

Study design and rationale for the Stabilization of pLaques using Darapladib—Thrombolysis in Myocardial Infarction (SOLID-TIMI 52) trial in patients after an acute coronary syndrome

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Background Higher levels of lipoprotein-associated phospholipase A₂ (Lp-PLA₂) are associated with a higher risk of cardiovascular events and may play a causal role in atherogenesis. Darapladib inhibits Lp-PLA₂ activity in plasma and in arterial plaques and may confer clinical benefit in preventing cardiovascular events.

Study Design The SOLID-TIMI 52 trial is a randomized, double-blind, placebo-controlled, multicenter, event-driven trial. Approximately 13,000 subjects are being randomized to darapladib (160 mg enteric-coated tablet daily) or matching placebo within 30 days of hospitalization with an acute coronary syndrome. The primary end point is the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Secondary end points include major and total coronary events, individual components of the primary end point, and all-cause mortality. The study will continue until approximately 1,500 primary end point events have occurred to achieve 90% power to detect a 15.5% reduction in the primary end point. The median treatment duration is anticipated to be approximately 3 years, with a total study duration of approximately 4.1 years.

Conclusions The SOLID-TIMI 52 trial will determine the clinical benefit of direct inhibition of Lp-PLA₂ activity with darapladib in patients after an acute coronary syndrome. (Am Heart J 2011;162:613-619.e1.)

Background

Inflammation plays a key role in the pathogenesis of atherosclerosis and plaque rupture.¹ Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is an enzyme that is secreted predominantly by inflammatory cells, including macrophages and lymphocytes. It circulates primarily bound to low-density lipoprotein (LDL) cholesterol in the circulation,^{2,3} and its activity is most concentrated in

atherogenic small, dense LDL particles.⁴ Several studies have demonstrated that higher levels of Lp-PLA₂ activity or mass are associated with an increased risk of cardiovascular (CV) events.⁵ In a recent meta-analysis that included data from 79,036 individuals across 32 studies, Lp-PLA₂ activity and mass showed continuous associations with the risk of coronary heart disease (CHD) that were similar in magnitude to non-HDL cholesterol and systolic blood pressure.⁵

Growing evidence suggests that Lp-PLA₂ may play a causal role in atherogenesis.^{6,7} Enzymatic activity of Lp-PLA₂ leads to the production of the proinflammatory and proapoptotic mediators lysophosphatidylcholine and oxidized nonesterified fatty acids from oxidized LDL particles (Figure 1).^{6,8,9} Also, Lp-PLA₂ has been identified in unstable and ruptured atherosclerotic plaques¹⁰ and is strongly expressed in macrophages in vulnerable lesions prone to rupture.¹¹ Furthermore, direct inhibition of Lp-PLA₂ activity has been shown to inhibit progression to advanced coronary atherosclerotic lesions in diabetic and hypercholesterolemic swine.¹² Most recently, in 2 large case-control studies in South Korean males, natural

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ClinicalTrials.gov identifier: NCT01000727.

Submitted May 11, 2011; accepted July 26, 2011.

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0002-8703/\$ - see front matter

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doi:10.1016/j.ahj.2011.07.018

