Rationale, design, and baseline characteristics in Evaluation of LIXisenatide in Acute Coronary Syndrome, a long-term cardiovascular end point trial of lixisenatide versus placebo

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Background Cardiovascular (CV) disease is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). Furthermore, patients with T2DM and acute coronary syndrome (ACS) have a particularly high risk of CV events. The glucagon-like peptide 1 receptor agonist, lixisenatide, improves glycemia, but its effects on CV events have not been thoroughly evaluated.

Methods ELIXA (www.clinicaltrials.gov no. NCT01147250) is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of lixisenatide in patients with T2DM and a recent ACS event. The primary aim is to evaluate the effects of lixisenatide on CV morbidity and mortality in a population at high CV risk. The primary efficacy end point is a composite of time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. Data are systematically collected for safety outcomes, including hypoglycemia, pancreatitis, and malignancy.

Results Enrollment began in July 2010 and ended in August 2013; 6,068 patients from 49 countries were randomized. Of these, 69% are men and 75% are white; at baseline, the mean ± SD age was 60.3 ± 9.7 years, body mass index was 30.2 ± 5.7 kg/m^2, and duration of T2DM was 9.3 ± 8.2 years. The qualifying ACS was a myocardial infarction in 83% and unstable angina in 17%. The study will continue until the positive adjudication of the protocol-specified number of primary CV events.

Conclusion ELIXA will be the first trial to report the safety and efficacy of a glucagon-like peptide 1 receptor agonist in people with T2DM and high CV event risk. (Am Heart J 2015;169:631-638.e7.)

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The increasing prevalence of type 2 diabetes mellitus (T2DM) represents a significant public health concern due to its cardiovascular (CV) and concomitant long-term health consequences.[1,2] Epidemiological studies have demonstrated that patients with T2DM have both a 2- to 3-fold increased risk for the development of CV disease,[1-3] and >60% of deaths are secondary to CV complications.[4] Because patients with T2DM and acute coronary syndrome (ACS) are at particularly high risk for morbidity and mortality despite modern therapies,[5,6] the identification of cardioprotective therapies is especially important.

The glucagon-like peptide 1 receptor agonists (GLP-1RAs) are glucose-lowering agents that may have beneficial CV effects.[7] The US Food and Drug Administration (FDA)[8] and the European Medicines Agency[9] have established guidelines for phase II/phase III clinical trials to ensure that new therapies for diabetes are not associated with increased CV

risk. These recommendations, prompted by adverse CV effects of other glucose-lowering agents,[10-12] specified enrollment of high-risk participants, minimum treatment exposure of 18 to 24 months, blinded central adjudication of CV events, and sufficient number of events to exclude a 30% increase in risk. The ELIXA trial was designed to test the efficacy and safety of the GLP-1RA, lixisenatide. In this article, we describe the rationale for using lixisenatide, trial design, and randomized patient characteristics.

Rationale

Glucose-lowering therapy and CV risk

Evidence-based primary and secondary CV risk reduction strategies, such as the use of statins,[13,14] angiotensin-converting enzyme inhibitors, and β-blockers,[15-17] are effective in patients with T2DM. However, the role of glycemic control in CV risk reduction is less clear. A meta-analysis of clinical trials suggested that intensive glycemic control in patients with T2DM reduced the risk of nonfatal myocardial infarction (MI) but did not reduce total or CV-related mortality.[18] Furthermore, safety concerns about glucose-lowering agents in patients with coronary heart disease have been raised,[19-21] and data demonstrate that sulfonylureas inhibit protective ischemic preconditioning[10,11] and thiazolidinediones and 1 dipeptidyl peptidase 4 (DPP-4) inhibitor increase heart failure (HF) risk.[12,22]

Glucagon-like peptide 1 receptor agonists. Glucagon-like peptide 1 (GLP-1) is a gastrointestinal hormone that potentiates glucose-dependent insulin release and inhibits glucagon secretion, thereby decreasing hepatic glucose production, lowering basal and postprandial blood glucose, and promoting weight loss by enhancing satiety. The therapeutic utility of native GLP-1 is limited by its rapid degradation by the enzyme DPP-4. Consequently, GLP-1RAs were developed to retain many biological actions of native GLP-1 while extending its half-life by preventing enzymatic degradation. Glucagon-like peptide 1 receptor agonists improve glycemic control with minimal hypoglycemia and enhance weight loss.[23,24]

Lixisenatide is a once-daily GLP-1RA that lowers both fasting and postprandial blood glucose.[25] It has been evaluated in the treatment of T2DM as monotherapy[26] and as add-on therapy with oral agents[27] or basal insulins[28-31] and both oral agents and basal insulins.[29,32] Clinical trials show that lixisenatide reduced glycated hemoglobin (HbA1c) by 0.9% in monotherapy,[26] 0.8% to 0.9% in combination with an oral agent,[27] and 0.7% when added to basal insulin and oral agent.[29] Lixisenatide also reduced weight[27,33] and was associated with low risk of hypoglycemic events.[34] Nonetheless, lixisenatide's long-term CV safety and benefit in patients with T2DM and ACS have not been established.

Acute coronary syndrome. Patients with an ACS and T2DM are at a significantly increased risk for mortality, recurrent MI, and HF compared to those without T2DM.[6,35,36] Several factors may contribute to this diabetes-associated risk, including concomitant conditions such as renal insufficiency and hypertension, greater cardiac dysfunction, proinflammatory and prothrombotic states, greater burden of atherosclerosis, and detrimental effects of hyperglycemia and insulin resistance.[37,38] Because of the increasing prevalence of T2DM and the greater risk of adverse outcomes in individuals with T2DM and ACS, it is important to assess the CV effects of glucose-lowering agents.

Methods

Study design and objectives

ELIXA (www.clinicaltrials.gov no. NCT01147250) is a randomized, double-blind, placebo-controlled, parallel-group, multicenter phase III event-driven trial designed to assess the effects of lixisenatide added to current T2DM therapy on CV morbidity and mortality in patients with a recent ACS. The primary outcome is the composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina (UA). Secondary trial objectives include the examination of lixisenatide's effects on composite end points including CV death, nonfatal MI, nonfatal stroke, hospitalization for UA, hospitalization for HF, or coronary revascularization. Another trial objective is to assess the safety and tolerability of lixisenatide in patients with T2DM and ACS.

Population recruitment

The inclusion and exclusion criteria are listed in Table I. Patients with T2DM were identified and screened for a spontaneous ACS within 180 days following the hospital admission for the ACS but after discharge. Patients could have T2DM diagnosed by World Health Organization criteria before or after the qualifying ACS.[39] *Acute coronary syndrome* was defined as an ST-segment elevation MI (STEMI), non-STEMI, or UA. The clinical presentation required admission to an acute care facility and elevation of a cardiac biomarker (troponin or creatine kinase-MB isoenzyme [CK-MB]) above the reference range for MI or intermediate range for UA.

