

# Design of the DEFINE trial: Determining the Efficacy and Tolerability of CETP INhibition with AnacEtrapib

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**Background** Residual cardiovascular (CV) risk often remains high despite statin therapy to lower low-density lipoprotein cholesterol (LDL-C). New therapies to raise high-density lipoprotein cholesterol (HDL-C) are currently being investigated. Anacetrapib is a cholesteryl ester transfer protein (CETP) inhibitor that raises HDL-C and reduces LDL-C when administered alone or with a statin. Adverse effects on blood pressure, electrolytes, and aldosterone levels, seen with another drug in this class, have not been noted in studies of anacetrapib to date.

**Methods** Determining the Efficacy and Tolerability of CETP INhibition with AnacEtrapib (DEFINE) is a randomized, double-blind, placebo-controlled trial to assess the efficacy and safety profile of anacetrapib in patients with coronary heart disease (CHD) or CHD risk equivalents (clinical trials.gov NCT00685776). Eligible patients at National Cholesterol Education Program-Adult Treatment Panel III LDL-C treatment goal on a statin, with or without other lipid-modifying medications, are treated with anacetrapib, 100 mg, or placebo for 18 months, followed by a 3-month, poststudy follow-up. The primary end points are percent change from baseline in LDL-C and the safety and tolerability of anacetrapib. Comprehensive preplanned interim safety analyses will be performed at the 6- and 12-month time points to examine treatment effects on key safety end points, including blood pressure and electrolytes. A preplanned Bayesian analysis will be performed to interpret the CV event distribution, given the limited number of events expected in this study.

**Results** A total of 2,757 patients were screened at 153 centers in 20 countries, and 1,623 patients were randomized into the trial. Lipid results, clinical CV events, and safety outcomes from this trial are anticipated in 2010. (Am Heart J 2009;158:513-519.e3.)

Elevated low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) are major risk factors for the development of cardiovascular (CV) disease (CVD). Low-density lipoprotein cholesterol lowering with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) reduces the risk of CV events in patients with and without coronary

heart disease (CHD).<sup>1</sup> In many patients, however, a high residual risk of CV events persists despite aggressive statin therapy to lower LDL-C.<sup>2-4</sup> Accordingly, targeting additional lipid risk factors is a current approach to further reduce CVD.

The inverse correlation between circulating levels of HDL-C and CV risk has encouraged the development of novel pharmacologic agents designed to raise HDL-C.<sup>5-8</sup> One approach is inhibition of cholesteryl ester transfer protein (CETP)—a plasma protein that facilitates the exchange of cholesteryl esters and triglycerides (TGs) between HDL and TG-rich lipoproteins.<sup>9</sup> The magnitude of HDL-C increases with CETP inhibitors is much greater than what has been observed with existing agents.<sup>10</sup> For instance, the CETP inhibitor torcetrapib produced HDL-C increases of >60%.<sup>11-14</sup> Unexpectedly, however, it was associated with an excess of deaths and CV events, leading to the early discontinuation of the torcetrapib clinical development program.<sup>14</sup> Whereas the precise reasons for the failure of torcetrapib remain elusive,<sup>15-20</sup> treatment with this agent was associated with an increase in blood pressure, alterations in serum electrolytes, and

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See Appendix A for a complete listing of DEFINE investigators.