Figure 1

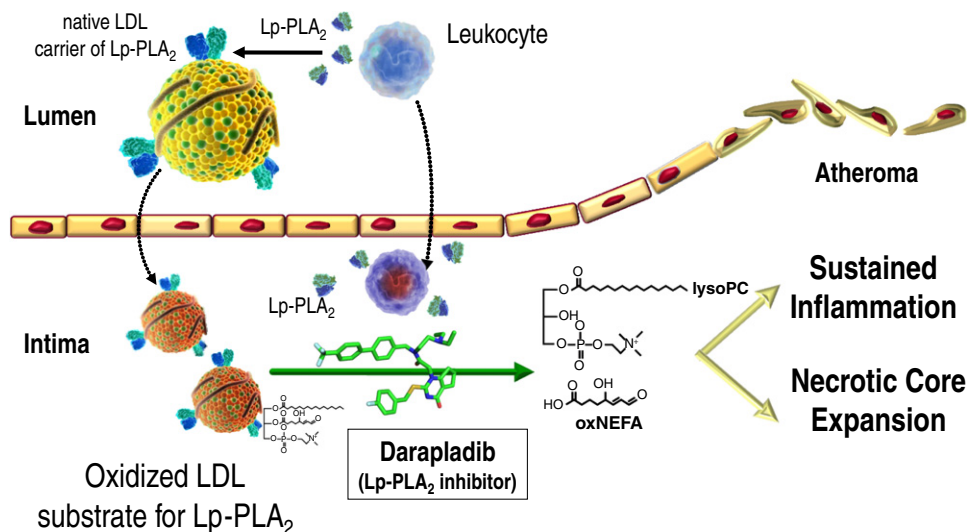


Illustration depicting Lp-PLA₂ and its reported role in atherogenesis. The Lp-PLA₂ enzyme circulates primarily bound to LDL cholesterol. It is delivered to atherosclerotic plaques and generates proinflammatory mediators in the presence of oxidized LDL that promote atherosclerosis and plaque instability. As the lesion matures, monocyte-derived macrophages act as an important secondary source for Lp-PLA₂ production. Darapladib inhibits Lp-PLA₂ activity in the circulation and in atherosclerotic plaques.

deficiency of Lp-PLA₂ activity due to carriage of the V279F null allele within the Lp-PLA₂ gene was associated with a lower risk of developing coronary artery disease (CAD).¹³

Background on darapladib

Darapladib is a novel, selective, reversible, orally active inhibitor of Lp-PLA₂ activity. The half-life of the parent compound is approximately 126 hours. Metabolism of darapladib is primarily mediated by cytochrome P450 (CYP) 3A4 with minor contributions from other CYP enzymes. As such, chronic administration of strong inhibitors of CYP3A4 are contraindicated in combination with darapladib.

In clinical studies, darapladib was shown to reduce Lp-PLA₂ activity both in plasma¹⁴ and in atherosclerotic plaques.¹⁵ On a background of statin therapy, 160 mg daily of darapladib led to sustained inhibition of Lp-PLA₂ activity by an average of 66% during 12 weeks of treatment.¹⁴ In a randomized, placebo-controlled trial of high-risk patients with CAD, darapladib (160 mg daily) halted the progression of the necrotic core of the atherosclerotic plaque, as assessed by intravascular ultrasound-based virtual histology imaging with no overall change in plaque volume, over the course of 12 months of treatment on a background of statin and aspirin therapy.¹⁶ In turn, emerging data suggest that atherosclerotic plaques with a large necrotic core and thin fibrous cap are those that are most vulnerable to rupture.¹⁷ Together, these data suggest that Lp-PLA₂ may contribute to vascular

inflammation and plaque instability in patients with atherosclerotic disease and support the concept of Lp-PLA₂ as a therapeutic target in patients after an acute coronary syndrome (ACS).

In the phase II program, the drug was well tolerated, except for a higher incidence of diarrhea, dysgeusia, and odor events (abnormal odor of feces, urine, breath, or skin) that were reported for patients on darapladib as compared with placebo. No safety concerns with darapladib were identified. Currently, darapladib is being evaluated in 15,828 subjects enrolled in the STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY; ClinicalTrials.gov identifier: NCT00799903) trial, a phase III trial of darapladib in patients with chronic CHD in addition to existing standard of care.¹⁸

