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

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Background  Reduction in low-density lipoprotein cholesterol (LDL-C) improves clinical outcomes in patients with chronic coronary artery disease and acute coronary syndromes (ACSs). The combination of ezetimibe/simvastatin produces greater reductions in LDL-C compared to simvastatin monotherapy. The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is a multicenter, randomized, double-blind, active-control trial designed to test the hypothesis that the addition of ezetimibe to statin therapy, using ezetimibe/simvastatin, will translate into increased clinical benefit on cardiovascular outcomes relative to simvastatin monotherapy in patients with ACS.

Study Design  The study will recruit up to 18,000 moderate- to high-risk patients stabilized after ACS. Patients are randomized in a 1:1 ratio to once-daily doses of either ezetimibe/simvastatin 10/40 mg or simvastatin monotherapy 40 mg. Follow-up visits are at 1 and 4 months, and every 4 months thereafter. If consecutive measures of LDL-C are >79 mg/dL at follow-up visits, the simvastatin dose will be increased to 80 mg in a double-blind manner. The primary end point is the first occurrence of cardiovascular death, nonfatal myocardial infarction, rehospitalization for unstable angina, coronary revascularization (occurring at least 30 days after randomization), or stroke. Patients will be followed for a minimum of 2.5 years and until at least 5,250 patients experience a primary end point.

Summary  IMPROVE-IT will determine whether the addition of ezetimibe to statin therapy, using ezetimibe/simvastatin, improves cardiovascular outcomes compared with simvastatin monotherapy in patients after ACS. In addition, the difference in achieved LDL-C levels between the groups will provide data on whether the target for LDL-C lowering should be reduced further.

Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for coronary heart disease (CHD). The effectiveness of lipid-lowering therapy in reducing the risk of coronary events in patients with and without CHD is firmly established with trials using 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) as well as nonstatin approaches to reduce cholesterol such as diet, cholestyramine, and ileal bypass surgery, showing significant reductions in the risk of coronary mortality and morbidity.

The Heart Protection Study found a significant reduction in clinical events regardless of the baseline LDL-C, leading many to believe that “lower is better,” whereby a lower achieved LDL-C results in more favorable clinical outcomes. The hypothesis that more intensive lowering of LDL-C would lead to greater clinical benefit has been tested in 4 completed and other ongoing outcomes trials. A meta-analysis found that intensive statin therapy led to a significant 16% odds reduction in coronary death or myocardial infarction (P = .00003), as well as a significant 16% odds reduction of coronary death or any cardiovascular (CV) event (P < .0001). In recognition of the benefits of intensive statin therapy, the National
Cholesterol Education Program published an update document, suggesting a lower optional therapeutic goal for LDL-C in high-risk patients. However, despite significant reductions in risk with statin therapy, most events are actually not prevented, leaving a substantial "residual risk" for patients and thus additional pharmacologic therapies for the prevention of CHD remains essential, particularly for high-risk patients with acute coronary syndrome (ACS).

Ezetimibe is the first member of a class of agents that inhibits the absorption of cholesterol from the intestine by blocking the Niemann-Pick C1 Like 1 receptor. It reduces absorption of both dietary and biliary cholesterol by 54% to 65%. The combination of ezetimibe and statins produces inhibition of both cholesterol synthesis and intestinal cholesterol absorption, resulting in approximately 18% greater reduction of LDL-C, versus statin alone, allowing a greater proportion of patients to reach their National Cholesterol Education Program goal.

Ezetimibe also significantly reduces c-reactive protein (CRP) when added to statins. In one study, these reductions did not translate into a difference in carotid intima media thickness in patients with familial hypercholesterolemia. Whether the additional LDL-C lowering achieved with the addition of ezetimibe to statin therapy will lead to clinical benefit is currently not known.

