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(54) Title: TREATMENT OF TYPE 2 DIABETES MELLITUS PATIENTS

(57) Abstract: The present invention refers to lixisenatide for use in the reduction of progression of urinary albumin excretion in a type 2 diabetes mellitus patient.

Treatment of type 2 diabetes mellitus patients

Description

Subject of the present invention is desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ (AVE0010, lixisenatide) or/and a pharmaceutically acceptable salt thereof, for the reduction of progression of urinary albumin excretion in a type 2 diabetes mellitus patient.

Yet another aspect of the present invention is lixisenatide or/and a pharmaceutically acceptable salt thereof, for use in the reduction of cardiovascular morbidity or/and cardiovascular mortality in a type 2 diabetes mellitus patient who experienced at least one acute coronary syndrome event.

Yet another aspect is a method for reduction of cardiovascular morbidity or/and cardiovascular mortality in a type 2 diabetes mellitus patient who experienced at least one acute coronary syndrome event, said method comprising administering lixisenatide or/and a pharmaceutically acceptable salt thereof.

An increased glucose level in the blood over several years without initial symptoms represents a significant health risk. It could clearly be shown by the large-scale DCCT study in the USA (The Diabetes Control and Complications Trial Research Group (1993) N. Engl. J. Med. 329, 977-986) that chronically increased levels of blood glucose are a main reason for the development of diabetes complications. Examples for diabetes complications are micro- and macrovascular damages that possibly manifest themselves in retinopathies, nephropathies or neuropathies and lead to blindness, renal failure and the loss of extremities and are accompanied by an increased risk of cardiovascular diseases.

In the past two decades the prevalence of type 2 diabetes has increased to epidemic proportions worldwide; the number of subjects with type 2 diabetes is set to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025. It could clearly be shown by the large-scale DCCT study in the USA (The Diabetes Control and Complications Trial Research Group (1993) N. Engl. J. Med. 329, 977-986) that chronically increased levels of blood glucose are

a main reason for the development of diabetes complications, leading to a decreased life expectancy. This is mainly due to cardiovascular deaths with a risk of coronary heart disease increased by two- to fourfold in this population.

Results from large controlled trials as well as smaller studies and numerous epidemiologic studies have demonstrated that intensive glycemic control decreases the risk of microvascular complications. On the basis of these findings the American Diabetes Association (ADA) and the International Diabetes Federation recommend a tight glycemic control with an HbA1c target < 7% and < 6.5%, respectively. Although an intensive glycemic management has also been shown to have beneficial effect on cardiovascular disease (CVD) complications in type 1 diabetes, there is still controversy whether this demonstration can also apply in patients with type 2 diabetes. Recent individual studies conducted in type 2 diabetes have failed to demonstrate a beneficial effect of intensive diabetes therapy on CVD. However meta-analyses recently performed, showed a reduction in coronary events; effect on cardiovascular death or all-cause mortality was less evident.

New types of antidiabetic medicines, such as GLP-1 receptor agonists may achieve physiological blood glucose-insulin response with a low risk of hypoglycemia and may offer a valuable new therapeutic approach. These drugs reduce blood glucose by glucose dependent stimulation of insulin release and inhibition of glucagon secretion, which decreases prandial blood glucose excursion and hepatic glucose production; they also delay gastric emptying and reduce appetite which is associated with weight loss.

Effects of lixisenatide on glycemia and weight reduction with a favourable safety and tolerability profile were evidenced in the dose-ranging DRI6012 study. This study was a placebo-controlled, randomized, parallel-group, 12 treatments groups [8 AVE0010 active treatment groups (5, 10, 20, or 30 µg BID before breakfast and dinner, or 5, 10, 20, or 30 µg QD before breakfast with volume-matched placebo before dinner) or volume-matched placebo groups], 13-week treatment, dose finding study being conducted on 542 patients with type 2 diabetes treated with metformin. The adjusted HbA1c mean change from baseline to endpoint at week

13 was -0.69% with lixisenatide 20 µg QD from a mean baseline of 7.58% (p <0.0001).

The example of the present invention is a secondary prevention study with the objective to evaluate lixisenatide in type 2 diabetic patients who recently experienced an acute coronary syndrome (ACS) event. The term acute coronary syndrome, as used herein, includes unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI) and will allow covering a large spectrum of patients for whom there is a common aetiology in the formation of thrombus on an inflamed and complicated atheromatous plaque. The requirement for either an elevated cardiac biomarker, or an occluded coronary artery at emergent angiography, is consistent with this pathology, and will reduce the incidence of false positives based on clinical history and/or ECG findings alone. Patients with ACS are at high risk for recurrence of cardiovascular events, indeed the 30-day and 6-months mortality is high, particularly in patients with NSTEMI (10.4% and 18.7% at 30 days and 6 months, respectively) and STEMI (12.9% and 19.2% at 30 days and 6 months, respectively) compared with unstable angina (4.5% and 8.6% at 30 days and 6 months, respectively) (20). In addition, it is also known that patients with diabetes have a substantially greater risk of death and ischemic complications following an ACS event than patients without diabetes (21).

The primary efficacy endpoint is to evaluate the effect of lixisenatide compared to placebo on the occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina. Based on published data the estimated cardiovascular event rate in the proposed population is to be approximately 10% within the first year after the ACS event (22) (23) (24) (25).

A secondary objective of this study is to evaluate the effect of lixisenatide on the urinary albumin excretion (calculated from the urinary albumin/creatinine ratio) which is a marker of development of nephropathy in type 2 diabetes. It is well known that for patients with type 2 diabetes an increased incidence of cardiovascular mortality is observed in those with microalbuminuria. This

observation was confirmed in a meta-analysis of 11 longitudinal studies that included 2,138 patients with type 2 diabetes and microalbuminuria followed for a mean of 6.4 years. The overall odds ratio was 2.0 (95% CI 1.4-2.7) for cardiovascular morbidity or mortality, and 2.4 (95% CI 1.8-3.1) for total mortality (26). Recent studies suggest that an increase in the urinary albumin excretion, even within the normal range, is also associated with a greater risk of cardiovascular disease (27), (28). Blood pressure lowering and blood glucose lowering have shown a reduction of albuminuria as well as a reduction of the development of nephropathy (6), (7), (29), (30).

It was surprisingly found that lixisenatide reduces the progression of urinary albumin excretion (albuminuria).

Metformin is a biguanide hypoglycemic agent used in the treatment of non-insulin-dependent diabetes mellitus (type 2 diabetes mellitus) not responding to dietary modification. Metformin improves glycemic control by improving insulin sensitivity and decreasing intestinal absorption of glucose. Metformin is usually administered orally. However, control of type 2 diabetes mellitus in obese patients by metformin may be insufficient. Thus, in these patients, additional measures for controlling type 2 diabetes mellitus may be required.

Metformin is the international nonproprietary name of 1,1-dimethylbiguanide (CAS number 657-24-9).

The compound desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ (lixisenatide) is a Glucagon-like peptide 1 (GLP-1) receptor agonists and is being developed for the treatment of patients with type 2 diabetes mellitus (T2DM). Lixisenatide is a derivative of Exendin-4. Lixisenatide is disclosed as SEQ ID NO:93 in WO 01/04156:

SEQ ID NO: 1: lixisenatide (44 amino acids)
H-G-E-G-T-F-T-S-D-L-S-K-Q-M-E-E-E-A-V-R-L-F-I-E-W-L-K-N-G-G-P-S-S-G-A-P-P-S-K-K-K-K-K-K-NH$_2$

SEQ ID NO: 2: exendin-4 (39 amino acids)
H-G-E-G-T-F-T-S-D-L-S-K-Q-M-E-E-E-A-V-R-L-F-I-E-W-L-K-N-G-G-P-S-S-G-A-P-P-P-S-NH$_2$

Exendins are a group of peptides which can lower blood glucose concentration. Lixisenatide is characterised by C-terminal truncation of the native Exendin-4 sequence. Lixisenatide comprises six C-terminal lysine residues not present in Exendin-4.

Lixisenatide is also termed des-38-proline-exendin-4(*Heloderma suspectum*)-(1-39)-peptidylpenta-L-lysyl-L-lysinamide (CAS number 320367-13-3).

An aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, in the reduction of cardiovascular morbidity or/and cardiovascular mortality in a type 2 diabetes mellitus patient who experienced at least one acute coronary syndrome event.

In particular, lixisenatide or/and a pharmaceutically acceptable salt thereof is used for reduction of the 30-day or/and the 6-months mortality in a type 2 diabetes mellitus patient who experienced at least one acute coronary syndrome event.

In particular, reduction of cardiovascular morbidity or/and cardiovascular mortality includes reduction of the risk of a cardiovascular event, more particular within one year after the at least one acute coronary syndrome event.

In the present invention, the cardiovascular event can include death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalization for unstable angina, non-fatal heart failure, hospitalization for heart failure or/and coronary revascularization procedure.

In the present invention, the cardiovascular event can include death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, or/and non-fatal heart failure.

