EXamination of CArdiovascular OutcoMes with AlogliptIN versus Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE): A cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome

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Comprehensive safety evaluation of new drugs for diabetes mellitus is needed in the area of cardiovascular (CV) outcomes, particularly in populations with high CV risk. Alogliptin, a dipeptidyl peptidase 4 inhibitor, is under development for the treatment of type 2 diabetes mellitus alone or in combination with other antidiabetic therapies. Long-term CV safety of alogliptin is being established in a randomized, placebo-controlled clinical study in patients with acute coronary syndrome (ACS) using an analytical approach that has both an interim and final assessment. The primary CV end point for this trial is a composite of CV death, nonfatal myocardial infarction, and nonfatal stroke. Approximately 5,400 men and women with type 2 diabetes and ACS (acute myocardial infarction or unstable angina) are being recruited and will be followed up for up to 4.5 years postrandomization. The statistical plan for the trial uses a design that evaluates the hazard ratio (HR) of alogliptin to placebo first based on the primary CV composite end point after accrual of 80 to 150 primary CV events and again when there are 550 to 650 primary CV events. In the first series of analyses, the upper bound of a group-sequential 1-sided repeated CI for the HR must be $\leq$1.8 for registration in the United States. At end of study, the upper bound of a subsequent group-sequential 1-sided repeated CI for the HR must be $\leq$1.3. For both group sequential analyses, the repeated CIs are calculated to insure simultaneous coverage probabilities of 97.5% for the true HR. *Study progress*: More than 2,000 ACS patients were randomized as of June 2011. EXAMINE will define the CV safety profile of this dipeptidyl peptidase 4 inhibitor in patients at high risk for CV events. (Am Heart J 2011;0:1-7.e1.)

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Background and study rationale

Type 2 diabetes mellitus is a chronic illness associated with both microvascular complications, such as nephropathy, retinopathy, and neuropathy, and macrovascular complications, including cardiovascular (CV) and peripheral vascular disease.[1] The risk of CV disease is 2 to 4 times higher in people with diabetes compared with those without diabetes.[2] Improved glycemic control has been shown to reduce the risk of many of the microvascular complications of diabetes. In general, every percentage point drop in hemoglobin A1c (HbA1c) can reduce the risk of retinal, renal, and neurologic diseases by 40%.[3] However, recent studies have not yet determined a favorable impact for glycemic control in reducing

Table I. Definitions for ACSs required for inclusion into the EXAMINE trial

Myocardial infarction

Evidence of myocardial necrosis consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for MI:

A defined rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least 1 of the following:

Symptoms of ischemia.

ECG changes indicative of new ischemia (new ST-T changes or new LBBB).

Development of pathologic Q waves in the ECG.

Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

For PCI in patients with normal baseline troponin values, increases of biomarkers >3× 99th percentile upper reference limit have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.

For CABG in patients with normal baseline troponin values, increases of biomarkers >5× 99th percentile URL plus either new pathologic Q waves or new LBBB, or angiography-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.

Hospitalization with unstable angina

An accelerating pattern or prolonged (>20 min) or recurrent episodes of chest pain at rest or with minimal effort within the preceding 24 h and

New ST-segment depression of at least 0.05 mV, transient (<20 min), or ST-segment elevation of at least 0.1 mV, or T wave inversion of at least 0.3 mV in at least 2 leads *and*

Evidence for coronary artery disease documented by significant stenosis on cardiac catheterization *or*

Documented prior MI

ECG, Electrocardiogram; *LBBB*, left bundle-branch block; *PCI*, percutaneous coronary interventions; *CABG*, coronary artery bypass grafting; *URL*, upper reference limit.

macrovascular events (Action to Control Cardiovascular Risk in Diabetes [ACCORD],[4] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE][5]).