Study design and objectives

The IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is a randomized, double-blind, active-control, multicenter, clinical trial designed to examine whether the use of the combination of ezetimibe and simvastatin, with its greater reductions in LDL-C, translates into clinical benefit on CV outcomes compared with simvastatin monotherapy in up to 18,000 patients stabilized after an ACS. We hypothesize that ezetimibe/simvastatin will reduce the incidence of the composite end point of CV death, nonfatal myocardial infarction (MI), rehospitalization for unstable angina, coronary revascularization (occurring at least 30 days after randomization) or stroke over at least 2.5 years of follow-up relative to simvastatin monotherapy (Figure 1).

Study population

The trial is enrolling men and women who have been hospitalized for ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA) within the previous 10 days. To be eligible, patients must have high-risk features (see below), meet lipid criteria, and be stabilized for at least 24 hours before randomization. Patients with STEMI must have electrocardiographic changes (persistent ST segment elevation ≥0.1 mV, new Q waves, or new left bundle-branch block), elevated troponin or creatine kinase (CK)–MB, and have either an anterior infarction or be at least 50 years of age.

Patients presenting with UA/NSTEMI must have ischemic discomfort at rest lasting at least 10 minutes, age ≥50 years, and have at least one of the following high-risk features: new ST-segment deviation of at least 1 mV, elevated troponin or CK-MB, diabetes mellitus, a history of prior MI, peripheral arterial disease or cerebrovascular disease, have undergone coronary artery bypass grafting (CABG) at least 3 years earlier, or have known multivessel disease with at least 2 major coronary arteries with stenosis of >50%. Patients enrolled in the Early glycoprotein IIb/IIIa inhibition in non-ST-segment elevation acute coronary syndrome (EARY-ACS) study, a study of early eptifibatide versus placebo in patients with high-risk UA/NSTEMI, can be considered for enrollment after completion of the primary end point assessment (96 hours after randomization) but within the first 10 days after presentation provided they also meet the IMPROVE-IT enrollment criteria.

In addition, an LDL-C measured within 24 hours of hospital admission for the ACS event must be ≥50 and ≤125 mg/dL (1.3–3.2 mmol/L) for patients not receiving chronic lipid-lowering therapy and ≥50 and ≤100 mg/dL (1.3–2.6 mmol/L) for patients receiving chronic statin therapy. For patients without an LDL-C measured in the first 24 hours, an LDL-C documented in the medical record within the prior 6 months may be used to qualify for the study. Subjects must have a fasting plasma triglyceride level ≤350 mg/dL (≤4 mmol/L).

Major exclusion criteria include the presence within 24 hours before enrollment of (1) hemodynamic events (hypotension, pulmonary edema/congestive heart failure, acute mitral regurgitation, acute ventricular septal...
defect); (2) ischemic events (stroke, recurrent symptoms of cardiac ischemia); and (3) arrhythmic events (ventricular fibrillation, sustained ventricular tachycardia, complete heart block, high-grade second-degree heart block). Patients in whom CABG is planned as treatment of their ACS event are excluded. Patients receiving ongoing treatment with cyclosporine, diltiazem, danazol, amiodarone, verapamil, niacin, fribates as concomitant medications, or any of the potent CYP3A4 inhibitors (itraconazole, ketoconazole, erythromycin, clarithromycin and telithromycin, HIV protease inhibitors, and nefazodone) are excluded from the study. Short-term therapy with antifungal medications or macrolide antibiotics is acceptable, provided that study medication is interrupted during the administration and resumed after the completion of short-term therapy. Other exclusion criteria include pregnancy or the intention to become pregnant; active liver disease or persistent unexplained serum transaminase elevations ($geq 2\times$ upper limit of normal [ULN]); history of alcohol or drug abuse; allergy/sensitivity to any statin, ezetimibe, or their excipients; and use of statin therapy with LDL-C lowering potency greater than simvastatin 40 mg. Patients are also excluded if the discontinuation of an existing lipid-lowering regimen poses a health risk. All study sites must have access to catheterization or other invasive procedures to ensure that all subjects are provided a similar standard of care. It is strongly recommended that each high-risk UA/NSTEMI patient undergo a cardiac catheterization before enrollment.