In the present invention, the cardiovascular event can a major adverse cardiovascular event (MACE). A MACE can be one of cardiovascular death (CV death), non-fatal myocardial infarction (non-fatal MI), and non-fatal stroke.

According to the present invention, the risk of the cardiovascular event can be expressed as the expected rate of cardiovascular events, for example for a period of 1 year.

In particular, the type 2 diabetes mellitus patient to be treated according to the present invention experienced the at least one acute coronary syndrome event within 1, within 2, within 3, within 4, within 5 or within 6 months prior to or at the onset of treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof. It is preferred that the type 2 diabetes mellitus patient to be treated according to the present invention experienced the at least one acute coronary syndrome event within 6 months prior to or at the onset of treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof.

In particular, the at least one acute coronary syndrome event according to the present invention has been diagnosed within 1, within 2, within 3, within 4, within 5 or within 6 months prior to or at the onset of treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof.

According to the present invention, the at least one acute coronary syndrome event can be a spontaneous acute coronary syndrome event.

According to the present invention, the at least one acute coronary syndrome event can include an ST-segment elevation myocardial infarction.

According to the present invention, the at least one acute coronary syndrome event can include a non-ST-segment elevation myocardial infarction.

According to the present invention, the at least one acute coronary syndrome event can include an unstable angina.

According to the present invention, the at least one acute coronary syndrome event can include one selected from the group consisting of an ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and unstable angina.

According to the present invention, the at least one acute coronary syndrome event can be a biomarker-proven or biomarker-positive acute coronary syndrome event (ACS event). The at least one ACS event can be an ACS event associated with a positive diagnosis of at least one cardiac biomarker, such as troponin or/and CK-MB. In particular, there must be an elevation of the at least one cardiac biomarker, in particular troponin or/and CK-MB, above the normal reference ranges.

According to the present invention, the ACS event may be a class I, II, III or IV ACS event according to the New York Heart Association (NYHA). This classification is known to the skilled person. Disclosure of Class I to IV ACS events according to the New York Heart Association can, for example. be found in "The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256" and

http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp#.VipEmbfhA3E.

Class I to IV ACS events according to the New York Heart Association can be defined as follows:

Functional Capacity Objective	**Assessment**
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in	**D.** Objective evidence of

inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	severe cardiovascular disease.

According to the present invention, the ACS event may also be a class I, II, III or IV angina pectoris according to the Canadian Cardiovascular Society. This classification is known to the skilled person. Disclosure of class I to IV of angina pectoris according to the Canadian Cardiovascular Society can be found in Campeau Lucien, Grading of Angina Pectoris. Circulation, 1976; 54:522–3, and http://www.sscts.org/pages/classificationanginaccs.aspx.

Class I to IV of angina pectoris according to the Canadian Cardiovascular Society can also be termed grade I to IV angina pectoris.

Class I to IV of angina pectoris according to the Canadian Cardiovascular Society can be defined as follows:

Class I: Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.

Class II: Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, in wind or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Class III: Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.

Class IV: Inability to carry out any physical activity without discomfort; angina may be present at rest. There are four sub-groups in CCS Class IV. Groups A to D:

A: Admitted to hospital, becomes relatively asymptomatic with aggressive medical therapy, and may be managed on an outpatient basis.

B: Admitted to hospital, continues to have angina despite aggressive medical therapy and cannot be safely discharged home, but does not require IV nitroglycerin.

C: Admitted to hospital and maximal medical therapy, including IV nitroglycerin, fails to control symptoms.

D: Patient in shock.

"At least one acute coronary syndrome event", as used herein, includes an acute coronary syndrome event, which can be the first acute coronary syndrome event the patient has experienced.

According to the present invention, the patient to be treated according to the present invention has a risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalization for unstable angina, non-fatal heart failure, hospitalization for heart failure or/and coronary revascularization procedure.

According to the present invention, the patient to be treated according to the present invention has a risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, or/and non-fatal heart failure.

Another aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, for the treatment of the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalization for unstable angina, non-fatal heart failure, hospitalization for heart failure or/and revascularization procedure in a type 2 diabetes mellitus patient who experienced at least one acute coronary syndrome event. The type 2 diabetes mellitus patient may be a patient as described herein. The at least one

acute coronary syndrome event may be at least one acute coronary syndrome event as described herein.

Another aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, for the treatment of the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, or/and non-fatal heart failure in a type 2 diabetes mellitus patient who experienced at least one acute coronary syndrome event. The type 2 diabetes mellitus patient may be a patient as described herein. The at least one acute coronary syndrome event may be at least one acute coronary syndrome event as described herein.

In particular the treatment according to the present invention of the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalization for unstable angina, non-fatal heart failure, hospitalization for heart failure or/and revascularization procedure reduces cardiovascular morbidity or/and cardiovascular mortality.

In particular the treatment according to the present invention of the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, or/and non-fatal heart failure reduces cardiovascular morbidity or/and cardiovascular mortality.

According to the present invention, the revascularization procedure can be a percutaneous coronary intervention or coronary artery bypass grafting.

The treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof according to the present invention can reduce the blood plasma concentration of hs-CRP, BNP or/and NT-proBNP.

Yet another aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, for reduction of the blood plasma concentration of hs-CRP, BNP or/and NT-proBNP.

According to the present invention, the type 2 diabetes mellitus patient can have a cardiovascular disease history prior to the at least one acute coronary syndrome event. In particular, the cardiovascular disease history includes at least one of coronary heart disease, cerebrovascular disease, peripheral artery disease, and cardiac arrhythmia.

According to the present invention, the type 2 diabetes mellitus patient can be a patient that has been diagnosed with a cardiovascular disease prior to the at least one acute coronary syndrome event. The cardiovascular disease can include at least one of coronary heart disease, cerebrovascular disease, peripheral artery disease, and cardiac arrhythmia.

According to the present invention, lixisenatide or/and a pharmaceutically acceptable salt thereof, can reduce the progression of urinary albumin excretion in a type 2 diabetes mellitus patient as described herein. The urinary albumin/creatinine ratio (UACR) increased in both treatment groups (24% and 34% change from baseline for the lixisenatide and placebo groups, respectively). Surprisingly, a smaller increase in the lixisenatide group as compared to the placebo group (the difference between lixisenatide versus placebo in the percent change from baseline of UACR was -0.10% with 95% CI:-0.17, -0.03) has been observed. Therefore, lixisenatide is capable of decreasing the worsening of albuminuria in type 2 diabetes patients, in particular in type 2 diabetes patients as described herein. The type 2 diabetes mellitus patient, as described herein, may suffer from microalbuminuria with an urinary albumin to creatinine ratio (UACR) of ≥30 to <300 mg/g, or the patient may suffer from macroalbuminuria with an urinary albumin to creatinine of ≥300 mg/g, as described herein. The patient may also suffer from mild renal impairment with a glomerular filtration rate of ≥60 to <90 mL/min/1.73 m^2, or from a moderate renal impairment with a glomerular filtration rate of ≥30 to <60 mL/min/1.73 m^2, or from a severe renal impairment with a glomerular filtration rate of >15 to <30 mL/min/1.73 m^2.

Yet another aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, for the reduction of urinary albumin excretion in a type 2 diabetes mellitus patient, as described herein.

Lixisenatide can also be used for the reduction of progression of urinary albumin excretion in a type 2 diabetes mellitus patient, as described herein.

Urinary albumin excretion is also termed albuminuria.

The type 2 diabetes mellitus patient suffering from albuminuria can be a patient as described herein. In particular, the patient suffering from urinary albumin excretion can have experienced at least one acute coronary syndrome event, as described herein.

In particular, the patient suffers from microalbuminuria with an urinary albumin to creatinine ratio of ≥30 to <300 mg/g, or the patient suffers from macroalbuminuria with an urinary albumin to creatinine ratio of ≥300 mg/g.

In particular, the patient suffers from mild renal impairment with a glomerular filtration rate of ≥60 to <90 mL/min/1.73 m^2, or the patient suffers from a moderate renal impairment with a glomerular filtration rate of ≥30 to <60 mL/min/1.73 $m^{2,}$, or the patient suffers from a severe renal impairment with a glomerular filtration rate of >15 to <30 mL/min/1.73 m^2.

The patient suffering from type 2 diabetes mellitus to be treated according to the present invention may be obese. A patient can be considered as obese if the body mass index is at least 30 kg/m^2. In the present invention, an obese patient may have a body mass index of at least 30 kg/m^2 or at least 31 kg/m^2. It is preferred that that the patient has a body mass index of at least 31 kg/m^2.

The patient suffering from type 2 diabetes mellitus to be treated according to the present invention preferably does not receive an antidiabetic treatment, for

example by insulin or/and related compounds, or/and by one or more oral antidiabetic compounds, such as metformin, sulfonylurea or/and a glinide.