Randomization and study treatment

Eligible patients entered a run-in period of 7 (+3) days (online Appendix A). Patients were trained in self-administration of daily subcutaneous injections of volume-matched placebo (equivalent to 10 μg/d lixisenatide). At the end of the run-in period, eligible patients were randomized 1:1 to lixisenatide or volume-matched placebo for the double-blinded study treatment. In accordance with protocol (online Appendix B), the dose could be down- or up-titrated to a maximum of 20 μg/d in the absence of symptoms, such as hypoglycemia or gastrointestinal distress. Glycemic control will be managed according to the best judgment of site investigators and informed by clinical practice guidelines. Adjustment of background and

Table I. ELIXA inclusion and exclusion criteria

Inclusion criteria
1. Spontaneous ACS defined as STEMI, non-STEMI, or UA
   - Presentation for ACS leading to acute care facility admission AND
   - Elevated cardiac biomarker (troponin or creatine kinase-MB) above ULN* AND
   - Screening within 180 days following the hospital admission for the ACS but after discharge
2. Type 2 diabetes history or newly diagnosed defined by World Health Organization criteria: fasting venous PG ≥7.0 mmol/L (126 mg/dL) or 2-h postglucose load venous PG ≥11.1 mmol/L (200 mg/dL), confirmed on 2 occasions
3. Informed written consent

Exclusion criteria
1. Age <30 y
2. Type 1 diabetes
3. History of metabolic acidosis, including diabetic ketoacidosis within 6 m
4. Use of incretin-based agents other than study agent
5. History of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, inflammatory bowel disease, personal or family history of medullary thyroid cancer, or genetic conditions that predispose to medullary thyroid cancer
6. Planned revascularization procedure (PCI or coronary artery bypass graft) or coronary angiogram within 90 d after screening or randomization
7. PCI within 15 d
8. Women who are pregnant, lactating, or of childbearing potential without contraception
9. Clinically relevant history of gastrointestinal disease associated with prolonged nausea and vomiting
10. Laboratory data at screening (1 retest within 1 wk of result receipt is permitted and second result is decisive):
    - HbA1c <5.5% or >11%
    - Amylase and/or lipase >3× ULN
    - Calcitonin >20 pg/mL (5.9 pmol/L)
    - Alanine transaminase >3× ULN or total bilirubin >1.5× ULN (excluding Gilbert disease)
    - Estimated glomerular filtration rate <30 mL/min/1.73 m^2
    - Hemoglobin level <10 g/dL and/or neutrophils <1500/mm^3 and/or platelets <100,000/mm^3

Abbreviation: *PG*, Plasma glucose.
* Intermediate range troponin for UA.

Table II. ELIXA end points

Time to first occurrence of any of the following composite end points adjudicated and validated by the CAC

Primary
- CV death
- Nonfatal MI
- Nonfatal stroke
- Hospitalization for UA

Secondary
- Primary end points (as defined in A.) or hospitalization for HF
- Primary endpoints (as defined in A.) or hospitalization for HF or coronary revascularization procedure
- Percent change in the urinary albumin/creatinine ratio from baseline to 108 wk

Additional end points
- Cardiometabolic markers: glycated hemoglobin, fasting plasma glucose, high-sensitivity C-reactive protein, BNP, N-terminal proBNP
- Body weight
- Patient reported outcomes
- The Seattle Angina questionnaire
- The Diabetes Health Profile-18
- Euroqol EQ-5DThe McMaster Overall Treatment Evaluation

Abbreviations: *CAC*, CV events adjudication committee; *BNP*, B-type natriuretic peptide.

investigational drug treatment will be permitted, as is the prescription of other glucose-lowering medications, excluding GLP-1RAs and DPP-4 inhibitors (online Appendix B).

End points and safety assessment

The ELIXA end points are listed in Table II and defined in online Appendix C. In addition to analysis of all reported adverse events, hypoglycemia will be systematically assessed at each visit. Symptomatic hypoglycemia was defined as symptoms consistent with hypoglycemia, blood glucose <60 mg/dL (3.3 mmol/L), and/or prompt recovery after treatment. *Severe hypoglycemia* was defined as symptomatic hypoglycemia requiring assistance by another person, blood glucose <36 mg/dL (2.0 mmol/L), and/or prompt recovery after treatment. Prespecified safety end points will be monitored, including local injection site or allergic reactions and suspected pancreatitis or pancreatic cancer.

Statistical analysis

Sample size determination. Recruitment of 6,000 patients was projected to occur over 37 months with at least 10 months of follow-up for the last randomized patient. This event-driven study was designed to continue until 844 positively adjudicated events for the primary composite CV end point occurred, assuming a 10% annual event rate for the first year and a 7% annual event rate subsequently. This prespecified number of events was estimated to provide 96% power to demonstrate noninferiority of lixisenatide over placebo with the 1.3 noninferiority boundary, assuming a true risk ratio (RR) of 1.0, and 90% power to demonstrate superiority of lixisenatide over placebo, assuming a RR of 0.80.

Primary end point analyses. The primary efficacy analysis will be performed according to the intent-to-treat principle. All randomized patients will be followed up to the end of study for all nonfatal outcomes. The time to the first occurrence of the primary composite CV end point will be analyzed using a Cox proportional hazards model with treatment (lixisenatide and placebo) and geographical region as fixed-effect factors. Treatment effects across subgroups of gender, age, race, and duration of T2DM will be examined similarly. The HR and 2-sided 95% CI between lixisenatide and placebo will be estimated. Noninferiority of lixisenatide versus placebo will be established if the

Table III. Baseline characteristics of randomized population (n = 6068)

Age, y, mean ± SD	60.3 ± 9.7
Age ≥65 y	2043 (33.7)
Male	4207 (69.3)
Race	
Asian	768 (12.7)
Black	221 (3.6)
White	4563 (75.2)
Other	516 (8.5)
Ethnicity	
Hispanic	1768 (29.1)
BMI, kg/m^2, mean ± SD	30.2 ± 5.7
18.5-24.9	1017 (16.8)
25.0-29.9	2297 (37.9)
≥30	2734 (45.1)
Cholesterol, mg/dL, mean ± SD*	
Total	153 ± 44
Triglycerides	164 ± 113
High-density lipoprotein	43 ± 11
Low-density lipoprotein	78 ± 35
Fasting plasma glucose, mg/dL, mean ± SD†	148 ± 52
HbA1c, %, mean ± SD	7.7 ± 1.3
Days between qualifying ACS and screening, mean ± SD	64.0 ± 43.6
<30	1462 (24.1)
≥30 to <60	1959 (32.3)
≥60	2643 (43.6)
Days between qualifying ACS and randomization, mean ± SD	72.0 ± 43.6
<30	796 (13.1)
≥30 to <60	2184 (36.0)
≥60	3084 (50.9)
Qualifying ACS event	
STEMI	2667 (44.0)
Non-STEMI	2346 (38.7)
UA	1042 (17.2)
ACS intervention	
Percutaneous coronary intervention	3741 (61.7)
Coronary artery bypass graft	41 (0.7)
Thrombolytic	476 (7.8)
Smoking	
Current	707 (11.7)
Former	2744 (45.2)
Diabetes duration, y, mean ± SD	9.3 ± 8.3
Retinopathy	648 (10.7)
Neuropathy	1050 (17.3)
Estimated glomerular filtration rate (mL/min/1.73 m^2), mean ± SD	76.0 ± 21.3
<30	8 (0.1)
30-60	1398 (23.1)
60-90	3228 (53.4)
≥90	1413 (23.4)
Baseline albumin/creatinine ratio (mg/g)	
<30	4434 (74.3)
30-300	1146 (19.2)
≥300	389 (6.5)

Data presented are number (pecentages) unless otherwise indicated. Percentages are calculated based on the number of patients with available data. Abbreviation: *BMI*, Body mass index.
* SI units (mmol/L) = mg/dL * 0.0259.
† SI units (mmol/L) = mg/dL * 0.0555.

upper bound of the 2-sided 95% CI of the HR is <1.3, in accordance with the FDA's requirement to confirm CV safety of lixisenatide. Next, the superiority of lixisenatide over placebo will be established if the upper bound of the 2-sided 95% CI of the HR is <1.0. The *P* value will be calculated using the log-rank test for descriptive purposes.