**Randomization and treatment protocol**

Participants are to be recruited at approximately 1,200 sites worldwide, including $geq 400$ within North America. During screening visits, informed consent is obtained and baseline medical history, examination, and laboratory testing are performed. Subjects entered into the study receive randomized, double-blind treatment assignment in a 1:1 ratio to either ezetimibe/simvastatin 10/40 mg or simvastatin 40 mg once daily. Randomized treatment assignment is stratified by 3 factors: (1) the randomized treatment assignment (epitifibatide or placebo) for patients who enter the current study from the EARLY-ACS trial; (2) prior statin use; (3) STEMI versus UA/NSTEMI. Study drug is administered once daily in the evening. After randomization, follow-up visits occur at the end of 1 and 4 months, and every 4 months thereafter. The protocol was reviewed and approved by each participating site’s ethics committee.

Subjects found to have LDL-C elevated to $>79$ mg/dL at scheduled visits are called back for repeat blood work. If the subject’s LDL-C is elevated $>79$ mg/dL on 2 consecutive draws, the simvastatin dose is increased to 80 mg (in either arm) in a double-blind manner at the next regularly scheduled visit.

Monitoring for safety includes blood testing every 4 months for liver function tests for the first 16 months and yearly thereafter. Subjects with elevated alanine aminotransferase and/or aspartate aminotransferase levels $geq 3$ times the upper limit of normal (confirmed on repeat blood work 1 week after the initial observation) have study drug interrupted until the transaminase activity decreases to $<2\times$ ULN, at which time administration of the study drug is resumed at the discretion of the investigator.

Muscle side effects are monitored using the approach suggested in the American College of Cardiology/American Heart Association/National Heart Lung and Blood Institute recommendations, which state: “Routine laboratory monitoring of CK is of little value in the absence of clinical signs or symptoms. Therefore, all persons beginning to receive statins should be instructed to report muscle discomfort or weakness or brown urine immediately, which should then prompt a CK measurement.” The Aggrastat to Zocor (A to Z) trial also observed that receipt of prohibited medications was associated with many of the cases of rhabdomyolysis. Accordingly, at each visit, patients are asked if they have experienced any unusual muscle symptoms or are taking any contraindicated medications that might increase the chance of muscle side effects. If patients report unusual muscle symptoms, or if their dose of simvastatin is increased to 80 mg, CK is measured. Patients with CK levels $geq 5\times$ ULN and muscle symptoms consistent with myopathy will have study medication interrupted (permanently if CK $>10\times$ ULN) and CK levels measured 1 week later. The CK level will be repeated until it decreases to $<2\times$ ULN. Study drug can be resumed (at the starting dose) at that time or if the original CK elevation was clearly not attributable to study drug.

All subjects, including those who discontinue study medication, are followed for any clinical end point event until the termination of the study. The study will continue until each patient has been followed for a minimum of 2.5 years after enrollment and the target number of events (5,250) is reached.

Mechanistic analyses done within the protocol will include blood samples obtained at baseline and during the study to evaluate inflammatory and other cardiac biomarkers, a proteomics evaluation, and a genetic substudy. During the trial, 3 amendments were introduced. The first clarified language surrounding inclusion/exclusion criteria and specifically noted that patients in whom CABG for management after the index ACS event are excluded. Also, patients with a calculated creatinine clearance of $<30$ mL/min were excluded. Amendment 2 capped the enrollment of STEMI patients. This cohort
had been planned to be approximately one third of the trial, but in the initial phase of the trial accounted for nearly half the patients. In addition, there was concern that STEMI patients would have less extensive CAD, with lower risk for long-term events, and thus might limit the ability reach the target number of events. The final component of the amendment 2 and the main purpose of amendment 3 provided reestimation of the sample size (see below).