According to the present invention, lixisenatide or/and the pharmaceutically acceptable salt thereof may be administered in combination with
(i) metformin or/and a pharmaceutically acceptable salt thereof,
(ii) insulin or/and a pharmaceutically acceptable salt thereof,
(iii) a glinide or/and a pharmaceutically acceptable salt thereof,
or/and
(iv) a sulfonylurea or/and a pharmaceutically acceptable salt thereof.

The insulin to be administered in combination with lixisenatide or/and the pharmaceutically acceptable salt thereof may be a premixed, rapid-acting, or regular insulin.

The patient to be treated according to the present invention may be a subject suffering from type 2 diabetes mellitus, wherein type 2 diabetes mellitus is not adequately controlled by treatment with
(a) metformin or/and a pharmaceutically acceptable salt thereof,
(b) insulin or/and a pharmaceutically acceptable salt thereof,
(c) a glinide or/and a pharmaceutically acceptable salt thereof,
or/and
(d) a sulfonylurea or/and a pharmaceutically acceptable salt thereof,
in particular prior to the onset of the treatment according to the present invention.

In particular, the type 2 diabetes mellitus is not adequately controlled by monotherapy with
(a) metformin or/and a pharmaceutically acceptable salt thereof,
(b) insulin or/and a pharmaceutically acceptable salt thereof,
(c) a glinide or/and a pharmaceutically acceptable salt thereof,
or
(d) a sulfonylurea or/and a pharmaceutically acceptable salt thereof,
in particular prior to the onset of the treatment according to the present invention.

In the present invention, "not adequately controlled" by the treatment with compound (a), (b), (c) or/and (d), or with monotherapy with compound (a), (b), (c) or (d), as indicated above, means in particular that this treatment is not sufficient to remove the symptoms of diabetes mellitus. More particular, "not adequately controlled" by the treatment with compounds (a), (b), (c) or/and (d), or with monotherapy with compound (a), (b), (c) or (d), as indicated above, means that the patient does not reach normoglycemic values in terms of, for example, HbA1c value or/and fasting plasma glucose concentration.

The term "not adequately controlled" by the treatment with compounds (a), (b), (c) or/and (d), or with monotherapy with compound (a), (b), (c) or (d), as indicated above, in particular relates to the period prior to the treatment according to the present invention. It can be diagnosed prior to the treatment according to the present invention if the therapy with compounds (a), (b), (c) or/and (d), as indicated above adequately controls the type 2 diabetes mellitus or not. For example, such diagnosis may be performed within 1 month, within 2 months or within 3 months prior to the treatment of the present invention with lixisenatide or/and a pharmaceutically acceptable salt thereof.

In particular, the type 2 diabetes mellitus patient does not receive lixisenatide or/and a pharmaceutically acceptable salt thereof, prior to the onset of the treatment according to the present invention.

In the present invention, normoglycemic values are blood glucose concentrations of in particular 60 – 140 mg/dl (corresponding to 3.3 to 7.8 mmol/L).

Criteria for a type 2 diabetes mellitus diagnosis include:

- the fasting plasma glucose concentration (FPG) is ≥ 7.0 mmol/L (126 mg/dl), or

- the post challenge plasma glucose concentration is > 11.1 mmol/L (200 mg/dl), performed as described by the World Health Organization (Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. WHO/NCD/NCS/99.2.

Geneva; 1999), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, or

- HbA1c values of ≥ 6.5%, or

- symptoms of diabetes and a casual plasma glucose ≥ 200 mg/dl (11.1 mmol/L).

These criteria are described in the Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence (International Diabetes Federation, ISBN 2-930229-72-1).

The diagnosis of type 2 Diabetes should not be based on a single plasma glucose concentration. Diagnosis may require continued observation with fasting and/or postprandial blood glucose levels and/or an oral glucose tolerance test.

According to Craig (Pediatric Diabetes 2014: 15(Suppl. 20): 4–17), fasting plasma glucose (FPG can be classified as follows:

- FPG < 5.6 mmol/L (100 mg/dL) = normal fasting glucose concentration.

- FPG 5.6 to 6.9 mmol/L (100–125 mg/dL) = impaired fasting glucose concentration.

- FPG ≥ 7.0 mmol/L (126 mg/dL) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above)

Impaired glucose tolerance (IGT) and impaired fasting glucose concentration (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes.

In the present invention, normoglycemic glucose concentrations can include impaired glucose concentrations, as described herein.

In the present invention, normoglycemic values of fasting plasma glucose are blood glucose concentrations of in particular < 5.6 mmol/L or < 7.0 mmol/L.

By the treatment according to the present invention, adequate control of type 2 diabetes mellitus may be achieved in patients not adequately controlled with metformin monotherapy, for instance with a dose of at least 1.0 g/day metformin or at least 1.5 g/day metformin for at least 3 months, or/and a dose of at the maximum 2.0 g/day metformin for at least 3 months.

In the present invention, the type 2 diabetes patient to be treated may have a HbA1c value in the range of 7 % to 10%. In particular the patient to be treated may have a HbA_{1c} value of at least about 7 %, at least about 7.5 %, at least about 7.6 %, at least about 7.7 %, at least about 8 %, at least about 8.5 %, or at least about 9 %, more particular prior to the onset of treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof. These HbA1c values exceed normoglycemic values.

In the present invention, the type 2 diabetes patient to be treated may have a HbA1c value in the range of 7 % to 10%, or a HbA_{1c} value of at least about 7 %, at least about 7.5 %, at least about 7.6 %, at least about 7.7 %, at least about 8 %, at least about 8.5 %, or at least about 9 % if the patient is treated with

(a) metformin or/and a pharmaceutically acceptable salt thereof,

(b) insulin or/and a pharmaceutically acceptable salt thereof,

(c) a glinide or/and a pharmaceutically acceptable salt thereof,

or/and

(d) a sulfonylurea or/and a pharmaceutically acceptable salt thereof,

or if the patient is treated with monotherapy with a compound selected from compound (a), (b), (c) or (d). In particular, the patient may have this value by treatment with compounds (a), (b), (c) or/and (d), or with monotherapy with compound (a), (b), (c) or (d), prior to the onset of treatment according to the present invention with lixisenatide or/and a pharmaceutically acceptable salt thereof, indicating that the type 2 diabetes mellitus is not adequately controlled.

In particular, a patient receiving metformin monotherapy (in particular before onset of therapy according to the present invention) may have a HbA1c value in the range of 7 % to 10%. In particular the patient receiving metformin monotherapy may have a HbA_{1c} value of at least about 7 %, at least about 7.5 %, at least about

7.6 %, at least about 7.7 %, at least about 8 %, at least about 8.5 %, or at least about 9 %, indicating that the type 2 diabetes mellitus is not adequately controlled by metformin monotherapy.

In the present invention, the type 2 diabetes patient to be treated may have a fasting plasma glucose concentration of at least 8 mmol/L or at least 8.5 mmol/L in particular prior to the onset of treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof. These plasma glucose concentrations exceed normoglycemic concentrations.

In the present invention, the type 2 diabetes patient to be treated may have a fasting plasma glucose concentration of at least 8 mmol/L or at least 8.5 mmol/L if the patient is treated with

(a) metformin or/and a pharmaceutically acceptable salt thereof,

(b) insulin or/and a pharmaceutically acceptable salt thereof,

(c) a glinide or/and a pharmaceutically acceptable salt thereof,

or/and

(d) a sulfonylurea or/and a pharmaceutically acceptable salt thereof,

or if the patient is treated with monotherapy with a compound selected from compound (a), (b), (c) or (d). In particular, the patient may have this fasting plasma glucose concentration by treatment with compounds (a), (b), (c) or/and (d), or with monotherapy with compound (a), (b), (c) or (d), prior to the onset of treatment according to the present invention with lixisenatide or/and a pharmaceutically acceptable salt thereof, indicating that the type 2 diabetes mellitus is not adequately controlled.

In particular, a patient receiving metformin monotherapy (in particular before onset of therapy according to the present invention) may have a fasting plasma glucose concentration of at least 8 mmol/L, or at least 8.5 mmol/L, indicating that the type 2 diabetes mellitus is not adequately controlled by metformin monotherapy.

In the present invention, the type 2 diabetes patient to be treated may have an age of at least 60 years.

In the present invention, metformin includes pharmaceutically acceptable salts thereof. The person skilled in the art knows suitable pharmaceutically acceptable salts of metformin.

In the present invention, metformin can be administered according to commonly known administration protocols of metformin in accordance with the terms of marketing authorization. For example, metformin can be administrated once daily, twice daily or three times a day. In particular, the metformin dose applied prior to the onset of the therapy as disclosed herein is continued in combination with lixisenatide or/and a pharmaceutically acceptable salt thereof, as disclosed herein.