As a result of concerns regarding the association of antidiabetic agents with adverse CV outcomes,[6] the Food and Drug Administration released a guidance in December 2008 titled, "Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes."[7] This guidance outlines requirements for CV safety assessment before and after approval of all new antidiabetic therapies. Specifically, sponsors must rule out an upper 95% CI of the hazard ratio (HR) of 1.8 before approval and 1.3 after approval. In most cases, these upper CI boundaries would be associated with HRs of 1.0 or less.

Alogliptin is a selective and potent dipeptidyl peptidase 4 (DPP-4) inhibitor under development for use in patients with type 2 diabetes. The enzyme DPP-4 rapidly degrades incretin hormones (glucagon-like peptide 1 [GLP-1] and glucose-dependent insulinotropic peptide).[8] By preventing the rapid degradation of GLP-1 through inhibition of DPP-4, alogliptin enhances the body's ability to control elevated blood glucose by triggering pancreatic insulin secretion and suppressing pancreatic glucagon secretion.[9] Alogliptin, alone or in combination with other antidiabetic agents, is similar to other DPP-4 inhibitors and lowers HbA1c levels by 0.6% to 1.0% in patients with type 2 diabetes mellitus and is rarely associated with induction of hypoglycemia.[9]

During its phase 3 development, alogliptin was studied in 3,489 patients with type 2 diabetes and compared with 1,213 patients on placebo in seven 26-week studies and one 12-week study. Analysis of adjudicated major adverse cardiovascular events (MACE) defined as death from CV disease, nonfatal myocardial infarction (MI), or nonfatal stroke calculated a 0.28% risk of CV events for patients receiving alogliptin versus a 0.50% risk for those patients receiving placebo (HR 0.61, 95% CI 0.24-1.56).[10] Although there was no imbalance in CV events on alogliptin relative to placebo during the phase 3 clinical trials, the CV event rate was too low to rule out a concern in patients with higher baseline risk. Thus, patients with type 2 diabetes who have much higher CV risk, acute coronary syndrome (ACS), are the focus of the next major CV safety evaluation of this DPP-4 inhibitor.

Study design and conduct

EXAMINE is a phase 3, multicenter, prospective, double-blind randomized trial in which alogliptin is being compared with placebo on CV outcomes in approximately 5,400 patients with type 2 diabetes and a well-defined ACS event (Table I). The primary objective of EXAMINE is to demonstrate the noninferiority of MACE on alogliptin versus placebo in the treatment of type 2 diabetes in a high-risk CV patient group. The general inclusion and exclusion criteria for the trial are outlined in Table II.

General study conduct

The study consists of a screening period of up to 2 weeks and a follow-up period of 4.75 years. The length of the study participation will vary but is estimated to be a median of 2 years of study drug treatment. The EXAMINE trial complies with the Declaration of Helsinki and subsequent revisions and follows Good Clinical Practice guidelines. Each of the investigative sites in this

Table II. EXAMINE inclusion and exclusion criteria

Inclusion criteria

1. Male or female patients 18 years or older who have a diagnosis of type 2 diabetes mellitus, who either are receiving monotherapy or combination antidiabetic therapy (with the exception of a DPP-4 inhibitor or GLP-1 analog) before screening.
2. HbA1c criteria:
   If on oral monotherapy or combination therapy, the patient must have an HbA1c level between 6.5% and 11.0%, inclusive, at screening.
   If the antidiabetic regimen includes insulin, the patient must have an HbA1c level between 7.0% and 10.0%, inclusive, at screening.
3. History of ACS (acute MI or unstable angina requiring hospitalization—see Table I for required definitions) within 15-90 d before randomization.
4. Female patients of childbearing potential who are sexually active must agree to routinely use adequate contraception from screening throughout the duration of the study.
5. Patients or the subject's legally acceptable representative are able and willing to provide written informed consent before the initiation of any study procedures.
6. The subject is capable of understanding and complying with protocol requirements, including scheduled clinic appointments.