End points
The primary efficacy end point is the time from randomization until the first occurrence of one of the following: CV death, major coronary events (nonfatal MI, documented unstable angina requiring hospital admission, all coronary revascularization with either percutaneous coronary intervention [PCI] or CAGB occurring at least 30 days after randomization), or nonfatal stroke.

The secondary efficacy end-point measures are time from randomization until the first occurrence of (1) death due to any cause, major coronary event, or nonfatal stroke; (2) CHD death, nonfatal MI, or urgent coronary revascularization with either PCI or CAGB occurring at least 30 days after randomization; (3) CV death, nonfatal MI, documented unstable angina requiring hospital admission, all revascularization (including noncoronary) occurring at least 30 days after randomization, and nonfatal stroke.

The tertiary efficacy end-point measures include other composite end points, CHF that requires hospitalization occurring at least 30 days after randomization, and the percentage of patients who achieve a “dual goal” of an achieved LDL-C <70 mg/dL and CRP <2.0 mg/L after 1 and 4 months of treatment with ezetimibe/simvastatin or simvastatin. Correlations of achievement of the dual goal (LDL-C <70 mg/dL and CRP <2.0 mg/L) with clinical outcomes will also be carried out.

Safety variables include safety laboratory tests (including liver function tests and CK levels), physical examinations, assessment of adverse events, and clinic assessments.

Statistical design and analysis
The trial was designed based on information available as of spring 2005. An initial sample size of 10,000 patients was selected to afford 90% power to detect a 10% relative risk reduction in the primary end point at a significance level of .05. The trial is an event-driven trial and originally was planned to continue until a minimum of 2,955 primary end point events had occurred and each patient completed a minimum 2.5 years of study exposure. The sample size was based on anticipated event rates at 2 years of 23.5% in the control arm (simvastatin 40 mg).

The publication of meta-analyses from the CTT and another of the 4 intensive versus standard-dose statin trials prompted review by the trial leadership of the statistical assumptions surrounding the relationship between LDL-C lowering and the expected reduction in clinical events. After careful deliberation, 2 changes in the assumptions were made. First, the relationship between LDL-C reduction and clinical benefit was felt to be best estimated as a 1.6-mg/dL LDL-C change translating into a 1% clinical benefit. Accordingly, the expected 15-mg/dL difference in LDL-C between the 2 groups would translate into a 9.375% hazard reduction. In addition, based on information from CTT, “discounting” the relative treatment effect in the first 6 months was felt to be reasonable. With these assumptions, it was determined and included in amendment 2 that a total of 5,250 clinical events would be required to have sufficient and appropriate power to detect a significant reduction in risk. An initial projection based on these numbers gave a sample size of 12,500 patients to reach the target number of primary end points; however, it was recognized that the ability to accrue these events in a timely fashion would depend heavily on the event rate observed during follow-up. Subsequent review of emerging (pooled and blinded) data from IMPROVE-IT, as well as of rates in prior studies in patients who would meet IMPROVE-IT eligibility criteria, found that a rate of 0.43% per month was a reasonable estimate. To complete the trial in as timely a fashion as possible, a larger sample size of up to 18,000 patients was included in amendment 3. However, because many factors will impact the ultimate number of patients needed to accrue the 5,250 events, it is planned that the data coordinating center, Duke Clinical Research Institute, would monitor event rates and model projections to refine the final sample size.

A second method to ensure that the trial will be able to achieve adequate power has been built into the trial. An independent lipid monitoring committee (LMC), separate from all other committees, will periodically review the achieved LDL-C results and metrics of study drug adherence (but not clinical outcome data). If the difference in median LDL-C between treatment groups is less than anticipated, the LMC may advise the executive committee that the number of subjects enrolled in the trial be increased and/or that the duration of monitoring be extended to capture more subjects reporting primary end points.