In the present invention, metformin may be administered orally. The skilled person knows formulations of metformin suitable for treatment of type 2 diabetes mellitus by oral administration. Metformin may be administered to a patient in need thereof, in an amount sufficient to induce a therapeutic effect. Metformin may be administered in a dose of at least 1.0 g/day or at least 1.5 g/day. Metformin may be administered in a dose of at the maximum of 2.0 g/day. The daily metformin dose can be divided into 2 or three separate doses. For oral administration, metformin may be formulated in a solid dosage form, such as a tablet or pill. Metformin may be formulated with suitable pharmaceutically acceptable carriers, adjuvants, or/and auxiliary substances.

In the present invention, lixisenatide or/and a pharmaceutically acceptable salt may be administered in an add-on therapy to administration of metformin.

In the present invention, the terms "add-on", "add-on treatment" and "add-on therapy" relate to treatment according to the present invention with an oral anti-diabetic, as described herein, in particular metformin, and lixisenatide. The oral anti-diabetic, in particular metformin, and lixisenatide each may be administered in a once-a-day-dosage. The oral anti-diabetic, in particular metformin, and lixisenatide may be administered by different administration routes. Metformin may be administered orally, and lixisenatide may be administered parenterally.

In particular, "add-on", "add-on treatment" and "add-on therapy" mean that the dose of the oral anti-diabetic, in particular metformin, administered prior to the onset of the treatment with lixisenatide or/and a pharmaceutically acceptable salt thereof, as disclosed herein, is continued in combination with lixisenatide or/and a pharmaceutically acceptable salt thereof.

In the present invention, lixisenatide includes pharmaceutically acceptable salts thereof. The person skilled in the art knows suitable pharmaceutically acceptable salts of lixisenatide. A preferred pharmaceutically acceptable salt of lixisenatide employed in the present invention is the acetate salt of lixisenatide.

In the present invention, lixisenatide or/and the pharmaceutically acceptable salt thereof may be administered to a patient in need thereof, in an amount sufficient to induce a therapeutic effect.

In the present invention, lixisenatide or/and the pharmaceutically acceptable salt thereof may be formulated with suitable pharmaceutically acceptable carriers, adjuvants, or/and auxiliary substances.

Lixisenatide or/and a pharmaceutically acceptable salt thereof may be administered parenterally, e.g. by injection (such as by intramuscular or by subcutaneous injection). Suitable injection devices, for instance the so-called "pens" comprising a cartridge comprising the active ingredient, and an injection needle, are known. Lixisenatide or/and a pharmaceutically acceptable salt thereof may be administered in a suitable amount, for instance in an amount in the range of 5 µg to 10 µg per dose or 5 to 20 µg per dose.

In the present invention, lixisenatide or/and a pharmaceutically acceptable salt thereof may be administered in a daily dose in the range of 5 to 10 µg or 5 to 20 µg. Lixisenatide or/and a pharmaceutically acceptable salt thereof may be administered by one injection per day. Lixisenatide or/and a pharmaceutically acceptable salt thereof may be administered about 30 min or 1 hour before breakfast.

In the present invention, lixisenatide or/and a pharmaceutically acceptable salt thereof may be provided in a liquid composition, which preferably is an aqueous formulation. It is preferred that the liquid composition is suitable for parenteral administration, in particular for injection. The skilled person knows such liquid compositions of lixisenatide. A liquid composition of the present invention may have an acidic or a physiologic pH. An acidic pH preferably is in the range of pH 1 – 6.8, pH 3.5 - 6.8, or pH 3.5 – 5. A physiologic pH preferably is in the range of pH 2.5 - 8.5, pH 4.0 - 8.5, or pH 6.0 - 8.5. The pH may be adjusted by a pharmaceutically acceptable diluted acid (typically HCl) or pharmaceutically acceptable diluted base (typically NaOH).

The liquid composition comprising lixisenatide or/and a pharmaceutically acceptable salt thereof may comprise a suitable preservative. A suitable preservative may be selected from phenol, m-cresol, benzyl alcohol and p-hydroxybenzoic acid ester. A preferred preservative is m-cresol.

The liquid composition comprising lixisenatide or/and a pharmaceutically acceptable salt thereof may comprise a tonicity agent. A suitable tonicity agent may be selected from glycerol, lactose, sorbitol, mannitol, glucose, NaCl, calcium or magnesium containing compounds such as $CaCl_2$. The concentration of glycerol, lactose, sorbitol, mannitol and glucose may be in the range of 100 – 250 mM. The concentration of NaCl may be up to 150 mM. A preferred tonicity agent is glycerol.

The liquid composition comprising lixisenatide or/and a pharmaceutically acceptable salt thereof may comprise methionine from 0.5 µg/mL to 20 µg/mL, preferably from 1 µg /ml to 5 µg/ml. Preferably, the liquid composition comprises L-methionine.

Yet another aspect of the present invention is a method for the reduction of cardiovascular morbidity or/and cardiovascular mortality in a type 2 diabetes mellitus patient who experienced at least one acute coronary syndrome event, said method comprising administering lixisenatide or/and a pharmaceutically acceptable salt thereof, to the patient in need thereof. Cardiovascular morbidity,

cardiovascular mortality and acute coronary syndrome event are defined as described herein. The patient is a type 2 diabetes mellitus patient as described herein.

A further aspect of the present invention is a method of treatment of the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalization for unstable angina, non-fatal heart failure, hospitalization for heart failure or/and revascularization procedure in a type 2 diabetes mellitus patient, said method comprising administering lixisenatide or/and a pharmaceutically acceptable salt thereof, to the patient in need thereof. The patient is a type 2 diabetes mellitus patient as described herein.

A further aspect of the present invention is a method of treatment of the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, or/and non-fatal heart failure in a type 2 diabetes mellitus patient, said method comprising administering lixisenatide or/and a pharmaceutically acceptable salt thereof, to the patient in need thereof. The patient is a type 2 diabetes mellitus patient as described herein.

A further aspect of the present invention is a method for the reduction of the blood plasma concentration of hs-CRP, BNP or/and NT-proBNP in a type 2 diabetes mellitus patient, said method comprising administering lixisenatide or/and a pharmaceutically acceptable salt thereof, to the patient in need thereof. The patient is a type 2 diabetes mellitus patient as described herein.

A further aspect of the present invention is a method for the reduction of urinary albumin excretion in a type 2 diabetes mellitus patient, said method comprising administering lixisenatide or/and a pharmaceutically acceptable salt thereof, to the patient in need thereof. The patient is a type 2 diabetes mellitus patient as described herein. In particular, the patient has experienced at least one acute coronary syndrome event. The at least one acute coronary syndrome event is the at least one acute coronary syndrome event as described herein. In particular, the patient may suffer from albuminuria or/and renal impairment, as described herein.

A further aspect of the present invention is a method for the reduction of progression of urinary albumin excretion in a type 2 diabetes mellitus patient, said method comprising administering lixisenatide or/and a pharmaceutically acceptable salt thereof, to the patient in need thereof. The patient is a type 2 diabetes mellitus patient as described herein. In particular, the patient has experienced at least one acute coronary syndrome event. The at least one acute coronary syndrome event is the at least one acute coronary syndrome event as described herein. In particular, the patient may suffer from albuminuria or/and renal impairment, as described herein.

A further aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the reduction of cardiovascular morbidity or/and cardiovascular mortality in a type 2 diabetes mellitus patient who experienced at least one acute coronary syndrome event. Cardiovascular morbidity, cardiovascular mortality and acute coronary syndrome event are defined as described herein. The patient is a type 2 diabetes mellitus patient as described herein. In particular, the patient may suffer from albuminuria or/and renal impairment, as described herein.

Another aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalization for unstable angina, non-fatal heart failure, hospitalization for heart failure or/and revascularization procedure in a type 2 diabetes mellitus patient. The patient is a type 2 diabetes mellitus patient as described herein.

Another aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, or/and non-fatal heart failure in a type 2 diabetes

mellitus patient. The patient is a type 2 diabetes mellitus patient as described herein.

Another aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the reduction of the blood plasma concentration of hs-CRP, BNP or/and NT-proBNP in a type 2 diabetes mellitus patient. The patient is a type 2 diabetes mellitus patient as described herein.

A further aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the reduction of urinary albumin excretion in a type 2 diabetes mellitus patient. The patient is a type 2 diabetes mellitus patient as described herein. In particular, the patient has experienced at least one acute coronary syndrome event. The at least one acute coronary syndrome event is at least one acute coronary syndrome event as described herein. In particular, the patient may suffer from albuminuria or/and renal impairment, as described herein.

A further aspect of the present invention is the use of lixisenatide or/and a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the reduction of progression of urinary albumin excretion in a type 2 diabetes mellitus patient. The patient is a type 2 diabetes mellitus patient as described herein. In particular, the patient has experienced at least one acute coronary syndrome event. The at least one acute coronary syndrome event is at least one acute coronary syndrome event as described herein. In particular, the patient may suffer from albuminuria or/and renal impairment, as described herein.

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The invention is further illustrated be the following example and figures:

Figure legends

Figure 1 - Kaplan-Meier cumulative curves of the primary CV endpoint (time to the first occurrence of the composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina) - ITT population. Only CAC positively adjudicated events are included.