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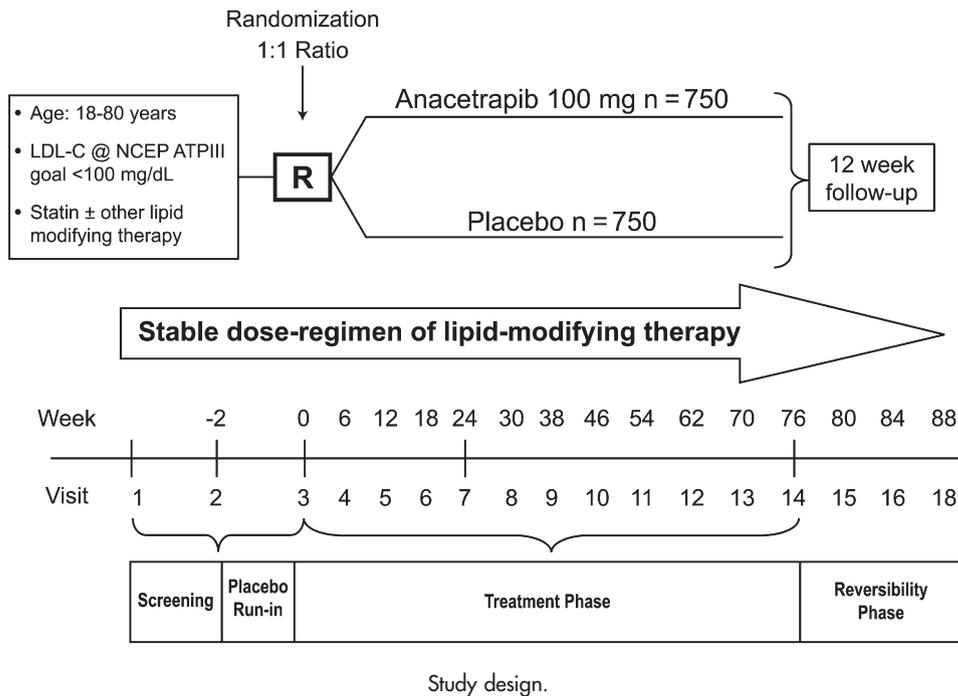
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Figure 1



an increase in circulating aldosterone levels.<sup>14</sup> These effects appear to be compound specific and unrelated to the mechanism of CETP inhibition.<sup>21-26</sup>

Anacetrapib is an orally active, potent, selective CETP inhibitor. Early studies in healthy volunteers demonstrated that single and multiple doses of anacetrapib were generally well tolerated and resulted in favorable lipid changes without changes in ambulatory blood pressure measurements.<sup>22</sup> Treatment with anacetrapib at doses of 10 to 300 mg for 8 weeks, as monotherapy or coadministered with atorvastatin, 20 mg, produced significant increases in HDL-C (up to approximately 130%) and reductions in LDL-C (up to approximately 60%) in patients with primary hypercholesterolemia or mixed hyperlipidemia, with no discernable effects on blood pressure, serum electrolytes, or aldosterone levels.<sup>23</sup>

The present report describes the design of the DEFINE (Determining the Efficacy and Tolerability of CETP INhibition with AnacEtrapib) trial. DEFINE is an ongoing randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of anacetrapib, 100 mg, in patients with CHD or CHD risk equivalents. DEFINE was designed with a novel Bayesian approach to safety that allows for decision making based upon a sparse number of expected CV events and the posterior probability of excluding the adverse CV signal that was observed with the CETP inhibitor torcetrapib.

## Methods

### Study design and objectives

DEFINE (ClinicalTrials.gov registration no. NCT00685776) is a 76-week, randomized, double-blind, placebo-controlled study designed to assess the tolerability and efficacy of anacetrapib when added to ongoing lipid therapies in patients with CHD or CHD risk equivalents. The study consists of a 2-week screening period, a 2-week single-blind placebo run-in period, an 18-month treatment period, and a 3-month reversibility phase (Figure 1). Patients with CHD or CHD risk equivalents with LDL-C <100 mg/dL on statins with or without other lipid-modifying therapy (at stable doses for at least 6 weeks) were eligible for screening. The primary objectives are to assess the lipid efficacy and the safety and tolerability of anacetrapib, 100 mg, particularly with respect to effects on blood pressure, serum electrolytes, and aldosterone. This study will provide safety experience with anacetrapib to inform decisions regarding initiation of a phase III outcomes trial.