Study organization and leadership

ELIXA was designed and will be managed by an executive committee comprising clinical experts in both cardiology and diabetes who are based in academic medical centers and sponsor representatives with clinical and methodological expertise in diabetes and clinical

Table IV. Baseline CV and diabetes medications

CV medications	
ACEI	3658 (60.3)
ARB	1604 (26.4)
ACE or ARB	5151 (84.9)
β-Blocker	5119 (84.4)
Diuretic	2015 (33.2)
Mineralocorticoid receptor antagonist	870 (14.3)
Calcium-channel blocker	1327 (21.9)
α1-Blocker	277 (4.6)
Hydralazine	51 (0.8)
Renin inhibitor	19 (0.3)
Nitrates	1541 (25.4)
Other antianginal	435 (7.2)
Aspirin	5726 (94.4)
Any thienopyridine	4495 (74.1)
Vitamin K antagonist	279 (4.6)
Factor Xa inhibitor	22 (0.4)
Other anticoagulant	480 (7.9)
Statin	5621 (92.6)
Ezetimibe	97 (1.6)
Fibrate	247 (4.1)
Nicotinic acid and derivatives	62 (1.0)
Digitalis glycoside	137 (2.3)
Amiodarone	139 (2.3)
Other antiarrhythmic	36 (0.6)
Other CV medications	125 (2.1)
Diabetes medications	
Any diabetes medications	5440 (89.7)
Metformin	3834 (63.2)
Sulfonylurea	1863 (30.7)
Glinide	71 (1.2)
Thiazolidinedione	84 (1.4)
Insulin	2292 (37.8)
Combination insulin and oral agent	1368 (22.5)
Combination metformin and sulfonylurea	1329 (21.9)
Other diabetes medications	329 (5.4)

Data presented are number (pecentages). Abbreviations: *ACEI*, Angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker.

Table V. Cardiovascular and diabetes history (n = 6068)

Coronary heart disease	
Stable angina pectoris	1313 (21.6)
UA pectoris	742 (12.2)
MI	1340 (22.1)
Percutaneous coronary intervention	1000 (16.5)
Coronary artery bypass graft	479 (7.9)
Cerebrovascular disease	
Stroke	314 (5.2)
Transient ischemic attack	135 (2.2)
Carotid artery stenosis (≥50%)	137 (2.3)
Carotid endarterectomy	35 (0.6)
Carotid artery stent insertion	34 (0.6)
Carotid artery bypass	8 (0.1)
Peripheral artery disease	365 (6.0)
Cardiac arrhythmia	
Atrial fibrillation or flutter	282 (4.6)
Ventricular fibrillation or tachycardia	66 (1.1)
Other CV history	
Hypertension	4581 (75.5)
Valvular heart disease	166 (2.7)
Implantable cardioverter defibrillator	41 (0.7)
Cardiac resynchronization therapy	8 (0.1)
Conventional pacemaker	65 (1.1)
Chronic HF	750 (12.4)
Other	507 (8.4)

Data presented are before qualifying ACS event and are number (percentages).

trials. The executive committee will assume responsibility for data integrity and interpretation, study content, and the primary manuscript. Additional committees established to ensure trial integrity as well as study drug safety and tolerability include a data monitoring committee consisting of members independent from the executive committee and sponsor to monitor patient safety; a CV event adjudication committee to evaluate and adjudicate, in a blinded fashion, all potential end points; a glycemia committee composed of endocrinologists to provide glycemic control support for site investigators and to ensure patient safety from hypoglycemia; an allergic reaction assessment committee composed of clinical immunologists independent of the sponsor and investigators and blinded to study treatment to assess allergic or allergic-like reactions; and a pancreatic safety assessment committee to review all pancreatic adverse events, including suspected pancreatitis and pancreatic cancer (online Appendix D).

ELIXA was approved by the appropriate institutional or central review boards. All trial participants provided written informed consent. This study was sponsored solely by Sanofi, and the authors were solely responsible for study design. The authors will be solely responsible for completion of the final manuscript, and statistical analyses (performed by the academic statistician and validated by the sponsor's statistician).

Results

Screening and enrollment into ELIXA began June 24, 2010, and randomization was completed on August 2, 2013. There were 7,718 candidates screened and 6,068 participants randomized to either lixisenatide or placebo (online Appendix A) from 49 countries across 6 regions (online Appendix E) with the support of 782 principal investigators (online Appendix F). One additional candidate was screened and randomized but excluded from analysis due to inadequate consent. Baseline data include data available and validated as of June 29, 2014.

Baseline clinical characteristics of the randomized population are shown in Table III. The mean ± SD age was 60.3 ± 9.7 years, 69.3% were male, and 75.2% were white. The index ACS events were STEMI (44.0%), non-STEMI (38.7%), and UA (17.2%). The mean ± SD duration between qualifying ACS and screening was 64.0 ± 43.6 days, and 61.7% of individuals had a percutaneous coronary intervention (PCI) after their ACS. The mean ± SD duration of T2DM was 9.3 ± 8.3 years, HbA1c was 7.7% ±

1.3%, and prevalence of obesity (BMI ≥30 kg/m^2) was 45.1%. Statin therapy was used by 92.6% of participants, and 37.8% were taking insulin (Table IV). Relevant CV and diabetic history before the qualifying ACS event is provided in Table V.

Discussion

ELIXA will determine the effects of lixisenatide, a GLP-1RA, compared to placebo on the burden of CV disease in patients with T2DM and ACS. Although native GLP-1 and GLP-1RAs exert favorable CV effects in animal models of MI and ischemia/reperfusion injury,[40-42] few data exist in humans. In small placebo-controlled studies, GLP-1RA treatment improved myocardial salvage and reduced infarct size.[43,44] A larger retrospective analysis revealed that the nonrandomized use of GLP-1RA was associated with a 19% lower CV event risk compared with other glucose-lowering agents.[45] In addition, a meta-analysis revealed a significant reduction in CV events among individuals taking GLP-1RAs rather than placebo or other glucose-lowering agents.[46] Therefore, ELIXA has been designed and powered to verify the CV safety of lixisenatide by demonstrating FDA-mandated noninferiority to placebo and to assess superiority in CV outcomes once noninferiority has been established.