Figure 2 - Forest plot: analyses of each individual cardiovascular event of the primary endpoint - ITT population. CV: cardiovascular, MI: myocardial infarction, HR: hazard ratio, CI: confidence interval. Only CAC positively adjudicated events are included.

Figure 3 - Forest plot: analyses of each individual cardiovascular event of the secondary endpoints - ITT population. MACE plus: Composite of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina. CV: cardiovascular, MI: myocardial infarction, HR: hazard ratio, CI: confidence interval. Only CAC positively adjudicated events are included.

Figure 4 - Plot of mean HbA1c (%) by scheduled visit - ITT population. SC: Screening, BL: Baseline. Only visits with at least 30 patients with measurements in each group are presented.

Example

A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate cardiovascular outcomes during treatment with lixisenatide in type 2 diabetic patients after an Acute Coronary Syndrome event

1 ABBREVIATIONS

ACS:	acute coronary syndrome
AE:	adverse event
ANCOVA:	analysis of covariance
BMI:	body mass index
CAC:	Cardiovascular Events Adjudication Committee
CI:	confidence interval
CV:	cardiovascular
EOS:	End of Study
GFR:	glomerular filtration rate
MACE:	major cardiovascular adverse event
MI:	myocardial infarction
PSAC:	Pancreatic Safety Assessment Committee
QD:	once daily
T2DM:	type 2 diabetes mellitus
TEAE:	treatment-emergent AE
UACR:	urinary albumin/creatinine ratio

2 SYNOPSIS

Title of the study: A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate cardiovascular outcomes during treatment with lixisenatide in type 2 diabetic patients after an Acute Coronary Syndrome event
Study centers: multicenter: 888 in 49 countries
Phase of development: Phase 3
Objectives: **Primary objective:** To demonstrate that lixisenatide can reduce cardiovascular (CV) morbidity and mortality (composite endpoint of CV death, non-fatal myocardial infarction [MI], non-fatal stroke, hospitalization for unstable angina) compared to placebo in type 2 diabetic patients who recently experienced a spontaneous, biomarker-positive acute coronary syndrome (ACS) event.
Methodology: Double-blind, placebo-controlled, 1:1 randomized, 2-arm, parallel-group, multinational, Phase 3 study conducted in adult patients with type 2 diabetes mellitus (T2DM).

Number of patients:	Planned 6000 Randomized: 6068 Treated: 6063
Evaluated:	Efficacy: 6068 Safety: 6063

Diagnosis and criteria for inclusion:

Patients with a history of T2DM as per World Health Organization criteria who had experienced a biomarker-proven spontaneous ACS event of ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction or unstable angina within 180 days prior to screening.

Study treatment

Investigational medicinal product: AVE0010/ lixisenatide

Formulations:

Control Drug: Volume-matched placebo, 3-mL aqueous solution (in cartridge)

Active drug: 3-mL aqueous solution (in cartridge) containing 300 µg of active ingredient (ie,100 µg/mL), glycerol, sodium acetate trihydrate, methionine, meta-cresol, HCL/NaOH, water for injection

Route of administration: subcutaneous injection

Dose regimen: The starting dose was 10 µg once daily (QD) for 2 weeks; the dose was then increased to the maintenance dose of 20 µg QD for the remainder of the treatment period, safety and tolerability permitting. The IMP dose could be down-titrated to 15 µg or 10 µg QD if the patient was intolerant of 20 µg or 15 µg QD. The IMP was administered in the morning within 1 hour prior to breakfast. However, if a patient experienced an adverse event (eg, nausea or vomiting) or other conditions that made the morning dosing difficult, the Investigator could change the dosing time to the evening (within 1 hour prior to dinner).

Non-investigational medicinal products: No background antidiabetic medications were specified in the study protocol. Patients were eligible for enrollment regardless of whether or not they were receiving pharmacologic therapy for diabetes treatment. During the double-blind treatment period, the management of glycemia was left to the Investigator's judgment in accordance with clinical guidelines. The Investigators were allowed to undertake appropriate action, ie, adjust the background antidiabetic treatment or prescribe an additional antidiabetic medication according to its labeling. Exceptions were other GLP-1 receptor agonists or DPP-IV inhibitors, which were prohibited throughout the study.

Duration of treatment: At least 10 months for the last randomized patients with variable treatment periods for all study patients until 844 patients had at least one positively-adjudicated primary CV event.

Duration of observation: A minimum of 10 months + 2 weeks (7+ 3 days run-in + variable double-blind treatment + 3 days post treatment follow-up)

Criteria for evaluation:

Efficacy

Primary Endpoint: Time to the first occurrence of any of the following events positively adjudicated by the Cardiovascular Events Adjudication Committee (CAC): Cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina

Secondary Endpoints:

- Time to the first occurrence of any of the following events positively adjudicated by the CAC: Cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or hospitalization for heart failure
- Time to the first occurrence of any of the following events positively adjudicated by the CAC: Cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or coronary revascularization procedure
- Percent change in the urinary albumin/creatinine ratio from baseline to Week 108 (ie, approximately 2 years)

Safety

Safety analyses included adverse events (AE), serious AEs, vital signs, and standard hematology and blood chemistry laboratory values.

Statistical methods:

Analysis of efficacy endpoints

All efficacy analyses were performed on the ITT population, defined as all randomized patients analyzed according to the treatment group allocated at randomization, regardless of treatment discontinuation. The analyses of CV efficacy endpoints were based on the positively-adjudicated CV endpoint events occurring from randomization to the study end date inclusive, even for patients who had discontinued study treatment.

The time to the first occurrence of the primary CV endpoint event was analyzed using a Cox proportional hazards model with treatment (lixisenatide, placebo), and region (North America, South and Central America, Western Europe, Eastern Europe, Africa/Near East, and Asia/Pacific) as the factors. The hazard ratio between lixisenatide and placebo was estimated along with the associated 2-sided 95% confidence interval (CI). Depending on the upper bound of the 2-sided 95% CI from the above Cox model: (1) non-inferiority to confirm an acceptable CV safety profile of lixisenatide was to be claimed if the upper bound of the 2-sided 95% CI of the hazard ratio was less than 1.3; and (2) superiority of lixisenatide versus placebo was to be claimed if the upper bound of the 2-sided 95% CI of the hazard ratio was less than 1.0. The p-value using the log-rank test was also calculated for descriptive purpose.

The two secondary composite CV endpoints were analyzed using the same Cox proportional hazards model as described for the primary efficacy endpoint. The time to the first occurrence of any major adverse cardiovascular event (MACE) (ie, cardiovascular death, non-fatal MI, or non-fatal stroke) was performed using the same Cox model as described for the analysis of the primary CV endpoint.

Percent change in the urinary albumin/creatinine ratio (UACR) from baseline to Week 108, was analyzed in the ITT population using an analysis of covariance (ANCOVA) model with treatment (lixisenatide, placebo), region, intake of ACE inhibitors at baseline (yes or no) and intake of angiotensin II receptor blockers at baseline (yes or no) as fixed effects and using the baseline urinary albumin/creatinine ratio as a covariate.

Analysis of safety endpoints

All safety analyses were performed on the safety population (ie, all randomized patients who received at least one dose of double-blind IMP) during the on-treatment period, which was defined as the time from the first administration of double-blind IMP up to 3 days after the last administration of double-blind IMP. The safety endpoints included AEs, clinical laboratory data, and vital signs. The events reported in the specific CV AE forms for "Myocardial infarction or hospitalization for unstable angina", "Stroke", "Hospitalization for heart failure", or "Coronary revascularization procedure" were not included in the safety analyses, regardless of adjudication results, seriousness, or relationship to IMP, because they were analyzed as efficacy endpoints.

Suspected events of pancreatitis reported during the on-treatment period and pancreatic neoplasms reported during the on-

treatment and post-treatment periods were summarized based on the adjudicated outcome. The number (%) of patients with overall malignancy and subcategories of major cancer types (thyroid, lung, colorectal, breast, and prostate) during the combined on-treatment and post-treatment periods were summarized.

Summary:

Population characteristics:

The demographics were well-balanced between the two treatment groups. The mean age of the ITT population was 60 years and more male (69%) and Caucasian (75%) patients were enrolled. The majority of patients were either obese or overweight (median BMI 29.4 kg/m^2). Baseline diabetes status (duration of diabetes, HbA1c, and incidence of diabetic complications) was generally similar between the treatment groups. The characteristics of the qualifying ACS were well-matched between the treatment groups, with most patients (72%) having had a qualifying ACS within 90 days prior to randomization. The most common type of qualifying ACS was ST-segment elevation MI (44 %); about 60% of patients in both groups underwent percutaneous coronary revascularization.

All 6068 randomized and 6063 randomized and treated patients were included for efficacy and safety analyses, respectively. Of these, 5853 patients completed the study, defined as patients who either performed the final study visit at the protocol-specified End of Study (EOS) or died during the study period. The median IMP exposure was 22.4 and 23.3 months for lixisenatide and placebo, respectively. At the time of the EOS, vital status was available for 98.8 % of patients.