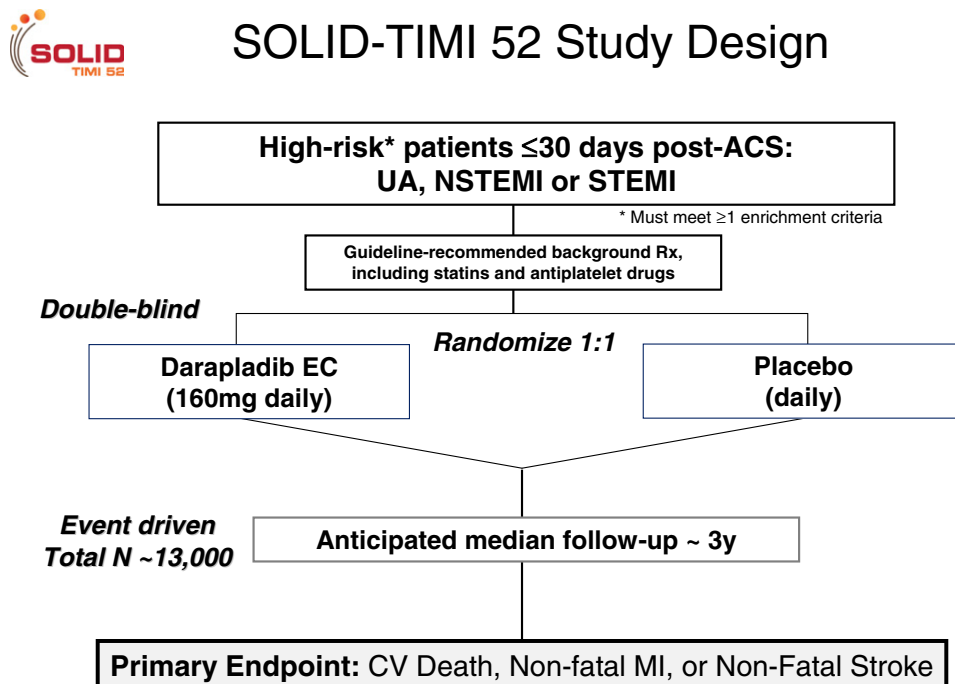
The objective of the current article is to outline the study design and rationale for the SOLID-TIMI 52 study in the context of the phase 3 program for darapladib.

Methods

Study design and population

The SOLID-TIMI 52 (ClinicalTrials.gov identifier: NCT01000727) study is a randomized, placebo-controlled, double-blind, parallel group, multicenter, event-driven trial (Figure 2). Approximately 13,000 subjects are being randomized at 890 sites in 36 countries within 30 days of hospitalization with an ACS, including unstable angina, non-ST-elevation myocardial infarction (MI) and ST-elevation MI (Table 1), to once daily oral darapladib (160 mg enteric-coated tablet) or matching placebo. All subjects are required to have at least 1

Figure 2



Study design of the SOLID-TIMI 52 trial. EC, Enteric coated.

additional predictor of CV risk (Table II). The inclusion and exclusion criteria are outlined in Tables I, II, and III. The median treatment duration is anticipated to be approximately 3 years, with a total study duration of approximately 4.1 years.

The SOLID-TIMI 52 trial is being conducted in parallel to the STABILITY trial. The 2 trials are designed to be complementary and cover the spectrum of CHD. In the SOLID-TIMI 52 trial, subjects are randomized within 30 days of ACS, whereas subjects with stable CHD in the STABILITY trial are randomized more than 1 month after ACS. The STABILITY trial completed enrollment in April 2010, and the trial is expected to conclude before the completion of the SOLID-TIMI 52 trial. The projected median treatment duration for both trials is approximately 2.75 to 3 years. However, because these are event-driven trials, the precise duration of follow-up is not known at this time. Study objectives, primary and secondary end points, and end point definitions are consistent between both trials.

Study objective. The primary objective of the SOLID-TIMI 52 trial is to evaluate the clinical efficacy of long-term treatment with darapladib as compared with placebo when added to the standard of care in patients after an ACS.

Study assessments. While on treatment, subjects are evaluated in clinic at months 1, 3, and 6 and every 6 months thereafter. An interim telephone call is conducted at month 9 and every 6 months thereafter to assess for end points, adverse events, concomitant medications, and study drug compliance between clinic visits. Thus, end points are ascertained during clinic visits or by telephone at least every 3 months during the trial. Clinical laboratory tests for safety are conducted at baseline and at all regularly scheduled clinic visits while on

treatment, except at month 1. Lp-PLA₂ activity and serum and plasma biomarker samples are to be collected at baseline and prespecified time points during follow-up.

Concomitant medications. It is recommended that subjects enrolled in the SOLID-TIMI 52 trial be treated according to the existing guidelines for patients after ACS.^{19,20} The background use of evidence-based medications including statins, antiplatelet drugs, and β-blockers is closely monitored throughout the course of the trial. The National Lead Investigators receive quarterly performance reports that document trial adherence to recommended therapies and treatment goals both for their country and their respective sites. Sites receive site-specific copies of these reports on a biannual basis. The National Lead Investigator communicates with the sites with a consistent pattern of poor adherence.