Exclusion criteria

1. Patient has signs of or is diagnosed with type 1 diabetes mellitus or latent autoimmune diabetes in adults.
2. Patient is currently receiving a GLP-1 analog for glycemic control of type 2 diabetes mellitus at screening.
3. Patient has received a DPP-4 inhibitor for either >14 d total or within the 3 m before screening.
4. Unstable CV disorder including heart failure (NYHA class 4), refractory angina, uncontrolled arrhythmias, critical valvular heart disease, and severe, uncontrolled hypertension.
5. Acute coronary syndrome event <15 d before randomization
6. Patient is still hospitalized at the time of the baseline/randomization visit. Patients in cardiac rehabilitation centers or nursing homes at the baseline/randomization visit are not excluded.
7. Dialysis within 14 d before screening.
8. Human immunodeficiency virus infection.
9. Alcohol or substance abuse/dependence within the 6 m before screening.
10. Investigational drug within the 30 d before the screening or has received an investigational antidiabetic drug within the 3 m before the screening.
11. Major illness or disability that, in the investigator's opinion, prohibits the subject from participating in the study.
12. Patient is a study site employee or is an immediate family member (ie, spouse, parent, child, and sibling) of a study site employee involved in the conduct of this study.
13. Pregnancy (confirmed by laboratory testing, ie, serum/urine hCG), intends to become pregnant during the study, or is lactating.

NYHA, New York Heart Association; *hCG*, human chorionic gonadotropin.

global trial has obtained approval for study conduct by an institutional review board. Study patients must review and sign informed consent before any study related procedure. The study has been registered on *Clinicaltrials.gov* (NCT00968708).

Study treatment and procedures

Treatment

Patients are randomized in a 1:1 ratio to receive either alogliptin (doses of 6.25-25 mg daily) or an identical placebo tablet daily in addition to standard of care treatment for type 2 diabetes mellitus. Investigators are instructed to manage type 2 diabetes according to standards established by clinical consensus guidelines in each geographic region. Subjects will be stratified based on country and screening renal function (normal to mild impairment [estimated glomerular filtration rate or eGFR >60 mL/min] vs moderate to severe impairment [eGFR <60 mL/min but not on dialysis]). Doses of alogliptin are modified according to renal function at any time during the postrandomization period: eGFR >60 mL/min, 25 mg daily; <60 mL/min but >30 mL/min, 12.5 mg daily; and <30 mL/min, 6.25 mg daily.

Study procedures

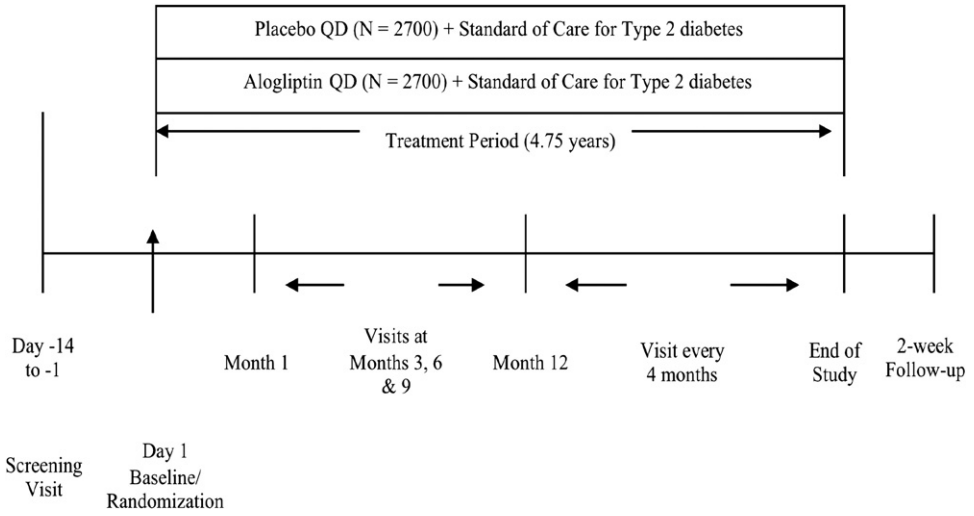
There will be approximately 20 clinical visits and telephone contacts during the course of the study (Figure 1). On-site office visits will occur at screening and randomization and at 1, 3, 6, 9, and 12 months postrandomization during the first year of the study and every 4 months during the subsequent years of participation. If the patient refuses to return for study visits, telephone contacts will be completed, but this is not preferred nor recommended to sites. Any potential CV events will be assessed at each patient visit in addition to other assessments of safety and tolerability and laboratory assessments. Patients who discontinue the study drug will continue as study participants throughout the remainder of the study.