	Placebo (N=3034)	**Lixisenatide (N=3034)**
Randomized and treated	3032 (>99.9%)	3031 (>99.9%)
Completed the study	2924 (96.4%)	2929 (96.5%)
Completed the double blind treatment	2264 (74.6%)	2147 (70.8%)
Vital status known at the end of study	2992 (98.6%)	3005 (99.0%)
Alive	2769 (91.3%)	2794 (92.1%)
Dead	223 (7.4%)	211 (7.0%)
LTFU	14 (0.5%)	11 (0.4%)

LTFU: patients discontinued study participation without a known reason and were not reachable via any means of contact by the Investigator until the EOS.

Efficacy Results:

Primary CV endpoint:

- The hazard ratio for lixisenatide versus placebo was 1.017 with an associated 2-sided 95% CI of 0.886 to 1.168. The upper bound of the 2-sided 95% CI estimated from the Cox model was below the pre-specified non-inferiority margin of 1.3 and above the superiority margin of 1.0.
- The percentage of patients with a primary CV endpoint event (13.4% and 13.2% for lixisenatide and placebo, respectively) as well as the incidence per 100-patient years (6.39 and 6.31 for lixisenatide and placebo, respectively) were comparable between treatment groups.
- Kaplan-Meier cumulative curves of time from randomization to the first primary CV endpoint event for lixisenatide and placebo were superimposed over the majority of the study period **(Figure 1)**.
- Results of the individual components of the composite endpoint were consistent with the analyses of the primary composite endpoint (Table 7).
- Results of the analysis of MACE (CV death, non-fatal MI, and non-fatal stroke) (HR 1.02, 95% CI of 0.887 to 1.172) were consistent with the results of the primary composite endpoint (MACE + hospitalization for unstable angina).

Secondary CV endpoints: Similarly, the incidence rates were comparable between the two treatments for both of the secondary composite CV endpoints.

- The hazard ratio of the composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or **hospitalization for heart failure** was 0.968 for lixisenatide versus placebo with an associated 2-sided 95% CI of 0.851 to 1.102.
- The hazard ratio of the composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or **coronary revascularization** was 0.997 for lixisenatide versus placebo with an associated 2-sided 95% CI of 0.895 to 1.111.
- The results for the individual components of the composite endpoints were consistent with analyses of the secondary composite endpoints (**Figure 3**).

Urinary albumin/creatinine ratio: Geometric mean urinary albumin/creatinine ratio (UACR) increased from baseline to Week

108 in both treatment groups (24% and 34% change from baseline for the lixisenatide and placebo groups, respectively), but showed a smaller increase in the lixisenatide group as compared to the placebo group (the difference between lixisenatide versus placebo in the percent change from baseline of UACR was -0.10% with 95% CI:-0.17, -0.03).

Safety results:

Safety endpoints were generally comparable between the two treatments:

- The proportion of patients with at least 1 treatment-emergent AE (TEAE) was numerically higher in the lixisenatide (80.7%) versus the placebo group (76.6 %).
- More patients in the lixisenatide than in the placebo group had a TEAE leading to IMP discontinuation (11.4% and 7.2%, respectively). The imbalance was mainly due to the higher frequency of TEAEs of nausea and vomiting, known side effects of GLP-1 receptor agonist treatment.
- Serious TEAEs were reported in 20.6% of patients in the lixisenatide and 22.1% in the placebo group. The frequencies were generally similar between treatments or numerically lower in the lixisenatide group compare to the placebo group with the exception of serious TEAEs categorized as gallbladder disorders (32 patients [1.1%] versus 19 [0.6%]), including cholecystitis (acute or chronic) and cholelithiasis.
- The incidence of all deaths (CV-death, non-CV death, or unknown death) was comparable between lixisenatide and placebo during the on-treatment (3.1% and 3.2%) and on-study (7.0% and 7.4%) periods. The incidences of CV deaths and non-CV deaths were also similar in the two treatment groups.
- The incidence of pancreatitis and pancreatic cancer as adjudicated by a blinded Pancreatic Safety Assessment Committee (PSAC) was lower with lixisenatide treatment than with placebo (5 patients [0.2%] versus.8 [0.3%] and 3 [<0.1%] versus 9 [0.3%] for pancreatitis and pancreatic cancer, respectively).
- Patients in the lixisenatide group had a lower rate of severe symptomatic hypoglycemia (16 versus 37 events [0.3 versus 0.6 per 100-patient years]) while maintaining better glycemic control as compared to the patients in the placebo group.

Conclusions:

The ELIXA study evaluated the CV effects of long-term administration of lixisenatide compared to placebo in patients with T2DM and a recent ACS; the results demonstrated the long-term CV safety of lixisenatide. Furthermore, lixisenatide was generally safe and well-tolerated; no unexpected safety concerns were identified.

- Demographics and disease characteristics were well matched between the two treatment groups
- More than 96% of the patients in both treatment groups completed the study and vital status at the end of the study was known for >98% of the patients in both treatment groups
- In the ELIXA study , lixisenatide administered for a median duration of 22.4 months to patients with T2DM and a high CV risk:
    - Met the pre-specified criterion of non-inferiority versus placebo for the composite primary endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina.
    - Did not demonstrate superiority over placebo in reducing the composite primary CV endpoint
    - Showed a consistent neutral effect on the individual components of the composite primary and secondary CV endpoints, including hospitalization for heart failure
    - Appeared to decrease the worsening of albuminuria
    - Was associated with:
        - No increased risk of pancreatitis
        - No increased risk of pancreatic neoplasm
        - No increased risk of severe, symptomatic hypoglycemia

3 RESULTS

3.1 STUDY PATIENTS

3.1.1 Patient accountability

A total of 7719 patients were screened from 888 study centers in 49 countries worldwide; of these, 6068 patients were randomized 1:1 to double-blind treatment with IMP: 3034 to placebo, 3034 to lixisenatide. One additional patient was randomized, but did not sign the Health Insurance Portability and Accountability Act form, and hence was not included in the 6068 patients in the ITT population.

Five of the randomized patients (2 in the placebo and 3 in the lixisenatide groups) did not receive IMP but were included in the analyses of the ITT population.

3.1.2 Study disposition

Patient disposition by treatment group is provided in Table 1. The number of patients in "Complete the study" included those who either performed the End of Study visit as defined in the protocol or died during the study period. At the End of Study, vital status was not obtained for 71 patients (42 [1.4%] for placebo and 29 [1.0%] for lixisenatide), including patients from sites that had been terminated by the Sponsor, patients lost to follow-up, and patients who withdrew prematurely from the study and refused further contact with the investigators.

Numerically more patients treated with lixisenatide prematurely discontinued study treatment as compared to patients treated with placebo. The most common reasons for treatment discontinuation were "Adverse events" and "Withdrawal by patient" in both groups.

The study discontinuation rate was comparable between treatment groups; the main reason for study discontinuation was "withdrawal by patients".

Table 1 - Patient disposition with reason for premature discontinuation - Randomized population

	Placebo (N=3034)	Lixisenatide (N=3034)
Randomized and not treated	2 (<0.1%)	3 (<0.1%)
Randomized and treated	3032 (>99.9%)	3031 (>99.9%)
Complete the study	2924 (96.4%)	2929 (96.5%)
Complete the final visit	2702 (89.1%)	2722 (89.7%)
Death	222 (7.3%)	207 (6.8%)
Vital status known at the global study end	2992 (98.6%)	3005 (99.0%)
Alive	2769 (91.3%)	2794 (92.1%)
Dead	223 (7.4%)	211 (7.0%)
Did not complete treatment	768 (25.3%)	884 (29.1%)
Adverse event	310 (10.2%)	418 (13.8%)
Site termination by sponsor	8 (0.3%)	4 (0.1%)

	Placebo (N=3034)	Lixisenatide (N=3034)
Withdrawal by patient	398 (13.1%)	414 (13.6%)
Unwilling to undergo injections	119 (3.9%)	116 (3.8%)
Unwilling or unable to perform study procedure	82 (2.7%)	83 (2.7%)
Personal or family issue	127 (4.2%)	137 (4.5%)
Unwilling or unable to attend study visits or to be contacted	70 (2.3%)	78 (2.6%)
Physician's decision due to potential risk of continued IMP administration	16 (0.5%)	24 (0.8%)
Protocol deviation	15 (0.5%)	10 (0.3%)
Other	21 (0.7%)	14 (0.5%)
Did not complete the study	110 (3.6%)	105 (3.5%)
Site termination by sponsor	13 (0.4%)	5 (0.2%)
Withdrawal by patient	83 (2.7%)	88 (2.9%)
Personal or family issue	21 (0.7%)	12 (0.4%)
Due to an adverse event	2 (<0.1%)	5 (0.2%)
Unwilling or unable to attend study visits or to be contacted	60 (2.0%)	71 (2.3%)
Patient lost to follow-up	14 (0.5%)	11 (0.4%)
Other	0	1 (<0.1%)

IMP: investigational medicinal product.
Note: Percentages are calculated using the number of randomized patients as denominator.