Study end points and definitions. An independent clinical end point committee (CEC) is adjudicating all investigator-reported cases of MI, hospitalization for unstable angina, urgent coronary revascularization, stroke, and hospitalizations for heart failure. In addition, the CEC is adjudicating causes of death. The CEC members are blinded to treatment assignment. Using the prespecified event definitions and agreed-upon event adjudication criteria, the CEC adjudicates each suspected event based on the preponderance of the evidence and the clinical knowledge and experience of the physician reviewers. If consensus cannot be reached between 2 reviewers, the case will be presented for review by one additional reviewer to establish a final adjudication. Relevant source documents are included for review by the CEC for all adjudicated end points.

Table I. Inclusion criteria

1. Signed written informed consent form before beginning the study-related procedures
2. Male or female aged at least 18 y, inclusive, at randomization. Female subjects must be postmenopausal or using a highly effective method for avoidance of pregnancy
3. Hospitalization for ACS (unstable angina, non-ST-segment elevation MI, or ST-segment elevation MI) ≤ 30 d before randomization
 - a. *Unstable angina* is defined as ischemic chest discomfort (or equivalent) that occurs at rest with at least 1 episode lasting ≥ 10 minutes and is accompanied by new or presumably new ST-segment deviation (transient [< 20 min] elevation ≥ 0.1 mV or dynamic horizontal/down-sloping depression ≥ 0.05 mV) in at least 2 contiguous leads without diagnostic biochemical changes in cardiac enzymes (serum troponin I or T, or creatine kinase-MB).
 - b. *Non-ST-segment elevation MI* is defined as ischemic chest discomfort (or equivalent) that occurs at rest with at least 1 episode lasting ≥ 10 minutes and is accompanied by a diagnostic elevation in cardiac biomarkers of myocardial injury (serum troponin I or T, or creatine kinase-MB) above the upper limit of normal without persistent ST-segment elevation.
 - c. *ST-segment elevation MI* is defined as prolonged symptoms of ischemic chest discomfort (or equivalent) at rest (with at least 1 episode lasting > 20 min) and new or presumably new electrocardiographic changes (persistent ST-segment elevation ≥ 0.1 mV in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads or new LBBB) that are accompanied by a diagnostic elevation in cardiac biomarkers (serum troponin I or T, creatine kinase, or creatine kinase-MB) above the upper limit of normal.
4. The subject must be clinically stable for 24 h before randomization.
5. For subjects in whom a percutaneous coronary intervention (PCI) is planned as part of management for the qualifying ACS event, the subjects should undergo PCI before randomization whenever possible.

LBBB, Left bundle branch block.

Table II. Additional predictors of CV risk

- All subjects must also have at least 1 of the following high-risk predictors:
- a. Age ≥ 60 y at randomization
 - b. History of documented MI before qualifying ACS event
 - c. Diabetes mellitus requiring pharmacotherapy
 - d. *Significant renal dysfunction* (defined as estimated glomerular filtration rate ≥ 30 and ≤ 59 mL/min per 1.73 m²), according to Modification of Diet in Renal Disease Study equation
 - e. Polyvascular disease manifested in this population with ACS as coexistent clinically diagnosed arterial disease in at least 1 peripheral arterial territory, defined as
 - cerebrovascular disease defined as carotid artery disease* or as prior ischemic stroke[†] that occurred > 3 mo before randomization, or
 - peripheral arterial disease[‡]

* Carotid disease is defined as unilateral or bilateral carotid stenosis $> 60\%$ or history of carotid surgery or stenting.

† Prior ischemic stroke is defined as documented focal neurologic deficit thought to be of vascular origin, with signs or symptoms lasting > 24 hours. It is strongly recommended that neuroimaging, such as computed tomography scan or magnetic resonance imaging be performed to confirm diagnosis. In the absence of neuroimaging, additional functional deficit must be documented by abnormalities in the modified Rankin score.

‡ Peripheral arterial disease is documented by one of the following: current intermittent claudication with objective evidence of vascular origin, history of peripheral arterial stenting or surgery (including amputation due to vascular causes), or ankle-brachial index < 0.9 in at least 1 ankle.