### Randomization and treatment protocol

A total of 2,757 participants were screened at 153 centers in 20 countries. Of these, 1,697 entered the placebo run-in phase, and 1,623 patients were randomized into the trial. During the screening visits, informed consent was obtained and baseline medical history, examination, and laboratory testing were performed. The patient eligibility criteria are provided in Table I. After eligibility was confirmed, patients were entered into a 2-week, single-blind placebo run-in phase. Patients who were >75% compliant with study medication during the single-blind placebo run-in phase (as determined by pill count) were eligible to be randomized. Patients who were <75% compliant

**Table I.** Eligibility criteria

Key inclusion criteria	Key exclusion criteria
1. Age $\geq 18$ and $\leq 80$ y	1. Severe chronic heart failure defined by NYHA classes III or IV*
2. CHD or CHD risk-equivalent disease† and LDL-C $< 100$ mg/dL	2. Uncontrolled cardiac arrhythmias, MI, PCI, CABG, unstable angina, or stroke MI within 3 m before visit 1
3. Treated with statin $\pm$ other lipid-modifying therapy and HDL-C $< 60$ mg/dL	3. LDL-C $< 50$ mg/dL
4. TG $\leq 400$ mg/dL	4. Uncontrolled hypertension defined as follows:
5. Patients of reproductive potential must agree to remain abstinent or use 2 acceptable methods of birth control for the duration of the study	<ul style="list-style-type: none"> <li>▪ Sitting diastolic blood pressure <math>\geq 100</math> mm Hg, or sitting systolic blood pressure <math>\geq 160</math> mm Hg (nondiabetic patients)</li> <li>▪ Sitting diastolic blood pressure <math>\geq 90</math> mm Hg, or sitting systolic blood pressure <math>\geq 150</math> mm Hg (diabetic patients)</li> </ul>
6. Patient is $> 75\%$ compliant during the single-blind placebo run-in phase	5. CPK $> 2 \times$ ULN
	6. ALT or AST $> 2 \times$ ULN
	7. Newly diagnosed (within 3 m of visit 1) or poorly controlled ( $HbA_{1c} > 8.5\%$ ) type 1 or type 2 diabetes
	8. Hyperthyroidism or hypothyroidism as defined by a TSH below the lower limit of normal or $> 20\%$ above ULN
	9. Homozygous familial hypercholesterolemia, types I or V hyperlipidemia
	10. Active or chronic hepatobiliary or hepatic disease
	11. eGFR $< 30$ mL/min per $1.73m^2$
	12. Ongoing treatment with warfarin, systemic corticosteroids, or anabolic steroids, and any potent CYP3A4 inhibitor or inducer

NYHA, New York Heart Association; CPK, creatine phosphokinase; ALT, alanine aminotransferase; AST, aspartate transaminase;  $HbA_{1c}$ , glycosylated hemoglobin; TSH, thyroid stimulating hormone; eGFR, estimated glomerular filtration rate.

\* The Criteria Committee of the NYHA. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston: Little Brown & Co; 1994:253-6.  
† Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.

were also randomized if they had the potential for improved compliance after additional counseling.

Subjects who successfully completed the run-in phase were randomized 1:1 to anacetrapib, 100 mg, or matching placebo in a double-blind fashion. The 100-mg dose selection was based upon pharmacokinetic/pharmacodynamic modeling and simulation of phase I and IIb data that evaluated doses up to 300 mg. The model indicates that the 100-mg dose was close to the plateau of LDL-C lowering and HDL-C raising. Patients were instructed to take 1 tablet daily with a meal. Patients return for study visits at regular intervals during the study (6-8 weeks). Assessments for adverse experiences (AEs), precise measurements of blood pressure, and collection of samples for

measurements of plasma lipids and safety laboratories (including serum chemistry, liver enzymes, hematology, and urinalysis) are performed. Aldosterone levels are collected and measured at baseline and at 12, 24, and 76 weeks by enzyme immunoassay (Diagnostics Biochem, London, Ontario, Canada). All laboratory measurements are performed by the study core laboratory (PPD, Highland Heights, KY).

All patients, including those who discontinued study medication, are observed for a 3-month posttreatment period. This period includes 2 telephone contacts and 1 clinic visit. Assessments of AEs are performed during the phone contacts, and AEs, vital signs, lipids, and safety laboratories are assessed at the posttreatment clinic visit. All patients, including those who discontinue, are also assessed for CV outcomes at 54 weeks and at the end of the study (88 weeks).