3.1.3 Demographics and baseline characteristics

Demographics were well-balanced between the two treatment groups (Table 2).

Median age was 60 years and about one quarter of the study population was 65 years or older. More male and Caucasian patients were enrolled in the study. The majority of patients were either obese or overweight with a median body mass index (BMI) of 29.4 kg/m^2.

Table 2 - Demographics and patient characteristics at screening or baseline - Randomized population

	Placebo (N=3034)	Lixisenatide (N=3034)	All (N=6068)
Age (years)			
Number	3034	3034	6068
Mean (SD)	60.6 (9.6)	59.9 (9.7)	60.3 (9.7)
Median	61.0	60.0	60.0
Min : Max	30 : 89	30 : 93	30 : 93

	Placebo (N=3034)	Lixisenatide (N=3034)	All (N=6068)
Age group (years) [n (%)]			
Number	3034	3034	6068
< 50	377 (12.4%)	464 (15.3%)	841 (13.9%)
≥50 to <65	1617 (53.3%)	1567 (51.6%)	3184 (52.5%)
≥65 to <75	792 (26.1%)	805 (26.5%)	1597 (26.3%)
≥75	248 (8.2%)	198 (6.5%)	446 (7.4%)
Gender [n (%)]			
Number	3034	3034	6068
Male	2096 (69.1%)	2111 (69.6%)	4207 (69.3%)
Female	938 (30.9%)	923 (30.4%)	1861 (30.7%)
Race [n (%)]			
Number	3034	3034	6068
Caucasian/White	2318 (76.4%)	2258 (74.4%)	4576 (75.4%)
Black	103 (3.4%)	118 (3.9%)	221 (3.6%)
Asian/Oriental	367 (12.1%)	404 (13.3%)	771 (12.7%)
Other	246 (8.1%)	254 (8.4%)	500 (8.2%)
Ethnicity [n (%)]			
Number	3034	3034	6068
Hispanic	903 (29.8%)	865 (28.5%)	1768 (29.1%)
Not hispanic	2131 (70.2%)	2169 (71.5%)	4300 (70.9%)
Baseline body weight (kg)			
Number	3032	3033	6065
Mean (SD)	85.06 (19.64)	84.64 (19.21)	84.85 (19.43)
Median	82.40	82.40	82.40
Min : Max	38.0 : 198.2	40.2 : 232.0	38.0 : 232.0
Baseline BMI (kg/m^2)			
Number	3032	3033	6065
Mean (SD)	30.20 (5.79)	30.12 (5.60)	30.16 (5.69)
Median	29.29	29.40	29.35
Min : Max	16.9 : 59.3	17.1 : 68.9	16.9 : 68.9
Baseline BMI Categories (kg/m^2) [n (%)]			
Number	3032	3033	6065
< 30	1681 (55.4%)	1649 (54.4%)	3330 (54.9%)
≥ 30	1351 (44.6%)	1384 (45.6%)	2735 (45.1%)

SD: standard deviation, BMI: body mass index.

Diabetes characteristics at screening or baseline were generally well-matched between treatment groups (Table 3. Around 40% of patients in both groups had long-standing T2DM (≥10 years). Glycemia at study entry as represented by HbA1c and FPG was relatively controlled and was balanced between treatment groups. Over 75% of patients had impaired renal function and more than 20% of patients had an estimated glomerular filtration rate (GFR) <60 mL/min/ 1.73 m^2. At screening, ~25% of patients in both treatment groups had microalbuminuria or overt proteinuria.

Table 3 - Disease characteristics at screening or baseline: Diabetes status - Randomized population

	Placebo (N=3034)	Lixisenatide (N=3034)	All (N=6068)
Duration of diabetes (years)			
Number	3034	3031	6065
Mean (SD)	9.38 (8.32)	9.20 (8.19)	9.29 (8.25)
Median	7.36	7.40	7.38
Min : Max	0.0 : 54.7	0.0 : 50.0	0.0 : 54.7
Duration of diabetes (years)			
Number	3034	3031	6065
<10	1789 (59.0%)	1828 (60.3%)	3617 (59.6%)
≥10	1245 (41.0%)	1203 (39.7%)	2448 (40.4%)
Age at onset of diabetes (years)			
Number	3034	3031	6065
Mean (SD)	51.29 (10.72)	50.76 (10.73)	51.02 (10.73)
Median	51.00	51.00	51.00
Min : Max	13.0 : 87.0	17.0 : 91.0	13.0 : 91.0
Baseline HbA1c (%)			
Number	3033	3034	6067
Mean (SD)	7.64 (1.28)	7.72 (1.32)	7.68 (1.30)
Median	7.50	7.50	7.50
Min : Max	5.0 : 11.5	4.9 : 13.3	4.9 : 13.3
Baseline FPG (mmol/L)			
Number	2947	2954	5901
Mean (SD)	8.20 (2.91)	8.27 (2.82)	8.23 (2.86)
Median	7.50	7.60	7.60
Min : Max	2.3 : 28.1	2.5 : 25.1	2.3 : 28.1
Baseline FPG (mg/dL)			
Number	2947	2954	5901
Mean (SD)	147.79 (52.34)	148.89 (50.86)	148.34 (51.60)
Median	135.11	136.91	136.91
Min : Max	41.4 : 506.2	45.0 : 452.2	41.4 : 506.2

	Placebo (N=3034)	Lixisenatide (N=3034)	All (N=6068)
Baseline urinary albumin/creatinine ratio (mg/g) [n (%)]			
Number	2994	2984	5978
<30 mg/g (normoalbuminuria)	2191 (73.2%)	2250 (75.4%)	4441 (74.3%)
≥30 to <300 mg/g (microalbuminuria)	596 (19.9%)	552 (18.5%)	1148 (19.2%)
≥300 mg/g (macroalbuminuria)	207 (6.9%)	182 (6.1%)	389 (6.5%)
Baseline estimated glomerular filtration rate (eGFR), n (%)			
Number	3026	3029	6055
≥15 to <30 mL/min/1.73 m^2 (severe renal impairment)	4 (0.1%)	4 (0.1%)	8 (0.1%)
≥30 to <60 mL/min/1.73 m^2 (moderate renal impairment)	744 (24.6%)	655 (21.6%)	1399 (23.1%)
≥60 to <90 mL/min/1.73 m^2 (mild renal impairment)	1603 (53.0%)	1632 (53.9%)	3235 (53.4%)
≥90 mL/min/1.73 m^2 (normal)	675 (22.3%)	738 (24.4%)	1413 (23.3%)

SD: standard deviation, HbA1c: glycosylated hemoglobin A1c, FPG: fasting plasma glucose. eGFR: estimated glomerular filtration rate, calculated by the 4-variable modification of diet in renal disease (MDRD) formula using the serum creatinine, race, age, and gender of the patient: GFR (mL/min/1.73 m^2) = 175 × serum creatinine (mg/dL)$^{-1.154}$ × age (years)$^{-0.203}$ × 1.212 [if black] × 0.742 [if female]

The majority of patients (>70%) in both treatment groups had a qualifying ACS within 90 days before randomization (Table 4). The most common type of qualifying ACS in both treatment groups was ST-segment elevation MI followed by non ST-segment elevation MI; less than 20% of patients experienced unstable angina. An equal percentage of patients in each treatment group (61%) underwent a percutaneous coronary revascularization for treatment of the ACS before entering the study. Heart function status and severity of angina as per New York Heart Association and Canadian Classification was similar in the two groups.