The primary end point of the SOLID-TIMI 52 trial is the composite of CV death, nonfatal MI, and nonfatal stroke. *Cardiovascular death* is defined as death due to documented CV

Table III. Exclusion criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Clinical or laboratory manifestations of ACS that is not believed to be thrombotic in origin or is believed to be secondary to other apparent illness
2. Absence of obstructive CAD (ie, at least 1 stenosis [$> 50\%$] in a major vessel, major branch, or bypass graft) based on angiography, if performed, between the time of presentation with ACS and randomization
3. Planned coronary artery bypass graft (CABG) surgery or CABG surgery performed after the qualifying event and before randomization
4. Cirrhosis, known biliary abnormalities (with the exception of Gilbert syndrome or asymptomatic gallstones), unstable liver disease, or evidence of abnormal liver function tests (total bilirubin or alkaline phosphatase $> 1.5 \times$ upper limit of normal [ULN], or alanine aminotransferase $> 2.5 \times$ ULN) or other hepatic abnormalities that, in the opinion of the investigator, would preclude the subject from participation in the study
5. Severe renal impairment (eg, patients with an estimated glomerular filtration rate < 30 mL/min per 1.73 m² or receiving chronic dialysis) or history of nephrectomy or kidney transplant (regardless of renal function)
6. Current severe heart failure (New York Heart Association class III or IV)
7. Poorly controlled hypertension despite lifestyle modifications and pharmacotherapy
8. Any life-threatening condition with life expectancy < 2 y, other than vascular disease, that might prevent the subject from completing the study
9. Severe asthma that is poorly controlled on pharmacotherapy
10. Positive pregnancy test (all female subjects of childbearing potential must have a urine or serum β -human chorionic gonadotropin pregnancy test performed within 7 d before randomization) or is known to be pregnant or lactating
11. History of anaphylaxis, anaphylactoid (resembling anaphylaxis) reactions, or severe allergic responses
12. Alcohol or drug abuse within the past 6 mo. Current mental condition (psychiatric disorder, senility, or dementia), which may affect study compliance or prevent understanding of the aims, investigational procedures, or possible consequences of the study
13. Current or planned chronic administration of strong oral or injectable CYP isoenzyme 3A4 (CYP3A4) inhibitors
14. Subjects with 2 known birth parents of at least 50% Japanese, Chinese, or Korean ancestry (or if unknown, a reasonable likelihood of such ancestry) must have a blood sample collected for assessment of Lp-PLA₂ activity by the central laboratory before randomization. Those with Lp-PLA₂ activity ≤ 20.0 nmol/min/mL will be excluded from participation in the study.*
15. Previous exposure to darapladib (SB-480848)
16. Use of another investigational product within 30 d or 5 half-lives (whichever is the longer) preceding the first dose of darapladib or matching placebo
17. Currently in a study of an investigational device
18. Any other reason the investigator deems the subject to be unsuitable for the study

* Subjects homozygous for the 279F variant have no circulating levels of Lp-PLA₂ and would not be expected to benefit from Lp-PLA₂-lowering therapy. This allele is most common in those of Japanese, Chinese, and Korean ancestry.

causes, which include but are not limited to deaths resulting from arrhythmia, sudden death (witnessed or unwitnessed), MI, heart failure, stroke, pulmonary embolism, peripheral arterial disease, or complications of a CV procedure. In addition, deaths not clearly attributable to non-CV causes will be considered CV deaths.

Table IV. The end point definition for MI in the SOLID-TIMI 52 trial

Part 1. Acute MI: evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Any one of the following criteria meets the diagnosis for MI

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of a normal reference population (URL) together with evidence of myocardial ischemia with at least 1 of the following (note: the MI decision limit or upper limit of normal can be used if 99th percentile is unavailable):
 - Symptoms of ischemia
 - ECG changes indicative of new ischemia
 - Development of pathological Q waves in ECG
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy
- For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural necrosis. By convention, increases of biomarkers greater than $3 \times 99^{\text{th}}$ URL have been designated as defining PCI-related MI.
- For CABG surgery in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than $5 \times 99^{\text{th}}$ percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.
- Pathological findings of an acute MI.

Part 2. Prior MI (ie, silent MI diagnosed postrandomization): any one of the following criteria meets the diagnosis for prior MI

- Development of new pathological Q waves with or without symptoms
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a nonischemic cause (pre-event imaging data required for verification of new abnormalities)
- Pathological findings of a healed or healing MI.

ECG, Echocardiogram; LBBB, left bundle branch block; CABG, coronary artery bypass graft.