The primary hypothesis is that in stabilized high-risk patients with ACS, the administration of ezetimibe/simvastatin will reduce the incidence of the composite end point of CV death, major coronary events, and nonfatal stroke compared with simvastatin monotherapy. This hypothesis will be evaluated using a Cox proportional hazard model with covariates of treatment and stratification factors (early use of epifibatide, statin experience, and high-risk ACS diagnosis). Estimates of the
data within the trial and will conduct one interim efficacy analysis. The LMC is separate from other committees and is planned to review data twice during the study.

**Current status**

Recruitment began in October 2005. As of June 2008, there are >800 participating sites in 30 countries with study drug. Recruitment is ongoing and >11,000 patients have been enrolled. Baseline characteristics of the first 10,000 patients enrolled are shown in Table I.

**Context**

The IMPROVE-IT trial has become even more important since the release of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial results, which compared the effects of ezetimibe and high-dose simvastatin with high-dose simvastatin alone on carotid intima-media thickness (IMT) in patients with heterozygous familial hypercholesterolemia. At 2 years, there was no significant difference between the 2 arms with respect to the primary outcome, the mean change from baseline in the carotid IMT nor in any of the secondary IMT measures. There were also no significant differences in the incidence of clinical CV events or adverse events between the 2 groups.

It should be noted that the ENHANCE trial was conducted in a very different population than those in the IMPROVE-IT trial (patients with familial hypercholesterolemia with few preceding cardiac events in the IMPROVE-IT trial (patients with familial hypercholesterolemia with few preceding cardiac events in ENHANCE compared to patients immediately after ACS for IMPROVE-IT). Furthermore, its initial design manuscript specifically pointed out that it was not designed to impact clinical practice because an outcome trial would be needed for that purpose. As a carotid artery imaging study, it is vastly underpowered to determine treatment effects on clinical outcomes. ENHANCE had only 21 clinical end points (in 17 patients), whereas IMPROVE-IT trial is planned to have 5,250 primary end points to have sufficient power to evaluate clinical outcomes. Thus, no conclusions can be drawn from this very small number of events in ENHANCE.

Accordingly, we feel that the IMPROVE-IT trial is in true equipoise—that is, it is not known whether the lowering of LDL-C with ezetimibe, when added to simvastatin, will translate into a reduction in clinical events when compared to simvastatin alone. Of note, there is evidence that lowering LDL-C by 3 different ways (bile acid resins, ileal bypass surgery, or diet) does reduce the risk of coronary mortality and morbidity (and interestingly each of these acts in part to reduce cholesterol absorption and ultimately leads to LDL receptor up regulation in the liver.) The goal of the IMPROVE-IT trial is to evaluate the relationship of

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### Table I. Baseline characteristics of the first 10,000 patients enrolled

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median [interquartile range]) in years</td>
<td>62 (55, 70)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>77</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>22</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>17</td>
</tr>
<tr>
<td>Acute event</td>
<td></td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>47</td>
</tr>
<tr>
<td>NSTEMI (%)</td>
<td>37</td>
</tr>
<tr>
<td>UA (%)</td>
<td>16</td>
</tr>
<tr>
<td>Preenrollment coronary angiography</td>
<td>91</td>
</tr>
<tr>
<td>Preenrollment PCI after ACS event</td>
<td>76</td>
</tr>
<tr>
<td>Baseline LDL-C (median [interquartile range]) (mg/dL)</td>
<td>97 (81, 112)</td>
</tr>
<tr>
<td>No prior lipid-lowering therapy</td>
<td>104 (89, 116)</td>
</tr>
<tr>
<td>Prior lipid-lowering therapy</td>
<td>80 (68, 90)</td>
</tr>
</tbody>
</table>

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hazard ratios and associated 95% CIs comparing ezetimibe/simvastatin to simvastatin will be provided with the use of this model. The statistical analyses for the primary and secondary end points will include all patients who receive randomized treatment assignment. Because revascularization procedures occurring up to 30 days after randomization will not be included in the prespecified end points, the effect of these early events will be assessed by sensitivity analyses on the primary end point.

