaa; Finland: Markku Niemenen; France: Nicolas Danchin; Georgia: Vakhtang Chumburidze; Germany: Nikolaus Marx; Greece: Evangelos Liberopoulos; Guatemala: Pablo Carlos Montenegro Valdovinos; Hong Kong: Hung Fat Tse; Hungary: Robert Kiss; India: Denis Xavier; Israel: Doron Zahger; Italy: Marco Valgimigli; Japan: Takeshi Kimura; Korea: Hyo Soo Kim; Latvia: Andrejs Erglis; Lithuania: Aleksandras

Laucevicius; Macedonia: Sasko Kedev; Malaysia: Khalid Yusoff; Mexico: Gabriel Ramos Lopez; Netherlands: Marco Alings; New Zealand: Harvey White; Norway: Sigrun Halvorsen; Peru: Walter Mogrovejo Ramos; Philippines: Rody Sy; Poland: Andrzej Budaj; Portugal: Joao Morais; Romania: Maria Dorobantu; Russia: Yuri Karpov; Serbia: Arsen Ristic; Singapore: Terrance Chua; Slovakia: Jan Murin; Slovenia: Zlatko Fras; South Africa: Anthony Dalby; Spain: Jose Tuñón; Sri Lanka: Asita de Silva; Sweden: Emil Hagström; Switzerland: Christian Mueller; Taiwan: Chern-En Chiang; Turkey: Sema Guneri; Ukraine: Alexander Parkhomenko; United Kingdom: Kausik Ray; United States: Patrick Moriarty, Matthew Roe, Robert Vogel.

*Data Safety Monitoring Board:* Bernard Chaitman (Chair), Sheryl F. Kelsey, Anders G. Olsson, Jean-Lucien Rouleau, Maarten L. Simoons

*Clinical Events Committee:* Pierluigi Tricoci (Chair), Renato Lopes, Kenneth Mahaffey, Luciana Armaganijan, Grégory Ducrocq, Zubin Eapen, J. Dedrick Jordan, Bradley Kolls, Sergio Leonardi, Adriana Bertolami Manfredi, Robin Mathews, Rajendra Metha, Etienne Puymirat, Matthew Roe, Bimal Shah