The definition of *MI* is adapted from the Universal Definition of MI (Table IV).^{18,21} *Stroke* is defined as the presence of a new focal neurologic deficit thought to be of vascular origin, with signs or symptoms lasting >24 hours, or resulting in death. If neurologic symptoms last <24 hours, new brain infarction has to be confirmed by neuroimaging showing the presence of a new brain infarct. Complete details regarding all end point definitions are outlined in a separate CEC charter. Coronary revascularization, a secondary end point, that is planned before randomization will not be included in the end point definition for coronary revascularization.

Secondary end points.

- The composite of major coronary events, including CHD death, nonfatal MI, or urgent coronary revascularization for myocardial ischemia
- The composite of total coronary events, including CHD death, nonfatal MI, hospitalization for unstable angina, or coronary revascularization

- The individual components of the primary end point, including CV death, MI (fatal and nonfatal), or stroke (fatal and nonfatal)
- The composite of all-cause mortality, nonfatal MI, or nonfatal stroke
- All-cause mortality

Other end points.

- All major adverse CV events (first and recurrent CV events, including CV death, nonfatal MI, or nonfatal stroke)
- Urgent coronary revascularization for myocardial ischemia
- Coronary revascularization procedures (excluding events planned before randomization)
- Heart failure requiring hospitalization
- The composite of total vascular events, including CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, hospitalization for noncoronary ischemic event (eg, transient ischemic attack or limb ischemia), any revascularization procedure (coronary or noncoronary), or limb amputation due to vascular causes
- The composite of total coronary events including CHD death, nonfatal MI, hospitalization for unstable angina, or any coronary revascularization procedure (excluding target lesion revascularization)
 - New-onset diabetes mellitus
 - Chronic inhibition of plasma Lp-PLA₂ activity
 - Health care resources utilization (ie, hospitalization and major procedures)

Efficacy and safety assessments. The darapladib phase 3 program is reviewed by a single Independent Data Monitoring Committee (IDMC) for both the STABILITY and SOLID-TIMI 52 studies. The IDMC is reviewing unblinded safety data throughout the trials and has the ability to recommend stopping either trial for safety at any time (online Appendix A). These safety data include CV events, serious adverse events, and changes in clinical laboratory values. Four safety reviews have thus far been conducted (October 2009 [STABILITY only], April 2010, October 2010, April 2011) with recommendations to continue the studies as planned without modification. In addition, 2 interim analyses will be performed in the future after approximately 850 and 1,150 first occurrence of primary end point events to assess for overwhelming efficacy and potential futility.

Current status. Between December 7, 2009, and June 23, 2011, a total of 10,696 subjects have been enrolled at 861 sites in 36 countries. Study enrollment is anticipated to conclude ahead of the original projected timeline of 24 months. The median duration of follow-up is 168 days. The current rate of event accumulation is consistent with protocol projections, as specified below.

Statistical considerations

Sample size and event number assumptions. The SOLID-TIMI 52 study is an event-driven trial and designed to have 90% power to detect a 15.5% reduction in the risk of CV death, nonfatal MI, or nonfatal stroke (hazard ratio 0.845) for subjects treated with darapladib compared with placebo on a background of standard care. Assuming a placebo event rate of approximately 7.5% for the first year and 3.5% per year thereafter, with an overall type I error rate (α level) of 5%, a total of 1,500 primary efficacy events are required to achieve approximately 90% power.

Sample size considerations during protocol design accounted for 2 sources of subject withdrawal. Subjects lost to follow-up, presumed to occur with an annual rate of 1%, will be censored at the time of withdrawal. Subjects who permanently discontinue the study drug, presumed to occur at an annual rate of 8%, will be followed for study end points until study conclusion. The projected rates of study drug discontinuation and subjects lost to follow-up were based on historic data from past ACS trials. By further assuming an on-therapy hazard ratio of 0.83 and a posttherapy hazard ratio of 1.0, the hazard ratio of 0.845 was arrived at under a study duration assumption based on enrolling 11,500 subjects.

In April 2011, the academic leadership at the TIMI Study Group and the SOLID-TIMI 52 Executive Steering Committee in conjunction with the sponsor agreed to increase the sample size from 11,500 to 13,000. Study enrollment is still anticipated to conclude before the end of the original 24-month enrollment period. Because enrollment in the trial has been more curvilinear than linear, the expansion in sample size will allow for more rapid accumulation of events, since the event rate is anticipated to be higher for subjects during the first year after ACS. Therefore, the increase in sample size increases the likelihood that the trial will conclude at the calendar time initially planned without shortening the originally planned median follow-up time. The decision to expand the sample size was independent of the IDMC.