Statistical considerations

The analysis of the primary variable will be conducted using a Cox proportional hazards model of the primary MACE composite with a factor for treatment and stratified by geographic region and screening renal function (see online Appendix A).

To test the alternative hypothesis that treatment with alogliptin results in no excess risk of events in the primary MACE composite compared with placebo, the upper

Figure 1



Study design and visits for the EXAMINE trial.

bound of a 1-sided repeated CI for the HR (alogliptin to placebo) will be calculated as part of a group sequential design using an O'Brien-Fleming-type spending function and compared with noninferiority margins.[11,12]

During the trial, prospective unblinded analyses of the primary variable will be conducted by an independent statistician and reviewed by the data safety monitoring committee (DMC) to determine whether excess risk >1.8 and 1.3 may be ruled out. The first analysis will be performed after approximately 80 adjudicated primary MACE composite events have been accrued; if necessary, subsequent analyses will be conducted after 100, 125, and 150 adjudicated primary MACE events have been accrued. For each analysis, the current 1-sided repeated CI for the HR will be calculated with critical values obtained using an O'Brien-Fleming-type spending function designed to preserve an overall false-rejection rate of 2.5% for ruling out excess risk greater than 1.8. If, at any unblinded analysis, the upper bound of the current 1-sided repeated CI for the HR is <1.8, this information will be communicated to the DMC by the independent statistician and, after their assessment, the analysis may be submitted to the appropriate regulatory authorities for review. In contrast, if the upper bounds of the 1-sided repeated CIs for the HR are ≥1.8 at all 4 unblinded interim analyses, then the study will be stopped for futility. To protect the overall statistical validity and integrity of the study, individuals associated with these unblinded analyses will not be involved in preparation and review of blinded data or involved in ongoing study conduct (eg, the steering committee).

Once the upper bound of the current 1-sided repeated CI for the HR is demonstrated to be <1.8, the study will continue to the next unblinded analysis, which will be conducted after approximately 550 adjudicated primary MACE composite events have accrued; if necessary, subsequent analyses will be conducted after approximately 600 and 650 adjudicated primary MACE composite events have been accrued. For this analysis, the current 1-sided repeated CI for the HR will be calculated with critical values obtained using an O'Brien-Fleming-type spending function designed to preserve an overall false-rejection rate of 2.5% for ruling out excess risk >1.3. If the upper bound of the 1-sided repeated CI is <1.3 at one of these analyses, the study will be considered to have met the noninferiority end point for alogliptin versus placebo. In contrast, if the upper bounds of the 1-sided repeated CIs for the HR are ≥1.3 at each of the 3 analyses, then the study will be considered complete without having ruled out excess CV risk.

There is also a provision for the possibility of superiority of alogliptin versus placebo at the end of the trial once noninferiority criteria have been met for the primary MACE composite (upper bound of the 1-sided repeated CI for the HR is <1.3). In this case, a corresponding 1-sided repeated CI for the secondary MACE composite will be created using the same critical value calculated for the primary MACE composite. If the upper bound of this 1-sided repeated CI is <1.0, then statistical superiority of alogliptin to placebo for the secondary MACE composite will be claimed and statistical superiority for the primary MACE composite will then be evaluated. If the upper bound of the 1-sided repeated CI for the primary MACE composite is <1.0, then statistical superiority of alogliptin to placebo for the primary MACE composite will also be claimed. Using the group

sequential approach and closed-testing procedures outlined above, the overall 1-sided false-rejection rate of the study is maintained at 2.5%.