### Concomitant treatment

Patients are instructed to follow the National Cholesterol Education Program Adult Treatment Panel Therapeutic Lifestyle Changes Diet<sup>27</sup> or a comparable cholesterol-lowering diet and to remain on prior lipid-modifying therapies for the duration of the study. Investigators and the sponsor are blinded to lipid measurements from the randomization visit forward. The central laboratory monitors individual LDL-C levels and provides flags to investigators if values meet one of the following criteria: (1) LDL-C  $> 15\%$  above National Cholesterol Education Program Adult Treatment Panel III goal,<sup>28</sup> (2) LDL-C  $> 15\%$  above the baseline value, or (3) LDL-C  $< 25$  mg/dL. Investigators are prompted to adjust LDL-C-lowering medications if patients have LDL-C values  $> 15\%$  above goal after repeat testing and medication compliance has been verified. Patients are discontinued for 2 consecutive flags of LDL-C  $< 25$  mg/dL.

### End points

The primary end points are the percent change from baseline in LDL-C and safety and tolerability assessments (ie, adverse experiences, laboratory values and vital signs, electrocardiogram [ECG], and physical examination). Secondary efficacy end points include change in concentrations of HDL-C, non-HDL-C, total cholesterol (TC), TG, apolipoprotein (apo) B, apo A-I, lipoprotein(a) [Lp(a)], high-sensitivity C-reactive protein, apo C-III, apo A-II, and apo E, and also the ratios of TC/HDL-C, LDL-C/HDL-C, apo B/apo A-I, and LDL-C/apo B. In addition, lipoprotein subfractions will be assessed on archived blood samples. Change in concentration of LDL-C was selected as the primary efficacy end point in the study because LDL-C is a recognized target for CV risk reduction, and anacetrapib treatment demonstrated robust, dose-dependent LDL-C lowering in the phase IIb study.<sup>23</sup> The study is generously sized versus typical lipid-lowering studies to allow for a comprehensive safety profile characterization of anacetrapib, including examination of serious CV events. Because of the limited number of serious CV events expected in this study, they are not listed as formal "efficacy" end points. However, they are part of prespecified Tier 1 safety parameters, subject to between treatment inferential testing. The prespecified CV end points being used for evaluation of safety are CV death, nonfatal myocardial infarction (MI), stroke, and hospitalization for unstable angina (see Appendix B for definitions). All CV events and death from any cause are adjudicated by an external, independent adjudication

committee. Rates for revascularization for nonacute ischemic events are being collected, and hospitalization for severe congestive heart failure is being collected and adjudicated but are not part of the CV ischemic safety end point. Additional Tier 1 (see later in Statistical design and analysis) and general (hematology, urinalysis, ECGs, and other clinical and laboratory AEs) safety parameters are also monitored throughout the study. An external independent safety monitoring committee monitors unblinded safety data on a regular basis throughout the study.

### Statistical design and analysis

The statistical analysis uses the prior data on the CETP inhibitor torcetrapib to assist with decision making from the limited number of CV events expected in the DEFINE trial. To accomplish this, use of commonly used frequentist-based approaches was deemed to be inadequate due to the limited power associated with the low number of events. Instead, a Bayesian-based approach was constructed for which predefined assumptions underlying the CV event rate are needed. These assumptions include definition of the underlying event rate distribution and an estimate of the event rate incidence. In addition, a prestated level of confidence is required to define how much the true incidence rate in CV events may vary versus the estimated event rate. Based upon the observed number of CV events, this Bayesian-based approach provides the mechanism to compute confidence levels to dismiss a deleterious safety signal of the magnitude of that observed for torcetrapib (ie, a 25% increase in CV events). Of course, a point-estimate of fewer comparative events in the anacetrapib group would help provide greater levels of confidence in dismissing a torcetrapib-like deleterious safety signal.