If the discontinuation rate is higher than projected, an increase in the target number of primary end point events may also be considered to maintain a prespecified power.

Statistical and analytical plans. Efficacy analyses will be conducted on the intention-to-treat study population consisting of all randomized subjects. Safety analyses will be conducted on those subjects who received at least 1 dose of study drug.

Multiplicity will be addressed by applying a hierarchical approach toward the evaluation of key end points of special interest. A flexible alpha-spending function will be applied to account for interim efficacy assessments made by the IDMC, and the final alpha for the trial will be adjusted accordingly. If the 2 interim analyses are conducted as planned, the primary end point will be assessed at a threshold of significance of $P < .0499$ at study conclusion. If the primary end point of CV death, nonfatal MI, or nonfatal stroke is statistically significant, the following end points will be tested in a hierarchical sequence: MI (fatal and nonfatal), coronary revascularization, CV death, and all-cause mortality.

Covariates and subgroups of interest will include but are not limited to the type of qualifying event (unstable angina, non-ST-elevation MI, ST-elevation MI), presence of elevated cardiac biomarkers (troponin or creatine kinase-MB), and cardiac catheterization or percutaneous coronary intervention for the qualifying event. Individual predictors of CV risk will be examined, in addition to baseline levels of LDL, Lp-PLA₂ activity, and background use of concomitant therapies including statins.

If there is homogeneity between the final results of the SOLID-TIMI 52 and STABILITY trials, then the databases will be combined to pursue prespecified analyses that include data from both trials.

A Cox proportional hazards regression model will be used to assess the effect of treatment on the primary end point and time-to-event outcomes. If the validity of the proportional

hazards assumption is not acceptable, the treatment effect will be assessed using the log-rank test. Cumulative event rates will be calculated using the Kaplan-Meier method. All CIs will be 2-sided, with a 95% confidence level.

Planned substudies

Biomarkers. Serum and plasma samples for biomarker assessments are being obtained at baseline and at prespecified time points during follow-up. These assessments may include high-sensitivity troponin, high-sensitivity C-reactive protein, interleukin-6, and natriuretic peptides. Other circulating biomarkers associated with atherosclerosis, coagulation, or related disease progression may be analyzed.

Genetics. A sample of whole blood is being collected at baseline in all subjects who provide informed consent to participate in the genetics portion of the study. The primary intent of the genetics study is to examine the relationship between genetic variants and the efficacy, safety, or tolerability of darapladib, as well as the relationship between genetic variants and CV disease. Additional analyses may be conducted.

Pharmacokinetic and pharmacodynamic substudy. In approximately 5% to 7% of enrolled subjects, the pharmacokinetics of darapladib and the pharmacokinetics-pharmacodynamic relationship between plasma concentration and Lp-PLA₂ activity in the study population is being assessed.

Health economic outcomes are also being assessed.

Study organization. The SOLID-TIMI 52 trial is coordinated by the TIMI Study Group and is sponsored by GlaxoSmithKline Pharmaceuticals. The TIMI Study Group provides site management services in North America. PPD acts as the contract research organization and provides site management services outside North America and site monitoring. The TIMI Study Group and academic members of the Executive Steering Committee designed the protocol of the SOLID-TIMI 52 trial in collaboration with the trial sponsor. The Executive and Steering Committees include academic members and sponsor representatives, overseeing medical, scientific, and operational conduct of the study.

The trial database is stored at GlaxoSmithKline and is protected by internal firewalls. The randomization code is stored separately from the trial database and the study team. The TIMI Study Group, an academic research organization within the Brigham and Women's Hospital (Boston, MA), will have full access to the complete database once the study is completed and will independently confirm key analyses including the primary efficacy analysis.

No extramural funding was used to support this work. The authors are solely responsible for the drafting and editing of the paper and its final contents. The SOLID-TIMI 52 trial adheres fully to the ethical principles of the Declaration of Helsinki, the specifications of the International Conference on Harmonization, and Good Clinical Practice, including approval by an independent ethics committee or institutional review board and the requirement for each patient's written informed consent.