Determination of sample size

The power and sample size for EXAMINE were calculated using East 5 software (Cytel Statistical Software, Cambridge, MA). Assuming an O'Brien-Fleming-type spending function, group sequential analyses after 550, 600, and 650 adjudicated primary MACE composite events will provide approximately 91% overall power to declare noninferiority of alogliptin to placebo with a noninferiority margin of 1.3, a true HR of 1.0, and an overall 1-sided 2.5% significance level. To calculate the sample size, the placebo primary MACE composite rate was estimated at 3.5% annually, and the lost to follow-up rate was estimated at 1% annually. With these rate assumptions, a total of 5,400 subjects (2,700 per treatment arm) enrolled approximately uniformly over 2 years, will result in a maximum trial duration of approximately 4.75 years and an expected trial duration of approximately 4.25 years. For the interim analysis, assuming an O'Brien-Fleming-type spending function,[10] group sequential analyses after 80, 100, 125, and 150 adjudicated primary MACE composite events will provide approximately 94% overall power to declare noninferiority of alogliptin to placebo with a noninferiority margin of 1.8, a true HR of 1.0, and an overall 1-sided 2.5% significance level.

Study organization and oversight

The EXAMINE trial has a steering committee that has the overall responsibility for study conduct, modifications or revisions to the study protocol, and oversight of public presentations or publications of the study findings (see online Appendix B). Operations for the trial are coordinated by the sponsor's (Takeda Global Research and Development Center, Inc., Deerfield, IL) research department with 2 contracted clinical research organizations. All serious events are reported to the operations group of the sponsor and forwarded to an independent cardiovascular endpoints committee (CEC). Members of the CEC review all serious events for a potential CV origin. All potential CV events undergo adjudication by the CEC for possible inclusion into the CV composite. Only adjudicated CV events are included in the analyses for the composite end point. Findings of the CEC will be conveyed by an independent statistician to the DMC. Based on regular reviews of all pertinent study data, including CV events, adverse events and laboratory data in the study, the DMC will provide recommendations to the steering committee and to the sponsor regarding continuing, stopping, or changing the study. The steering committee and sponsor will be responsible for reviewing DMC recommendations, deciding whether to continue or terminate the study, and determining whether amendments to the protocol or changes in study conduct must be implemented.

Table III. Baseline characteristics of the study population in EXAMINE*

Age (y), mean ± SD (range)	60.9 ± 10.0 (29-91)
Gender (male/female) (%)	69.7/30.3
Race or ethnicity, n (%)	
White	1445 (67.7)
Black	90 (4.2)
Hispanic or Latino	598 (28)
Asian	510 (23.9)
Native American	51 (2.4)
Multiracial	34 (1.6)
Qualifying ACS event for trial entry, n (%)	
Spontaneous MI	1379 (64.6)
Procedural MI	179 (8.4)
Unstable angina pectoris	549 (25.7)
Baseline cardiovascular history, n (%)	
Myocardial infarction	1813 (84.9)
Coronary revascularization	1495 (70.0)
Hospitalized unstable angina	758 (35.5)
Cardiac arrhythmia	261 (12.2)
Hypertension	1723 (80.7)
Congestive heart failure	517 (24.2)
Peripheral arterial disease	190 (8.9)
Stroke	147 (6.9)
Medication treatment at baseline, n (%)	
Antiplatelet agents	1125 (53.4)
β-Blockers	518 (24.6)
Cholesterol-lowering agents	440 (20.9)
Diabetic agents (including metformin)	708 (33.6)
Renin-angiotensin system–blocking agents	554 (26.3)

* As of May 1, 2011 (n = 2,107); Patients in the EXAMINE trial are enrolled in North America, South America, Europe, Asia, and South Africa. Approximately 20% of the patients in this table are from North America.