All intermediate statistical analyses will be conducted by the Independent Statistical Data Analysis Center (ISDAC; see Appendix A; note that the ISDAC is independent of the sponsor); the study sponsor will remain blinded to the individual treatment level data until study completion. For the lipid efficacy end points, a full likelihood longitudinal data analysis model<sup>29</sup> will be used to compare anacetrapib with placebo based on appropriate contrasts under the longitudinal data analysis model. Across the primary and key secondary efficacy hypotheses, Hochberg's method<sup>30</sup> for multiplicity control will be used based upon 2 families of hypotheses: the first family defined at weeks 24 (primary study time point) and the second family defined at 76 weeks (end of study).

For the analysis of safety data, all randomized patients who received at least one dose of study treatment will be used. The analysis of safety results will follow a tiered approach. Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety end points, and they will be subject to inferential testing for statistical significance. Tier 1 safety parameters include the following AEs: hepatic (2 consecutive alanine aminotransferase and/or aspartate aminotransferase elevations  $\geq 3 \times$  upper limit of normal [ULN]), muscle-related (creatinine phosphokinase elevations  $\geq 10 \times$  ULN with or without muscle symptoms), aldosterone-related electrolytes (proportion of patients with elevations in sodium, chloride, or bicarbonate elevations greater than ULN, or with reduction in potassium levels less than lower limit of normal), and specific AEs of interest (myalgia, rhabdomyolysis, prespecified adjudicated CV serious AEs, and death from any cause). Adverse experiences (specific terms and system organ class terms), predefined limits

**Table II.** Confidence in dismissing a torcetrapib-type adverse effect on CV events\* (assuming 16 events;  $pT < 1.25 \times pC$ )

16 total events (based on 1.1% 24 wk-event rate)		Confidence ( $pT < 1.25 \times pC$ )
Anacetrapib (pT)	Placebo (pC)	$pT=pC$
0	16	1
1	15	0.999
2	14	0.998
3	13	0.994
4	12	0.982
5	11	0.958
6	10	0.913
7	9	0.838
8	8	0.730
9	7	0.595
10	6	0.447
11	5	0.305
12	4	0.187
13	3	0.102
14	2	0.048
15	1	0.020
16	0	0.007

The green confidence values of  $>30\%$  suggest study continuation. The red confidence values of  $\leq 30\%$  suggest study termination.

\* Prespecified CV events include CV death, nonfatal MI, stroke, and hospitalization for unstable angina.

of change in laboratory, vital signs, and ECG parameters that are not prespecified as end points of special interest will be classified as "Tier 2" (requiring that at least 4 patients in each treatment to exhibit the event) or "Tier 3" ( $<4$  patients in each group). Safety analyses of cumulative AEs at weeks 24, 54, end of the treatment period, and during the posttreatment period are prespecified.

This study is overpowered for lipid efficacy end points; instead, it is intended to provide a broad safety experience in a patient population that will ultimately derive potential benefit from the drug. Based upon the limited number of CV events predicted for this study, varying levels of confidence may be computed toward dismissing a 25% increase in CV events attributable to anacetrapib, the level observed with torcetrapib in the ILLUMINATE trial.<sup>14</sup>

To compute the probability that such a deleterious safety effect can be dismissed, assumptions toward the underlying comparator event rate must be made as well as classification of the distributions of the event rates themselves. These assumptions are (1) the expected 24-week CV event rate in both treatment groups is assumed to be equal at 1.1% (the rate of primary CV events in the ILLUMINATE trial,<sup>14</sup> down-weighted by approximately 33% to account for the contemporaneous timing of DEFINE and the lower estimated CV risk in DEFINE subjects); (2) there is 90% probability that the true CV event rates are not  $>50\%$  larger than the expected rates; (3) true CV event rates for anacetrapib and placebo were drawn from a  $\beta$  distribution; and (4) marginal distributions for number of treatment CV events were based on a  $\beta$ -binomial distribution.<sup>31</sup>

Based on these assumptions, Bayesian confidence levels may be computed toward dismissing a deleterious treatment effect of anacetrapib, of the magnitude observed from the ILLUMINATE