To date, prior randomized CV studies of glycemic agents have demonstrated mixed and, sometimes, unexpected results. In the PROactive study, the thiazolidinedione, pioglitazone, reduced the secondary composite end point of nonfatal MI, stroke, and death but was associated with increased HF events.[47] Although a meta-analysis suggested rosiglitazone increased ischemic events, the RECORD trial demonstrated no effect on CV events or mortality, although HF events were increased.[48]

Recently, CV trials of the DPP-4 inhibitors, saxagliptin (SAVOR-TIMI 53)[49] and alogliptin (EXAMINE),[50] demonstrated noninferiority compared to placebo for primary CV efficacy end points, but superiority was not demonstrated. Notably, an increase in HF hospitalizations was observed with saxagliptin.[49] A phase III clinical trial of aleglitazar, a combined peroxisome proliferator-activated receptor-α/γ agonist (ALECARDIO), was halted due to safety and efficacy concerns, despite favorable effects on HbA1c and lipids.[51] Finally, a pragmatic design CV outcome trial (TECOS) is currently investigating the CV safety of the DPP-IV inhibitor, sitagliptin, in more than 14,000 patients with T2DM and vascular disease.[52] These studies highlight the importance of CV outcome trials in patients with T2DM.

Several trials are ongoing or planned to investigate the safety and efficacy of GLP-1RAs in patients with high CV risk (online Appendix G). LEADER, a phase IIIB placebo-controlled trial, is evaluating the CV safety of liraglutide in patients with T2DM.[53] In addition, studies of exenatide, dulaglutide, and semaglutide will focus on patients with T2DM and either established or high risk for CV disease. ELIXA will be the first to report long-term CV outcomes of a GLP-1RA in patients with T2DM and recent ACS event.

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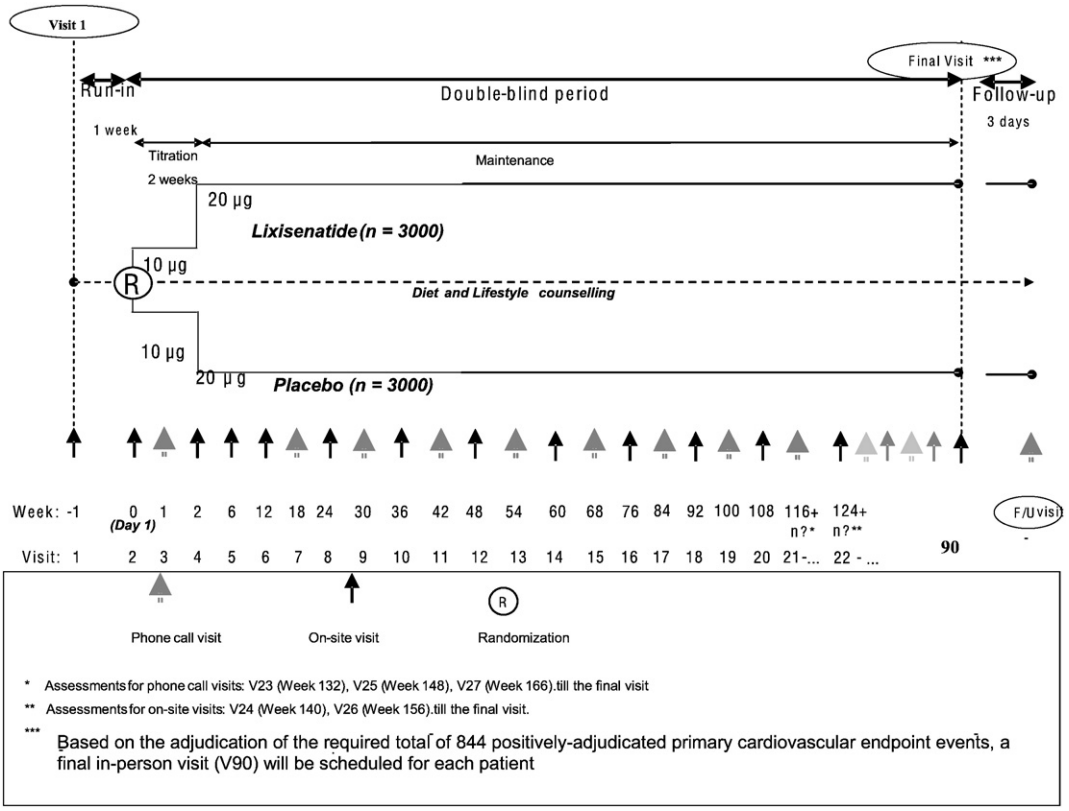
Appendix A. ELIXA trial design



Appendix B. Guidance for protection against hypoglycemia

- For patients with a screening HbA_{1c} <8.5% and treated with either insulin, glinide, or a sulfonylurea (SU), the dose should be decreased at baseline (visit 2, randomization). The following guidance should be applied:
  - For SU or glinide, decrease the dose by 25% to 50% (or discontinue in case of minimum dose).
  - For insulin, decrease the total dose by 20%.
- After randomization, SU, glinide, or insulin dose can be adjusted at the investigator's discretion.

Appendix C. ELIXA end point definitions

Appendix C.1. Cardiovascular death

Appendix C.1.1. Fatal MI.

a. Death occurring within 14 days after a documented MI, in which there is no conclusive evidence of any other cause of death. Subjects who are being treated for a MI and who die as a result of complications of the MI (eg, sudden death, pump failure, or cardiogenic shock) will be classified as having had an MI-related death
   OR
b. Autopsy evidence if a recent infarct with no conclusive evidence of any other cause of death.
   OR
c. An abrupt death that has characteristics suggestive[n] of an acute infarct but do not meet the strict definition of an MI.

Appendix C.1.2. Pump failure. Death occurring in the context of clinically worsening symptoms and/or signs of HF without evidence of another cause of death.

Death occurring after the implementation of a ventricular assist device or after surgery primarily for refractory HF.

[n] Suggestive characteristics are presentation with acute ischemic symptoms and electrocardiographic changes indicative of an acute injury or abnormal cardiac biomarkers or other evidence (eg, echocardiography, ventriculography, or scintigraphy) of new ventricular wall motion abnormality.

Death occurring after referral to hospice specifically for progressive HF.

Note: If worsening HF is secondary to MI, then MI should be listed as the primary cause of death if the subject had an MI within 14 days of death (as above).

Appendix C.1.3. Sudden death. Death occurring unexpectedly in an otherwise stable subject. Further subclassification:

(1) death witnessed or subject last seen alive <1 hour previously or
(2) subject last seen alive ≥1 hour and <24 hours previously

Appendix C.1.4. Presumed sudden death. Death occurring unexpectedly in an otherwise stable subject last seen alive 24 hours previously with circumstances suggestive of sudden death.

Appendix C.1.5. Presumed CV death. Death likely due to a CV cause in which the available clinical data are insufficient to support a more specific cause of death.

Appendix C.1.6. Fatal stroke.

a. **Ischemic stroke.** Death occurring as a result of documented ischemic stroke.
b. **Hemorrhagic stroke.** Death occurring as a direct result of documented hemorrhagic stroke.
c. **Clinical stroke.** Death occurring as a direct result of documentation based on clinical circumstances and identified as unknown type stroke.

Appendix C.1.7. Fatal pulmonary embolism. Death occurring as a direct result of documented pulmonary embolism.

Appendix C.1.8. Procedure-related death. Death occurring during a CV procedure-related death or as a result of procedure-related complications (usually within 14 days of the CV procedure).