One interim efficacy analysis will be performed when approximately 50% of the expected total primary events are available. The primary analysis will be based on the adjudicated events. The O’Brien-Fleming methodology will be implemented to protect the overall type I error of 0.05 using the East 3 software. Specifically, it is expected that a nominal $\alpha$ level of .003 will be used for the interim analysis. For the final analysis, the primary end point will be tested at an expected nominal $\alpha$ level of .049. Details for the interim analyses are provided in the Data Safety Monitoring Board charter.

Descriptive statistics will be provided for safety data. All safety and efficacy data will include all patients who receive randomized treatment assignment.

**Study organization**

The executive committee is responsible for the overall design, conduct, and supervision of the study, including the development of any protocol amendments. It adjudicates policy among the various constituencies of the study and is responsible for reviewing the progress of the study at regular intervals to ensure patient safety and study integrity. The executive committee is composed of representatives from the TIMI Study Group (Boston, MA), Duke Clinical Research Institute (Durham, NC), and the sponsor (Merck/Schering Plough Pharmaceuticals, North Wales, PA) (see Appendix A). A clinical events committee reviews and adjudicates each suspected clinical end point event in a blinded fashion. An independent Data Safety Monitoring Board is monitoring the accumulating safety data within the trial and will conduct one interim efficacy analysis.
ezetimibe treatment to clinical events; answering this question is of critical importance because it could influence the treatment of many hundreds of thousands of patients.

References

28. Sniderman AD. Is there value in liver function test and creatine phosphokinase monitoring with statin use? Am J Cardiol 2004;94(Suppl 9A):30F-4F.
Appendix A

Executive Committee: Representatives from Thrombolysis in Myocardial Infarction (TIMI), Duke Clinical Research Institute (DCRI), and the sponsors.

TIMI Study Group, Brigham and Women’s Hospital, Boston, MA: Eugene Braunwald (Study Chairman), Christopher P. Cannon (Principal Investigator), Robert Giugliano (Co-Principal Investigator), Carolyn McCabe (Project Director), Amy McCagg (Project Manager).

Data Coordinating Center: Duke Clinical Research Institute, Durham NC: Robert M. Califf (Study Co-chairman), Robert A. Harrington, Michael A. Blazing, John L. Petersen, Craig Reist (Project Leader), Jennifer White (Statistician), Lisa Ezkenazi (Data Management), Cathy Martz (Site Management)

Data Safety Monitoring Board: Scott Grundy, (Chairman), Michel Bertrand, David DeMets, John Kjekshus, Bernard Gersh

Lipid Monitoring Committee: Michael Davidson, David Waters

Clinical Events Committee: Chairman—Stephen D. Wiviott

Steering Committee

National Lead Investigators: Enrique Gurfinkel (Argentina), Philip Aylward (Australia), Gerald Maurer (Austria), Frans Van de Werf (Belgium), Jose C. Nicolau (Brazil), Pierre Theroux (Canada), Ramon Corbalan (Chile), Daniel Isaza (Colombia), Jindrich Spinar (Czech Republic), Peer Grande (Denmark), Juri Voitk (Estonia), Antero Kesaniemi (Finland), Jean-Pierre Bassand (France), Harald Darius (Germany), Matyas Keltai (Hungary), Sanjay Mittal, Krishna Reddy, and Atul Mathur (India), Basil Lewis (Israel), Gaetano De Ferrari (Italy), Ton Oude Ophuis (Netherlands), Harvey White (New Zealand), Terje Pedersen (Norway), Frank Britto (Peru), Witold Ruzyllo (Poland), Manuel Carrageta (Portugal), Tibor Duris (Slovakia), Anthony Dalby (South Africa), Ki-Bae Seung (South Korea), Jose Lopez-Sendon (Spain), Mikael Dellborg (Sweden), Francois Mach (Switzerland), Sema Guneri (Turkey), Alexander Parkhomenko (Ukraine), Adrian Brady (United Kingdom), Christopher Cannon (United States), Robert Harrington (United States).