**Table III.** Patient disposition

Patient disposition	n	%
Patients screened	2757	
Excluded during screening (visit 1)	1060	38.4%
Screen failure	936	33.9%
Adverse event	1	0.03%
Withdrawal by subject	102	3.7%
Protocol violation	6	0.2%
Lost to follow-up	14	0.5%
Study terminated by sponsor	1	0.03%
Patients entered placebo—run-in (visit 2)	1697	61.6%
Excluded	74	2.7%
Screen failure	33	1.2%
Adverse event	6	0.2%
Withdrawal by subject	18	0.7%
Lost to follow-up	11	0.4%
Low compliance to study drug	6	0.2%
Patients randomized	1623	58.9%

**Table IV.** Baseline characteristics\*

n	1623
Age (median, range), y	63 (31-81)
Gender, n (%)	
Female	376 (23.2%)
Male	1247 (76.8%)
Race, n (%)	
White	1435 (88.4%)
Asian	123 (7.6%)
Black	41 (2.5%)
Other	24 (1.5%)
Hypertension, n (%)	1087 (67%)
Diabetes, n (%)	853 (53%)
TC mg/dL, mean (SD)	151 (26)
LDL-C mg/dL, mean (SD)	82 (21)
HDL-C mg/dL, mean (SD)	40 (9)
TG mg/dL, median	128
SBP mm Hg, mean (SD)	124 (14)
DBP mm Hg, mean (SD)	75 (9)
BMI kg/m <sup>2</sup> , mean (SD)	30 (5)

SBP, Systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index. Lipid values reported are those from the randomization visit—at the end of the run-in period.

\*Based on a data analysis as of April 15, 2009.

trial<sup>14</sup> (ie, a 25% increase in CV events). Table II provides the confidence in dismissing a torcetrapib-type adverse effect on CV events, assuming 16 CV events are observed at the 6-month time point. The resulting confidence levels in the lack of a torcetrapib-type of safety signal (according to the distribution of events between the 2 study arms) are provided. The green confidence values of >30% suggest study continuation. The red confidence values of ≤30% suggest study termination. Ultimately, the recommendation to continue or terminate the trial rests with the sponsor-independent safety monitoring committee.

### Current status

Recruitment began on April 1, 2008, and ended on January 15, 2009. Patient disposition is shown in Table III. Baseline characteristics of the patients enrolled are shown in Table IV. Final results are anticipated in 2010.

### Discussion

The excess of both CV events and total mortality in participants taking torcetrapib in the ILLUMINATE trial<sup>14</sup> did not support the hypothesis that CETP inhibition is cardioprotective. Torcetrapib increased blood pressure, reduced serum potassium, and increased serum levels of bicarbonate and sodium—effects that were all consistent with an observed torcetrapib-induced increase in serum aldosterone.<sup>14</sup> It has since been found in basic studies conducted after termination of the ILLUMINATE trial that torcetrapib induces the synthesis of both aldosterone and cortisol in adrenal cortical cells.<sup>21</sup> Furthermore, this effect is shared by analogs of torcetrapib that do not inhibit CETP.<sup>32</sup> The discovery that torcetrapib had off-target adverse effects (unrelated to CETP inhibition) that may have been responsible for the harm caused by this agent has left the door open for retesting the hypothesis with a CETP inhibitor that does not share the off-target effects of torcetrapib.

The observation that anacetrapib appears not to possess the known off-target effects of torcetrapib

provides a compelling case for using this drug as an agent with which to retest the hypothesis that CETP inhibition may indeed be cardioprotective. Anacetrapib did not raise blood pressure in phase I/II studies<sup>22,23</sup> and does not increase aldosterone synthesis in adrenal cortical cells.<sup>21,32</sup> The safety of anacetrapib will be further studied in patients with CHD disease/CHD risk equivalents in the DEFINE trial. The preplanned interim safety analyses (at the 6- and 12-month time points) will examine treatment effects on key safety end points, including blood pressure, electrolytes, aldosterone, and the limited number of CV events expected. The analyses in the DEFINE study will inform decisions regarding continuation of the DEFINE trial and the initiation of a fully powered phase III outcomes trial in a patient population with CVD at high risk for recurrent events.