Appendix C.1.9. Other CV death. Death resulting from a specifically documented CV cause other than those listed above.

Appendix C.2. Non-CV death

If an unequivocal and documented non-CV cause can be established as the primary cause of death, the event will be classified as non-CV. Non-CV deaths will be further classified into the following categories:

A. Infection
B. Malignancy
C. Pulmonary
D. Gastrointestinal
E. Renal
F. Accidental
G. Suicide
H. Diabetes related
I. Other non-CV (specify)

Appendix C.3. Unknown death

Death in which insufficient data are available to make a reasonable differentiation between CV and non-CV causes of death.

Appendix C.4. Nonfatal end point definitions

The CV events adjudication committee will receive for review and adjudicate all occurrences of the following nonfatal end points:

1. Hospitalization for HF[o]
2. Myocardial infarction
3. Hospitalization for UA[†]
4. Stroke
5. Coronary revascularization

1. Hospitalization for HF
Unplanned presentation to an acute care facility for an exacerbation of HF requiring an overnight stay (change in calendar day) which meets the following criteria (I-III):
I. Symptoms of HF:
At least 1 of the following:
a. Worsening dyspnea
b. Worsening orthopnea
c. Paroxysmal nocturnal dyspnea
d. Increasing fatigue/worsening exercise tolerance
II. Signs of HF:
At least 2 of the following:
a. Rapid weight gain
b. Pulmonary edema or rales
c. Elevated jugular venous pressure
d. Radiologic signs of HF
e. Peripheral edema
f. Increasing abdominal distension or ascites
g. S3 gallop
h. Hepatojugular reflux/hepatomegaly
i. Elevated BNP or NT-pro-BNP
III. Treatment for HF:
At least 1 of the following:
a. Treatment with intravenous diuretics, vasodilators, or inotropes.
b. Mechanical fluid removal (eg, ultrafiltration or dialysis).
c. Insertion of an intraaortic balloon pump for hemodynamic compromise.
d. Initiation of oral diuretics or intensification of the maintenance oral diuretic dose.

[o] *Hospitalization* is defined as admission to an acute care facility (ie, hospital, emergency department, observation unit) with a change in calendar day from hospital presentation to discharge.

2. Myocardial infarction
   Summary criteria for positive adjudication:
   - Spontaneous MI: Elevated cardiac markers (CM) and either new electrocardiographic (ECG) changes or a clinical presentation consistent with an acute MI.
   - PCI-related MI: Elevated CM (or other criteria in the absence of elevated CM).
   - Coronary artery bypass graft (CABG)–related MI: Elevated CM and new ECG changes (or other criteria).

Detailed criteria for positive adjudication:

a. Spontaneous MI:
   Cardiac markers:
   - Troponin[p] >upper limit of normal (ULN) or
   - CK-MB >ULN

and at least 1 of the following:
   - Ischemic symptoms: rest or accelerated symptoms (pain, dyspnea, and pressure) consistent with myocardial ischemia.
   - ECG changes consistent with infarction:

- New significant Q waves (or R waves in V_1-V_2) in 2 contiguous leads in absence of previous left ventricular hypertrophy or conduction abnormalities. OR
- Evolving ST-segment to T-wave changes in ≥2 contiguous leads.
- Development of new left bundle-branch block.
- ST-segment elevation requiring thrombolytics or PCI.

b. PCI-related MI:
   Cardiac markers[q]:
   1. Assuming baseline value <ULN
   2. Within 48 hours of procedure

a. Troponin[p] >3× ULN OR
b. CK-MB >3× ULN

c. CABG-related MI:
   Cardiac markers:
   1. Assuming baseline value <ULN
   2. Within 72 hours of procedure

a. Troponin[p] >5× ULN OR
b. CK-MB >5× ULN
   AND
c. New pathologic Q waves or left bundle-branch block, new native or graft vessel occlusion, or imaging evidence of loss of viable myocardium.

3. Hospitalization for UA
   a. Unplanned hospitalization for worsening angina defined as rest or accelerated symptoms (pain, dyspnea, and pressure) consistent with myocardial ischemia AND
   b. Cardiac markers (CK-MB or troponin) suggestive of myocardial injury but not meeting MI criteria.

Note: if abnormal troponin, value must be in the suggestive (middle) range and below the threshold for MI.

4. Stroke:
Stroke is defined as one of the following (1-4):
   1. A new, focal neurologic deficit of central origin lasting >24 hours, irrespective of imaging findings.
   2. A new, focal neurologic deficit of central origin lasting <24 hours with imaging evidence of new cerebral infarction or intracerebral hemorrhage consistent with the reported deficits.
   3. A new, focal neurologic deficit of central origin lasting <24 hours that was treated with thrombolytic therapy or directed percutaneous intervention.
   4. A new, nonfocal encephalopathy lasting >24 hours with imaging evidence of cerebral infarction or hemorrhage adequate to account for the clinical state.

Note: retinal artery ischemia or hemorrhage is included in the definition of stroke.

Classification:
Stroke will be further classified as follows:

   a. Ischemic stroke: stroke with imaging suggesting ischemic changes
   b. Ischemic stroke with hemorrhagic conversion: stroke with evidence of hemorrhage on imaging, judged to be hemorrhagic transformation of a primary ischemic stroke.
   c. Primary intracranial hemorrhage: stroke with evidence on imaging of intracerebral hemorrhage not due to a transformation of an ischemic stroke.
   d. Unknown: imaging is unavailable or inconclusive.

5. Coronary revascularization
   Urgent coronary revascularization is defined as nonelective coronary revascularization[r] (PCI or CABG) for the management of ACS (hospitalization for myocardial ischemia, UA, or MI) performed as soon as can be arranged. Nonurgent revascularization is any PCI or CABG not meeting criteria for urgent revascularization.

[p] If troponin given in ranges, the ULN for MI will be the lowest value in the necrosis range.

[q] In the absence of cardiac markers, new pathologic Q waves that are persistent upon discharge or documentation of new wall motion abnormality (other than septal) will also meet criteria.

[r] Note for PCI: includes balloon angioplasty (or PTCA), coronary stenting, atherectomy, brachytherapy, laser, and rotational ablation.