Summary

The SOLID-TIMI 52 study is a phase 3, randomized, double-blind, international clinical trial to assess the efficacy and safety of darapladib as compared with placebo

in patients after an ACS. The study is being conducted in parallel with the STABILITY trial, a phase III trial of darapladib in patients with chronic CHD.¹⁸ Together, these trials will determine whether direct inhibition of Lp-PLA₂ activity with darapladib in patients receiving guideline-directed medical therapy leads to improved clinical outcomes in patients with ACS or chronic CHD. The results of these trials may provide valuable insights into the underlying pathobiology of atherothrombotic events and plaque rupture.

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Appendix A

Executive Committee

Chairperson:

Eugene Braunwald, MD TIMI Study Group, Brigham and Women's Hospital, Boston, MA

Members:

Christopher P. Cannon, MD TIMI Study Group, Brigham and Women's Hospital, Boston, MA

Ph. Gabriel Steg, MD Hopital Bichat-Claude Bernard, Paris, France

Christoph Bode, MD Medizinische Universitätsklinik, Freiburg, Germany

Aldo Maggioni, MD ANMCO Research Center, Firenze, Italy

Judith Hochman, MD New York University School of Medicine, New York, NY

Douglas Weaver, MD Henry Ford Heart and Vascular Institute, Detroit, MI

Patrick Serruys, MD Thoraxcenter-Erasmus University, Rotterdam, The Netherlands

Harvey D. White, MD Green Lane CV Service, Auckland City Hospital, Auckland, New Zealand

Members of the Independent Data Monitoring Committee

Chairperson:

Rory Collins, FRCP, FMedSci CTSU, Oxford, UK

Members:

Jeffrey Anderson, MD Intermountain Medical Center, Murray UT

Peter Ganz, MD University of California, San Francisco, CA

Peter Sandercock, DM, FRCPE Western General Hospital, Edinburgh, Scotland

Michael Weber, MD Downstate College of Medicine, Brooklyn, NY

David DeMets, PhD University of Wisconsin, Madison, WI

Clinical Events Committee

Chairperson:

Stephen D. Wiviott, MD TIMI Study Group, Brigham and Women's Hospital, Boston, MA

Steering Committee and National Lead Investigators

National lead investigators: Ernesto Paolasso (Argentina), Philip Aylward (Australia), William Wijns (Belgium), Jose C. Nicolau (Brazil), Assen Goudev (Bulgaria), Pierre Theroux (Canada), G.B. John Mancini (Canada), Ramon Corbalan (Chile), Runlin Gao (China), Daniel Isaza (Colombia), Jindrich Spinar (Czech Republic), Peer Grande (Denmark), Gilles Montalescot (France), Christian Hamm (Germany), Robert Kiss (Hungary), Bhoopathira Somaraju (India), Sanjay Mittal (India), Krishna Reddy (India), Atul Mathur (India), Basil Lewis (Israel), Diego Ardissino (Italy), Takeshi Kimura (Japan), Ki-Bae

Seung (Korea), Robbert J. deWinter (Netherlands), Ton Oude Ophuis (Netherlands), Harvey White (New Zealand), Frank Britto (Peru), Noe Babilonia (Philippines), Andrzej Budaj (Poland), Maria Dorobantu (Romania), Nikolay Gratsiansky (Russia), Tibor Duris (Slovakia), Anthony Dalby (South Africa), Jose Lopez-Sendom (Spain), Mikael Dellborg (Sweden), Shih-Ann Chen (Taiwan), Piyamitr Sritara (Thailand), Sema Guneri (Turkey), Kausik Ray (United Kingdom), Alexander Parkhomenko (Ukraine), Christopher P. Cannon (United States). Other steering committee members: Juri Voitek (Estonia), Terje Pederson (Norway), John Lekakis (Greece), and Guillermo Llamas Esperon (Mexico).

Appendix B

Countries participating in SOLID-TIMI 52

Countries

Canada
United States
Belgium
Denmark
France
Germany
Israel
Italy
The Netherlands
South Africa
Spain
Sweden
Turkey
United Kingdom
Bulgaria
Czech Republic
Hungary
Poland
Romania
Russia
Slovakia
Ukraine
Argentina
Brazil
Chile
Colombia
Peru
Australia
China
India
Japan
Korea
New Zealand
Philippines
Taiwan
Thailand