### Disclosures

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M. Davidson has no stock ownership in Radiant Research, Cincinnati, OH, a Division of Swiss BioScience. In the past 3 years, M. Davidson has received grant/research support, honorarium, served as consultant/speakers' bureau for: Abbott, Whippany, NJ, Academic CME, Chicago, IL, AstraZeneca Pharmaceuticals, Daiichi-

Sankyo Inc, Tokyo, Japan, diaDexus Inc, South San Francisco, CA, GlaxoSmithKline, Kinemed, Emeryville, CA, LipoScience, Raleigh, NC, Merck & Co Inc, Merck/Schering-Plough, Omthera, New York, NY, Professional Evaluation Inc, Chicago, IL, Roche Pharmaceuticals, Sabel, Switzerland, Sanofi-Aventis, Synarc, San Francisco, CA, Takeda Pharmaceuticals and Vindico, Thorofare, NJ. He has served on advisory boards at Abbott, AstraZeneca, Daiichi-Sankyo, GlaxoSmithKline, Kinemed, Merck, Merck/Schering-Plough, Roche, and Takeda; holds equity or serves on the Board of Directors of Omthera (board of directors); Professional Evaluation Inc Medical Education Company (board of directors); and Sonogene, Glen Illyn, IL, (board of directors).

A.M. Gotto, Jr, has served on the Board of Directors for Aegerion Pharmaceuticals, Bridgewater, NJ, and Arisaph Pharmaceuticals, Boston, MA; on the Health Advisory Board for DuPont, Wilmington, DE; as a consultant for Genentech, South San Francisco, CA, KOWA, Montgomery, AL, Merck & Co Inc, and Merck/Schering Plough; and on the Data Safety Monitoring Board for Novartis Pharmaceutical Corporation.

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P. Barter has served as a consultant for AstraZeneca, Merck, Pfizer, Roche, and Sanofi-Aventis; has received honorarium from Abbott, AstraZeneca, BMS, Merck, Pfizer, Roche, and Sanofi-Aventis; and is a patent holder in the field for Nil.

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## Appendix A. DEFINE Investigators

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### Steering Committee

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## Appendix B. Definitions for end points used by the Adjudication Committee

### Nonfatal events

**Acute MI.** Acute MI (based on the Universal definition of MI (Thygesen K, et al. *J Am Coll Cardiol.* 2007;50: 2173-2195) can be defined by any one of the following criteria as excerpted from the universal definition of MI:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
  - symptoms of ischemia;
  - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
  - development of pathologic Q waves in the ECG; and
  - imaging evidence of new loss of viable myocardial or new regional wall motion abnormality.
- For percutaneous coronary interventions (PCIs) 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  $>3 \times$  99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) 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  $>5 \times$  99th percentile URL plus either new pathologic 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.
- Pathologic findings of an acute MI.

**Stressor relationship.** For acute MI, the adjudicator is asked to make a determination as to any possible association between the MI and antecedent "major

stressors,” specifically coronary revascularization procedures (ie, percutaneous transluminal coronary angioplasty, atherectomy, stent, or CABG). The following guidelines should be used in making these determinations:

1. Complication of a coronary revascularization procedure: an MI that, in the clinical judgment of the adjudicator, occurred coincident with (or within 72 hours after) and was probably a complication of an anteceding coronary revascularization procedure.
  - (a) For PCIs 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  $>3 \times$  99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.
  - (b) For CABG 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  $>5 \times$  99th percentile URL plus either new pathologic 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.

*Clinical classification of different types of MI.* Type 1 is spontaneous MI related to ischemia due to a primary coronary event such as a plaque erosion and/or rupture, fissuring, or dissection.

Type 2 is MI secondary to ischemia due to either increased oxygen demand or decreased supply, for example, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.

Type 3 is sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of a fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of biomarkers in the blood.

Type 4a is MI associated with PCI.