Appendix D. Committee membership

Appendix D.1. Executive committee

Marc A. Pfeffer, MD, PhD (Chair)	United States
Rafael Diaz, MD	Argentina
Kenneth Dickstein, MD	Norway
Hertzel Gerstein, MD	Canada
Lars Køber, MD	Denmark
Eldrin Lewis, MD	United States
Aldo Maggioni, MD	Italy
John McMurray, MD	United Kingdom
Jeffrey Probstfield, MD	United States
Matthew Riddle, MD	United States
Scott Solomon, MD	United States
Jean-Claude Tardif, MD	Canada

Appendix D.2. Cardiovascular events adjudication committee

Scott D. Solomon, MD (Chairman)
Eldrin F. Lewis, MD (Co-Chairman)
Ebrahim Barkoudah, MD
Rhonda Bentley-Lewis, MD
Abdel Brahimi, MD
David Charytan, MD
Peter Finn, MD
Aiden Flynn, MD
L. Howard Hartley, MD
Galen Henderson, MD
Jacob Joseph, MD
Kayode Odutayo, MD
Vinutha Rajesh, MD
Ali Vazir, MD
Larry Weinrauch, MD

Appendix D.3. Glycemia committee

Matthew Riddle, MD (Chair)	United States
Rhonda Bentley-Lewis, MD	United States
Stefano del Prato, MD	Italy
John Petrie, MD	United Kingdom

Appendix D.4. Allergic reaction assessment committee

Allen Kaplan, MD (Chair)	United States
Phil Lieberman, MD	United States
Bruce L. Zuraw, MD	United States

Appendix D.5. Pancreatic safety assessment committee

Eileen O'Reilly, MD (Chair)	United States
Keyur Patel, MD (Co-Chair)	United States
Peter Allen, MD	United States
Aldo Scarpa, MD	Italy
Mark Schattner, MD	United States

Appendix D.6. Data monitoring committee

Christopher Granger, MD (Chair)	United States
Jean Rouleau, MD	Canada
David DeMets, PhD	United States
Nishi Chaturvedi, MD	United Kingdom
Denis Raccah, MD (non-voting)	France

Appendix E. Randomized participants by region

Region	n (%)
United States and Canada	807 (13)
Central and South America and Mexico	1944 (32)
Eastern Europe	1587 (26)
Asia and Pacific islands	703 (12)
Africa/Near East	296 (5)
Western Europe	731 (12)

Appendix F. ELIXA participating countries (no. of patients) and principal investigators

Argentina (399): Aizenberg, Diego; Alvarez, Carlos; Alvarisqueta, Andres; Baccaro, Claudia; Bartolacci, Ines; Bordonava, Anselmo; Bustamante Labarta, Miguel; Caccavo, Alberto; Calella, Pedro; Cantero, Maria; Codutti, Renzo; Commendatore, Victor; Costamagna, Osvaldo; Cuello, Jose; Fernandez, Alberto; Garcia Duran, Ruben; Gomez Vilamajo, Oscar; Gorban de Lapertosa, Silvia; Grinfeld, Diego; Hermida, Sonia; Lagrutta, Mariana; Leon de la Fuente, Ricardo; Licheri, Alberto; Luciardi, Hector; Mackinnon, Ignacio; Maffei, Laura; Marino, Javier; Montaña, Oscar; Novaretto, Leonardo; Orio, Silvia; Orlandini, Andres; Oviedo, Alejandra; Pérez Manghi, Federico; Patocchi, Cristian; Ramos, Hugo; Rolandi, Florencia; Saa Zarandon, Raquel; Saavedra, Silvia Salome; Schiavi, Lilia; Schygiel, Pablo; Trivi, Marcelo; Ulla, Maria; Urdiales, Pedro; Vallejos, Julio; Vico, Marisa; Waisman, Florencia. Australia (17): Amerena, John; Paul, Vincent; Sangla, Kunwarjit; Van Gaal, William; Yeap, Bu. Austria (4): Fasching, Peter; Pieber, Thomas. Belarus (34): Danilova, Larisa; Mitkovskaya, Natalya; Sudzhaeva, Svetlana. Belgium (15): Mathieu, Chantal; Pouleur, Anne–Catherine. Brazil (448): Botelho, Roberto Vieira; Cerqueira, Maria Jose; Chacra, Antonio; Dos Santos, Fabio; Feitosa, Gilson; Forti, Adriana; Golbert, Milton; Halpern, Alfredo; Hissa, Miguel; Lisboa, Hugo; Moraes Junior, Joao; Nery, Max; Quadros, Alexandre; Raduan, Roberto; Reis, Gilmar; Ribeiro Filho, Fernando; Rollin, Guilherme; Rossi, Paulo; Santos, Elizabete; Sgarbi, Jose; Souza, Juliana; Souza, Maria Regina.

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Estonia (52): Ambos, Anu; Jakovlev, Ulle; Lubi, Maire; Märtsin, Kaja; Rosenthal, Svea; Vides, Hella. Finland (44): Alanko, Juha; Korsoff, Pirkko; Koski, Anna-Mari; Lahtela, Jorma; Nelimarkka, Lassi; Tuomilehto, Jaakko. France (38): Cariou, Bertrand; Catargi, Bogdan; Ducloux, Roxane; Hadjadj, Samy; Kerlan, Veronique; Malecot, Jean-Marc; Petit, Catherine; Rodier, Michel. Georgia (58): Chumburidze, Vakhtang; Glonti, Salome; Lominadze, Zaza; Todua, Fridon. Germany (96): Contzen, Christel; Dr. Marck, Cornelia; Fischer, Hermann; Hagenow, Andreas; Himpel-Bönninghoff, Agnes; Kihm, Lars; Killat, Holger; Kleinertz, Klaus; Kosch, Christine; Kreutzmann, Kristin; Lappo, Mariola; Mertes, Bernardo; Piechatzek, Richard; Prohaska, Martin; Rinke, Andrea; Schellenberg, Detlev; Toursarkissian, Nicole. Guatemala (142): Arango, Juan; Gonzalez, Ronaldo; Granados, Arnoldo; Herrera, Milton; Montenegro, Pablo; Munoz, Ricardo; Rodriguez, Edgar; Turcios, Erick; Villalobos, Renato; Wyss, Fernando. India (317): Hatterjee, Sanjay; Chopda, Manoj; Chopra, Vijay; Deshpande, Neeta; Dutta, R; Dwivedi, Sudhanshu; Gandhi, Pramod; Gupta, Dr. Sandeep Kumar; Gupta, Jugal Bihari; Gupta, Sunil; Hiregouder, Narendra; Jha, Sujeet; Joshi, Abhijeet; Khan, Noor; Kumbla, Mukund; Magdum, Mohan; Murthy, Keshava; Prabhu, Mukhya; Sahay, Rakesh; Sethuraman, Selvamani; Shah, Dr Navneet; Shamanna, Paramesh; Singh, K. Singh; Singh, Paminder; Somasekharan, Arun; Sreenivasamurthy, Lakshminarayanappa; Supe, Pravin. Israel (65): Adawi, Faiad; Atar, Shaul; Cohen, Ohad; Efrati, Shai; Karnieli, Eddy; Klainman, Eliezer; Minuchin, Oscar; Mosenzon, Ofri; Stern, Naftali; Turgeman, Yoav; Wainstein, Julio. Italy (69): Aimaretti, Gianluca; Berra, Cesare; Ciardullo, Anna Vittoria; Consoli, Agostino; Cucinotta, Domenico; Del Prato, Stefano; Di Marco, Sandra; Giorda, Carlo; Giordano, Carla; Mannucci, Edoardo; Orsi, Emanuela; Piatti, Piermarco; Pontiroli, Antonio; Ponzani, Paola; Pozzilli, Paolo; Rivellese, Angela. Japan (103): Akahori, Hiroshi; Eki, Yutaka; Fujii, Kenshi; Hata, Yoshiki; Himeno, Hideo; Hirayama, Atsushi; Kishimoto, Ichiro; Kobayashi, Youichi; Miyaoka, Hiroaki; Niiya, Tetsuji; Nishi, Yutaro; Nozaki, Akira; Nunohiro, Tatsuya; Saito, Tomiyoshi; Satoh, Yasuhiro; Takahashi, Akihiko; Takahashi, Junichiro; Takase, Hiroyuki; Takase, Shinichi; Tsuboko, Yusuke; Tsujimoto, Mitsuru; Tsujino, Motoyoshi; Tsuzuki, Masahiro; Watanabe, Shuichi; Yamada, Takahisa. Republic of Korea (74): Chung, Wook Jin; Rim, Sejoong; Jang, Hakchul; Kim, Ung; Chung, Choon Hee; Shin, Sung-Hee; Kim, Kyehun; Kim, Jaetaek; Rha, Seungwoon; Lee, Nae Hee; Kim, Chong-Jin; Park, Kyong Soo. Latvia (56): Amolina, Ildze; Ducena, Kristine; Helda, Renate; Konrade, Ilze; Pirags, Valdis; Sime, Iveta; Sokolova, Jelena. Lithuania (48): Kakariekiene, Vaida; Kavaliauskiene, Roma; Petrulioniene, Zaneta; Sakalyte, Gintare; Urboniene, Audrone; Zarankiene, Rima. Mexico (301): Uribe, Marittza; Garcia–Hernandez, Pedro; Garza, Jose; Vazquez-Garcia, Abraham; Gonzalez, Jose Gerardo; Escalante, Miguel; Zavala, Alejandro; Bayram, Edmundo; Hernandez-Muñuzuri, Jesus; Ramos; Lopez, Gabriel Arturo; Lujan, Jesus; Garcia-Soria, Martin; Velasco-Sanchez, Raul; Rodriguez, Ignacio; Jimenez, Silvia; Galeana, Cielmar; Reyes, Eduardo; Lara, Susano; Garcia-Castillo, Armando; Castro, Maria Guadalupe; Aguilar-Orozco, Raul; Lopez Rosas, Enrique; Vidrio, Maricela; Llamas, Guillermo; Stobschinski de Alba, Carlos Alejandro; Carranza-Madrigal, Jaime; Cardosa-Torres, Francisco. Netherlands (27): Cornel, Jan Hein; Dekkers, Paulus; Frederiks, J; Hermans, Wrm; Lok, Dirk; Meeder, Joan; Nierop, Peter. Norway (30): Cooper, John; Lappegård, Knut Tore; Nedrebø, Bjørn Gunnar. Panama (9): Castro, Eholo; Gonzalez Castillo, Baldomero; Gonzalez, Elis; Nieto Ortega, Ruben. Peru (107): Andrade, Miguel; Calderon, Jorge; Chavez, Carlos; Correa Flores, Roger Martin; Farfan, Julio; Lu, Libia; Luque, Edith; Manrique, Helard; Mogrovejo, Walter; Pariona-Javier, Marcos; Pinto, Miguel; Roldan, Yudy; Zubiate, Carlos. Philippines (50): Dans, Antonio; Gomez, Maria Honolina; Panelo, Araceli; Rey, Nannette; Sulit, Dennis Jose; Sy, Rosa Allyn; Timonera, Miriam. Poland (250): Bednarski, Janusz; Bijata-Bronisz, Renata; Bryniarski, Leszek; Busz-Papiez, Benita; Czajkowska-Kaczmarek, Eugenia; Drzewiecka, Anna; Dulak, Elzbieta; Gorska, Maria; Hamankiewicz, Maciej; Janik, Krzysztof; Kincel, Krzysztof; Konieczny, Marek;