Study progress and baseline characteristics

The EXAMINE trial was initiated in 2009; more than 1025 research sites experienced in CV outcome studies in North America, South America, Europe, Asia, and South Africa have been enrolling patients. All investigative personnel were trained at formal 2-day investigator meetings, site initiation visits, and continuous education on study conduct via clinical monitoring visits, newsletters, and sponsor letters. Patients have been recruited from coronary care units at the investigative sites, through referrals, and via local advertising campaigns.

At present, more than 2,300 patients have been randomized into the trial, and recruitment is ongoing as of June 2011. Baseline characteristics of the first 2,107 patients are shown in Table III. The patient characteristics show a mean age of 61 ± 10 years, with a high proportion of study patients with multiple risk factors for coronary artery disease. The characteristics of

the patients in EXAMINE reflect a population with moderately to markedly elevated CV risk compared with prior studies of therapies for type 2 diabetes mellitus. Although the patients in the EXAMINE trial may not be representative of all patients who will be taking the drug for type 2 diabetes, they represent an appropriate population to evaluate the CV safety of alogliptin because of their high risk for CV events. It is presumed that if safety of a drug is documented in a population with high CV risk, then it should also be safe in a population at lower CV risk.[7,13]

Discussion

The EXAMINE trial represents the first study that will evaluate DPP-4 inhibitors in diabetic patients with a recent ACS event. Although the general safety and tolerability findings of alogliptin and other DPP-4 inhibitors in patients with type 2 diabetes have been acceptable for clinical use,[14] their long-term CV safety has not been established. The primary safety outcome of EXAMINE will determine the effect of alogliptin versus placebo on a composite of major CV events. The EXAMINE study population will include patients at substantially elevated CV risk to reach an event rate high enough to adequately determine the CV safety of alogliptin. Consequently, our study population has been enriched with patients with type 2 diabetes and CV diseases (Table III) and represents patients who are likely candidates for the drug in clinical practice but with elevated CV risk.

In some previous studies conducted in subjects with type 2 diabetes mellitus and ACS, composite annualized incidence rates of CV death, MI, and stroke ranged from 9% to 14%[15,16]; however, these studies were conducted in subjects who were randomized immediately post-ACS event. In contrast, in the PROACTIVE study,[17] which enrolled subjects with type 2 diabetes mellitus who were at high risk for CV events but who were not immediately post-ACS event, a broad CV composite incidence rate was 4%. Taking into account that this study population is not purely reflective of either of these populations, the assumed 3.5% annualized composite incidence rate is conservatively estimated based on a longer post-ACS interval before randomization, improvements in standard of care, and the need to account for a longer period of follow-up. With these assumptions, a total of 2700 subjects per treatment arm (5400 subjects overall) will be required and followed for approximately 4.75 years.

With the safety issues that have been arising with new chemical entities for a variety of therapeutic indications, scrutiny surrounding the extent of exposure of many agents before regulatory approval has increased in recent years.[7,13] The standard means for establishing CV safety in a placebo-controlled trial is to determine an HR with enough events to yield CIs narrow enough to provide assurance to both regulators and practitioners that a certain level of harm can be "ruled out." The event rate in populations targeted for certain noncardiac drugs may never be great enough to achieve high levels of confidence through standard statistical assessments, including some patient populations with type 2 diabetes. Therefore, by enrolling subjects with substantially elevated CV risk in EXAMINE, it is more likely that if alogliptin does not induce CV harm, the CV safety of the drug will be established.