Type 4b is MI associated with stent thrombosis as documented by angiography or at autopsy.

Type 5 is MI associated with CABG.

**Unstable angina pectoris.** *Unstable angina pectoris* is defined as new or accelerating symptoms of myocardial ischemia (prolonged and/or repetitive anginal-like chest discomfort, anginal pain at rest, or ischemia-mediated hemodynamic instability) accompanied by new ischemic ST-T-wave changes (ST depression or ST elevation or T-wave inversion). In addition, such an event does not qualify as an MI as defined above. In the

absence of ECG changes with the above clinical presentation, either of the following criteria can be used as supporting evidence of unstable angina pectoris: (1) a thrombus seen within the coronary arteries during a cardiac catheterization or (2) a history of worsening angina for a period of 6 weeks with episodes of chest pain at rest and emergency coronary revascularization.

Available ECGs include ST-T-wave changes as follows:

- (a) persistent or transient ST-segment depression  $>0.5$  mm (0.08 seconds after the J point) in 2 contiguous leads, not known to be old, or
- (b) persistent or transient T-wave inversion ( $>1$  mm) in 2 contiguous leads, not known to be old, or
- (c) pseudonormalization of the T wave in 2 contiguous leads,
- (d) persistent or transient ST-segment elevation  $>1$  mm in 2 contiguous leads, not associated with elevated markers and not known to be old.

**Resuscitated cardiac arrest.** A *resuscitated cardiac arrest* is defined as the occurrence of verified hemodynamic collapse of cardiac origin (ie, tachyarrhythmia, bradyarrhythmia, electromechanical dissociation) in which criteria for nonfatal acute MI, or pulmonary embolism are not met, and after which the patient survives for at least 24 hours as a result of cardioversion and/or electrical or pharmacologic cardiopulmonary resuscitation.

**Cardiac heart failure.** The diagnosis of heart failure (HF) requires the following:

- hospital admission or presentation to the ED,
- symptoms consistent with HF, and
- HF treatment.

The diagnosis may be supported by signs of HF or imaging and/or laboratory evidence of cardiac dysfunction and/or structural abnormality. The presence of objective evidence of cardiac dysfunction is determined and recorded on the adjudication form.

Symptoms of HF are required and may include the following:

- dyspnea;
- orthopnea;
- paroxysmal nocturnal dyspnea, and
- fatigue, peripheral edema, not due to alternate causes (eg, venous stasis disease in the case of peripheral edema).

The presence of clinical as well as imaging and/or laboratory signs of HF supports the diagnosis. The diagnosis should be questioned in the absence of one or more of these signs. Clinical signs of HF include elevated jugular venous pressure, third heart sound, pulmonary rales, hepatojugular reflux, hepatomegaly, ascites, and

peripheral edema. Imaging and/or laboratory findings include elevated brain natriuretic peptide or N-terminal probrain natriuretic peptide, abnormal chest x-ray, left ventricular (LV) dilation or reduced LV ejection fraction by echocardiogram, LV hypertrophy by echocardiogram, elevated pulmonary capillary wedge pressure, or reduced cardiac index, measured by right heart catheterization (Swan-Ganz catheter).

#### Fatal events

**Fatal MI.** A fatal MI is one as defined previously and that is documented to directly result in death within 30 days of the onset of the signs or symptoms of the event or a death with an autopsy report of findings consistent with an acute MI.

It may cause 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 new evidence of

fresh thrombus by coronary angiography, and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

**Sudden death and/or unexplained death.** *Sudden and/or unexplained death* is defined as witnessed instantaneous or near-instantaneous death that occurs without warning or within 1 hour of nondiagnostic symptoms, or as an unwitnessed, unexpected death in which criteria for a fatal coronary or cerebrovascular event are not met.

Deaths that are considered to be nonatherothrombotic or embolic and that are judged to be from unknown causes do not meet the criteria for “sudden and/or unexplained death.” Such deaths will be adjudicated as “event unrelated to atherothrombotic/embolic conditions,” and the adjudicators will indicate that the cause of death is unknown.