Lubinski, Andrzej; Olszanecka-Glinianowicz, Magdalena; Ponikowski, Piotr; Pulka, Grazyna; Rekosz, Jerzy; Skudlarski, Dariusz; Szymkowiak, Katarzyna; Wilczewski, Przemyslaw. Portugal (24): Bragança, Nuno; Duarte, João; Monteiro, Pedro; Rodrigues, Elisabete; Vinhas, Margarida. Romania (230): Adina, Pop-Moldovan; Avram, Rodica Ioana; Cif, Adriana; Creteanu, Gabriela; Dragomir, Dinu; Ferariu, Ioana Emilia; Iancu, Adrian-Corneliu; Istratoaie, Octavian; Ivanica, Gabriel; Lichiardopol, Radu; Militaru, Constantin; Minescu, Bogdan; Onaca, Adriana; Pintilei, Ella; Podoleanu, Cristian; Pop, Lavinia; Popa, Bogdan; Ranetti, Aurelian Emil; Rosu, Doina; Tase, Adrian; Tesloianu, Dan Nicolae; Vinereanu, Dragos. Russian Federation (587): Ageev, Fail; Akhmedzhanov, Nadir; Barbarash, Olga; Barbarich, Vladimir; Belousov, Yury; Berns, Svetlana; Bokarev, Igor; Bolshakova, Olga; Boyarkin, Mikhail; Chumakova, Galina; Dmitry, Platonov; Fitilev, Sergey; Galyavich, Albert; Glezer, Maria; Ivanova, Luidmila; Kalashnikov, Victor; Kalashnikova, Marina; Karpov, Yuri; Khaisheva, Larisa; Khalimov, Yuri; Kobalava, Zhanna; Kosmachova, Elena; Kostenko, Victor; Koziolova, Natalya; Kulibaba, Elena; Lesnov, Victor; Libov, Igor; Lyamina, Nadezhda; Markov, Valentin; Moiseev, Valentin; Molchanova, Olga; Oleynikov, Valentin; Orlikova, Olga; Panov, Alexey; Rafalskiy, Vladimir; Rodionova, Tatiana; Samitin, Vasily; Schokotov, Vladimir; Shilkina, Nataliya; Shogenov, Zaur; Shustov, Sergey; Shvarts, Yuri; Sobolev, Konstantin; Stryuk, Raisa; Suplotova, Ludmila; Viktorova, Inna; Vishnevsky, Alexander; Vorokhobina, Natalia; Yakusevich, Vladimir; Yakushin, Sergey; Zadionchenko, Vladimir; Zalevskaya, Alsu; Zalevsky, Grigory; Zateyshchikova, Anna. Serbia (69): Andjelic Jelic, Marina; Kocic, Radivoj; Komnenovic, Snezana; Lalic, Katarina; Lalic, Nebojsa; Micic, Dragan; Otasevic, Petar; Pesic, Milica; Seferovic, Petar; Stankovic, Goran. South Africa (130): Arnold, Susan; Burgess, Prof Lesley; Coetzee, Kathleen; Dawood, Saleem; Delport, Eluned; Ebrahim, I; Ellis, Graham; Ismail, Siddique; Kelbe, Dudley; Naidoo, Visvakuren; Ntsekhe, Mpiko; Sebastian, Peter John; Siebert, Mirna; Van Zyl, Louis; Venter, Tjaart. Spain (154): Lonso, Elena; Antorrena, Isabel; Bodi, Vicent; Botella, Marta; De La Fuente, Javier; Delgado, Elias; Duran Garcia, Santiago; Elorza, Jose; Enciso, Fidel; Gaztambide, Sonia; Marin, Francisco; Martin, Victoria; Mauricio, Didac; Soto, Alfonso; Vida, Manuel. Sweden (43): Boberg, Gunnar; Jörneskog, Gun; Jendle, Johan; Mathiesen, Ulrik; Svensson, Karl-Axel; Torstensson, Ingemar; Vasko, Peter. Switzerland (8): Moccetti, Tiziano. Taiwan (29): Chiang, Chern-En; Chiu, Yu-Wei; Huang, Tsuei-Yuan; Lu, Chieh-Hsiang; Pei, Dee; Shyu, Kou-Gi; Ueng, Kwo-Chang; Wang, Tzung-Dau. Tunisia (26): Abid, Mohamed; Ben Abdallah, Nejib; Haouala, Habib; Slimane, Hedia; Zidi, Borni. Turkey (55): Bascil Tutuncu, Neslihan; Camsari, Ahmet; Delibasi, Tuncay; Dinccag, Nevin; Kultursay, Hakan; Oto, Ali; Sahin, Mahmut; Saygili, Fusun; Yigit, Zerrin; Zorkun, Cafer. Ukraine (127): Karpenko, Oleksandr; Korpachev, Vadym; Koval, Olena; Maslyanko, Vitaliy; Perepelytsya, Mykhaylo; Pertseva, Tetyana; Petrosyan, Olena; Rudenko, Leonid; Sychov, Oleg; Synenko, Volodymyr; Tseluyko, Vira; Zhuravleva, Larisa. United Arab Emirates (14): Al Mahmeed, Wael; Kaddaha, Ghaida Mohamad. United Kingdom (125): Andrews, Robert; Bain, Stephen; Basu, Ambar; Bhatnagar, Deepak; Bickerton, Alex; Browne, Duncan; Gibson, Martin; Hammond, Peter; Hanna, Fahmy; Issa, Basil; Jaap, Alan; Joseph, Franklin; Jude, Edward; Kelly, Chris; Khan, Atir; Malik, Rayaz; Mukhopadhyay, Babu; O'kane, M; Rayman, Gerry; Robinson, Anthony; Rooney, Desmond; Sainsbury, Chris; Saravanan, Ponnusamy; Shakher, Jayadave; Singh, Baldev; Turner, Jeremy; Whitelaw, Donald; Wilding, John; Wiles, Philip. United States of America (696): Adenuga, Babafemi; Ahmad, Zia; Akinboboye, Olakunle; Akright, Laura; Alappat, Paul; Alawad, Mohamad; Alfonso, Teresa; Alimard, Ramin; Alzohaili, Opada; Ariani, Mehrdad; Arora, Chander; Azad, Nasrin; Azzam, Samir; Benjamin, Sabrina; Block, Bradley; Borzadek, Eliza; Breisblatt, Warren; Bright, Tamis; Byrd, Leroy; Chiou, Choyen; Chochinov, Ronald; Christensen, Tom; Christofides, Elena; Cohen, Robert; Dawood, Gamil; De Souza, Jose; Dempsey, Michael; Eagerton, Donald; East, Cara; Elder, Charles; Fernando, Ronald; Fogelfeld, Leon; Foucauld, Jean; French, William; Frohnauer, Mary; Gaffney, Mary; Gangopadhyay, Subroto; Gogia, Harinder; Gosmanov, Aidar; Greenberg, Craig; Greenway, Frank; Hanna, Edward; Hargrove, Joe; Harris, Anthony; Harris, Bill; Hart, Terence; Herrington, David; Hewitt, Mitzie; Howard, David; Izuora, Kenneth; Jetty, Preetham; Kapoor, Anoop; Kasper, Joseph F; Kelehan, Shaun; Kelly, Richard; Kereiakes, Dean; Khaira, Ajit; Khan, Misal; Khan, Salman; Korban, Elie; Kosiborod, Mikhail; Laguerre, Jacques; Larocque, James; Latif, Kashif; Lester, Frank; Levin, Philip; Levine, Steven; Li, Charles; Lovell, Charles; Lupovitch, Steven; Madu, Ivy-Joan; Mahabadi, Vahid; Mahmood, Asif; Maragos, Stavros; Mariash, Cary; Martin, Paul; Mathew, James; Mathew, John; May, Michael; Mayfield, Ronald; McCall, Anthony; Mcdaniel, Clayton; Mcgrew, Frank; Mckenzie, Marcus; Mefford, Ivan; Mehta, Arvind; Mikdadi, Ghiath; Mikhail, Magdy; Monchamp, Travis; Moore Ii, Charles; Moran, Michael; Morrar, Nidal; Mosley, Jonathan; Mulford, Mim; Murray, John; Nakhle, Samer; Nallasivan, Mani; Odio, Alberto; Oh, Charles; Olelewe, Sarah; Palchick, Bryce; Paliwal, Yogesh; Papademetriou, Vasilios; Parikh, Naresh; Patel, Sudhirkumar; Phillips, Lawrence; Pitts, Thomas; Prieto, Francisco; Puttnam, Rachel; Quyyumi, Arshed; Randhawa, Preet; Rendell, Marc; Rhie, Francis; Roberts, James; Robinson, Jerome; Robinson, Michael; Rubino, John; Ryan, Eugene; Saathoff, Steven; Sachmechi, Isaac; Saifi, Ali; Salacata, Abraham; Sanders, Robyn; Sanson, Jodi; Savin, Virginia; Schabauer, Alex; Schmedtje, John; Schwartz, Alan; Scott, Cranford; Selagamsetty, Munni; Shannon, Michael; Shaw, Sylvia; Singal, Dinesh; Sjoberg, Robert; Smith, Kenneth; Sofley, Carl; Sonn, Anthony; Sorof, Suzanne; Soroka, Eugene; Spellman, C.W.; Steinhoff, Jeffrey; Suresh, Damodhar; Tahir, Mohammad; Tanenberg, Robert; Thawani, Hemant;