There are a number of unique aspects of EXAMINE among type 2 diabetes studies. First, the trial is attempting to rule out a preapproval level of risk after approximately 1 year of treatment in a portion of the study population but then continuing the study for up to 3 to 4 additional years to continue to collect CV safety data. Although the intent of EXAMINE is to first rule out harm of the study drug, there is also the possibility that alogliptin may reduce CV harm and testing for superiority of the agent over that of placebo is part of the analysis plan if noninferiority is proven. This uniquely high CV risk study population should allow the investigators to answer a number of questions related to prediction of outcomes in ACS patients with type 2 diabetes because it relates to clinical parameters, concomitant drug therapies, and pharmacogenomic assessment of the patients at baseline.

Conclusions

EXAMINE is an important and novel trial for establishing CV safety of the DPP-4 inhibitor alogliptin in patients with type 2 diabetes and ACSs. The study has been ongoing since 2009 and has randomized approximately half of the study population. EXAMINE will provide extensive information on the safety of alogliptin for patients with type 2 diabetes who have substantially elevated CV risk. The results of the CV safety of alogliptin in patients with ACS could allow for calculation of the risk versus benefit for the more common lower CV risk groups with type 2 diabetes.

Acknowledgements

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Appendix A. Primary, secondary, and exploratory end points in EXAMINE

Primary end point will be the time from randomization to the first occurrence of any event in the primary MACE composite:

- CV death
- Nonfatal MI
- Nonfatal stroke

Secondary end point will be the time from randomization to the first occurrence of any event in the secondary MACE composite:

- CV death
- Nonfatal MI
- Nonfatal stroke
- Urgent revascularization because of unstable angina

Exploratory end points

Time from randomization to the occurrence of each event counted in the primary MACE composite end point:

- CV death
- Nonfatal MI
- Nonfatal stroke

Time from randomization to the first occurrence of any event in the exploratory MACE composite:

- All-cause mortality
- Nonfatal MI
- Nonfatal stroke
- Urgent revascularization because of unstable angina

Time from randomization to the first occurrence of any event in the exploratory MACE composite:

- All-cause mortality
- Nonfatal MI
- Nonfatal stroke
- Urgent revascularization because of unstable angina
- Hospitalization for heart failure

Time from randomization to CV death

- Recurrence of each of the following:

- Nonfatal MI
- Nonfatal stroke

Time from randomization to the first occurrence of any event in the exploratory CV composite:

- All-cause mortality
- Nonfatal MI
- Nonfatal stroke.
- Urgent revascularization because of unstable angina.
- Hospitalization for heart failure.
- Stent thrombosis.
- Hospitalization for other CV causes.
- Lower extremity amputation.

Renal function

- Changes from baseline in serum creatinine and eGFR, including the incidence of marked abnormalities.
- Incidence of renal dialysis.
- Incidence of kidney transplant.

Appendix B. EXAMINE steering committee, data safety monitoring committee, and CV end points committee members

Steering Committee:

William B. White, MD, Farmington, CT (Chair); George L. Bakris, MD, Chicago, IL; Richard M. Bergenstal, MD, Minneapolis, MN; Christopher P. Cannon, MD, Boston, MA; William C. Cushman, MD, Memphis, TN; Penny Fleck, MT (ex officio), Deerfield, IL; Simon Heller, MD, Sheffield, United Kingdom; Cyrus Mehta, PhD, Cambridge, MA; Steven E. Nissen, MD, Cleveland, OH; Alfonso Perez, MD, (ex officio), Deerfield, IL; and Faiez Zannad, MD, PhD, Nancy, France.

Data Safety Monitoring Committee:

Vivian A. Fonseca, MD, New Orleans, LA (Chair); Peter A. McCullough, MD, MPH, Southfield, MI; Cyrus Desouza, MBBS, Omaha, NE; David C. Goff, MD, PhD, Winston-Salem, NC; Frank E. Harrell, Jr, PhD, Nashville, TN.

Cardiovascular Endpoints Committee:

Venugopal Menon, MD, Cleveland, OH (Chair); Cathy Sila, MD, Cleveland, OH (Neurology); Vidyasagar Kalahasti, MD, Cleveland, OH (Cardiology).