Thomson, Stephen; Thrasher, James; Trachtenbarg, David; Trotta, Michael; Tuan, Weiming; Twahirwa, Marcel; Umpierrez, Guillermo; Vaid, Brij; Vance, Carl; Wang, Thomas; Warner, Alberta; Watson, Henry; Weber, Sandra; Webster, Brian; Weindorff, Kathleen; Welch, Michelle; Welker, James; White, Anthony; White, Lindsey; Williams, Marcus; Wu, Wen-Chih; Wynne, Alan; Yocono, Mark; Yuen, Kevin.

Appendix G. GLP-1 CV outcome trials in type 2 diabetes

Agent	Trial	Start date	Expected completion date	n	Trial details	Inclusion criteria	HbA1c
Exenatide	EXSCEL	June 2010	April 2018	14,000*	http://clinicaltrials.gov/ct2/show/NCT01144338	T2DM only	6.5%-10%
Lixisenatide	ELIXA	June 2010	January 2015	6068	http://clinicaltrials.gov/ct2/show/NCT01147250	ACS	5.5%-11%
Liraglutide	LEADER	August 2010	October 2015	9340	http://clinicaltrials.gov/ct2/show/NCT01179048	CVD or age/CV risk factors	≥7%
Dulaglutide	REWIND	July 2011	April 2019	9622	http://clinicaltrials.gov/ct2/show/NCT01394952	CVD or age/CV risk factors	≤9.5%
Semaglutide	SUSTAIN 6	February 2013	January 2016	3260	http://clinicaltrials.gov/ct2/show/NCT01720446	CVD or age/CV risk factors	≥7%

*Estimated enrollment, phase IV study.