Table 4 - Disease characteristics at baseline: History of qualifying acute coronary syndrome - Randomized population

	Placebo (N=3034)	Lixisenatide (N=3034)	All (N=6068)
Duration (days) between qualifying ACS and screening			
Number	3031	3033	6064
Mean (SD)	64.11 (43.81)	63.77 (43.35)	63.94 (43.58)
Median	52.00	52.00	52.00
Min : Max	3.0 : 220.0	3.0 : 251.0	3.0 : 251.0
Duration (days) between qualifying ACS and randomization			
Number	3031	3033	6064
Mean (SD)	72.19 (43.85)	71.83 (43.37)	72.01 (43.61)
Median	60.00	60.00	60.00
Min : Max	10.0 : 227.0	9.0 : 261.0	9.0 : 261.0

	Placebo (N=3034)	Lixisenatide (N=3034)	All (N=6068)
Duration between qualifying ACS and randomization by time category [n (%)]			
Number	3031	3033	6064
<30 days	399 (13.2%)	397 (13.1%)	796 (13.1%)
≥30 days - <60 days	1099 (36.3%)	1086 (35.8%)	2185 (36.0%)
≥60 days - <90 days	675 (22.3%)	722 (23.8%)	1397 (23.0%)
≥90 days	858 (28.3%)	828 (27.3%)	1686 (27.8%)
Qualifying ACS [n (%)]			
Number	3032	3033	6065
ST-segment elevation MI	1317 (43.4%)	1349 (44.5%)	2666 (44.0%)
Non ST-segment elevation MI	1183 (39.0%)	1165 (38.4%)	2348 (38.7%)
Unstable angina	528 (17.4%)	514 (16.9%)	1042 (17.2%)
Unknown	4 (0.1%)	5 (0.2%)	9 (0.1%)
Qualifying ACS: New York Heart Association (NYHA) class [n (%)]			
Number	2936	2948	5884
I	1754 (59.7%)	1816 (61.6%)	3570 (60.7%)
II	962 (32.8%)	940 (31.9%)	1902 (32.3%)
III	190 (6.5%)	166 (5.6%)	356 (6.1%)
IV	30 (1.0%)	26 (0.9%)	56 (1.0%)
Qualifying ACS: Worst severity of angina per Canadian Classification [n (%)]			
Number	3020	3015	6035
I	610 (20.2%)	611 (20.3%)	1221 (20.2%)
II	488 (16.2%)	466 (15.5%)	954 (15.8%)
III	212 (7.0%)	234 (7.8%)	446 (7.4%)
IV	122 (4.0%)	145 (4.8%)	267 (4.4%)
NA	1588 (52.6%)	1559 (51.7%)	3147 (52.1%)
Patient underwent percutaneous coronary revascularization for qualifying ACS [n (%)]			
Number	3032	3033	6065
Yes	1865 (61.5%)	1875 (61.8%)	3740 (61.7%)
No	1167 (38.5%)	1158 (38.2%)	2325 (38.3%)

SD: standard deviation, ACS: acute coronary syndrome, CABG: coronary artery bypass graft, MI: myocardial infarction

3.1.4 Dosage and duration of exposure

The starting dose of IMP was 10 µg QD for the first 2 weeks, after which the dose was increased to 20 µg QD and then maintained at that dose for the duration of the study. In case of intolerance,

investigators were allowed to reduce the dose to 15 µg or 10 µg QD. The majority of patients in both groups received the maximal study dose of 20 µg QD (Table 5). More patients treated with placebo (96.5%) than with lixisenatide (85.5%) maintained the target dose of 20 µg QD until the end of the study.

Table 5 - Number (%) of patients by final dose at the end of the double-blind treatment period - Safety population

Final Dose	Placebo (N=3032)	Lixisenatide (N=3031)
5 µg	0	5 (0.2%)
10 µg	86 (2.8%)	312 (10.3%)
15 µg	18 (0.6%)	122 (4.0%)
20 µg	2926 (96.5%)	2591 (85.5%)
30 µg	1 (<0.1%)	0
40 µg	1 (<0.1%)	1 (<0.1%)

Dose = Dose of lixisenatide or volume-matched placebo.
Note: Percentages are calculated using the number of randomized and exposed population as the denominator.

The cumulative duration of treatment exposure was numerically higher for placebo versus lixisenatide. The median treatment exposure was 22.4 months for lixisenatide and 23.3 months for placebo (Table 6). More than 80% of patients in the lixisenatide group were treated for over 1 year, 66% for ≥1.5 years, and 45% for ≥2 years.

Table 6 - Exposure to investigational product - Safety population

	Placebo (N=3032)	Lixisenatide (N=3031)
Cumulative duration of treatment exposure (patient years)	5888.7	5690.2
Duration of study treatment (days)		
Number	3007	3005
Mean (SD)	715.3 (330.7)	691.6 (348.1)
Median	698.0	673.0
Min : Max	1 : 1548	1 : 1572
Duration of study treatment by category [n(%)]		
Missing	25 (0.8%)	26 (0.9%)
< 26 weeks	255 (8.4%)	348 (11.5%)
≥26 to <52 weeks	156 (5.1%)	163 (5.4%)
≥52 to <78 weeks	498 (16.4%)	484 (16.0%)
≥78 to <104 weeks	680 (22.4%)	643 (21.2%)
≥104 to <130 weeks	561 (18.5%)	545 (18.0%)
≥130 to <156 weeks	436 (14.4%)	406 (13.4%)
≥156 to <182 weeks	261 (8.6%)	255 (8.4%)
≥182 to <208 weeks	149 (4.9%)	143 (4.7%)

	Placebo (N=3032)	Lixisenatide (N=3031)
≥208 weeks	11 (0.4%)	18 (0.6%)
Cumulative duration of study treatment by category [n (%)]		
≥26 weeks	2752 (90.8%)	2657 (87.7%)
≥52 weeks	2596 (85.6%)	2494 (82.3%)
≥78 weeks	2098 (69.2%)	2010 (66.3%)
≥104 weeks	1418 (46.8%)	1367 (45.1%)
≥130 weeks	857 (28.3%)	822 (27.1%)
≥156 weeks	421 (13.9%)	416 (13.7%)
≥182 weeks	160 (5.3%)	161 (5.3%)
≥208 weeks	11 (0.4%)	18 (0.6%)

SD: standard deviation.IMP: investigational medicinal product. Note: Patients are considered in the group of treatment they actually received at randomization. Duration of exposure = (date of the last double-blind IMP injection - date of the first double-blind IMP injection) + 1 day.

3.2 EFFICACY

3.2.1 Primary efficacy endpoint

The percentage of patients with a primary CV endpoint event (13.4% and 13.2% for lixisenatide and placebo, respectively) as well as the incidence per 100-patient years (6.39 and 6.31 for lixisenatide and placebo, respectively) were comparable between treatment groups (Table 7).

The hazard ratio for lixisenatide versus placebo was 1.017 with an associated 2-sided 95% CI of 0.886 to 1.168. The upper bound of the 2-sided 95% CI estimated from the Cox model was below the pre-specified non-inferiority margin of 1.3 but above 1.0; thus, lixisenatide demonstrated non-inferiority but did not show superiority versus placebo for the primary CV endpoint.

The percentages of each type of primary endpoints included in the primary composite endpoint by treatment group were consistent with the results of the composite endpoint (Table 7).

Table 7 - Analysis of the primary cardiovascular endpoint (time to the first occurrence of the composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina) - ITT population

	Placebo (N=3034)	Lixisenatide (N=3034)	Hazard ratio (95% CI)[c]	Log-rank test p-value
Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina*			1.017 (0.886, 1.168)	0.8542
Number of patients with event (%)	399 (13.2%)	406 (13.4%)	-	-
Total patient years for the event[a]	6328.2	6356.8	-	-
Incidence rate per 100 patient years[b]	6.31	6.39	-	-

	Placebo (N=3034)	Lixisenatide (N=3034)	Hazard ratio (95% CI)[c]	Log-rank test p-value
Type of the first event of the composite endpoint				
CV death	93 (3.1%)	88 (2.9%)	-	-
Non-fatal MI	247 (8.1%)	255 (8.4%)	-	-
Non-fatal stroke	49 (1.6%)	54 (1.8%)	-	-
Hospitalization for unstable angina	10 (0.3%)	9 (0.3%)	-	-

* Only CAC positively adjudicated events are included.

CV: cardiovascular, MI: myocardial infarction, CI: confidence interval.

[a] Calculated as time from randomization date to the first event date or censoring date (the end of study date) for patients who had no events.

[b] Calculated as number of patients with an event divided by total patient years for the event and multiplied by 100.

[c] Hazard ratio of lixisenatide versus placebo estimated using Cox proportional hazards model based on ITT population, with treatment (lixisenatide, placebo), and region (North America, South and Central America, Western Europe, Eastern Europe, Africa/Near East, and Asia/Pacific) as covariates, and the associated two-sided 95% CI.

In case of multiple events occurred on the same date, event is counted in the categories following the order of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina.

Kaplan-Meier cumulative curves of time from randomization to the first primary CV endpoint event for lixisenatide and placebo were superimposed over the majority of the study period **(Figure 1)**.

Analysis of MACE endpoint

The results of the composite MACE endpoint, which excluded "hospitalization for unstable angina", showed a result consistent with the primary endpoint with similar incidence rates between treatment groups (Table 8). A neutral HR for lixisenatide versus placebo was observed with an associated upper bound of the 2-sided 95% CI below 1.3.

Table 8 - Analysis of Major Adverse Cardiac Event (MACE) (time to the first occurrence of the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) - ITT population

	Placebo (N=3034)	Lixisenatide (N=3034)	Hazard ratio (95% CI)[c]	Log-rank test p-value
Composite of CV death, non-fatal MI, or non-fatal stroke*			1.02 (0.887, 1.172)	0.8234
Number of patients with event (%)	392 (12.9%)	400 (13.2%)	-	-
Total patient years for the event[a]	6340.2	6368.7	-	-

	Placebo (N=3034)	Lixisenatide (N=3034)	Hazard ratio (95% CI)[c]	Log-rank test p-value
Incidence rate per 100 patient years[b]	6.18	6.28	-	-

CV: cardiovascular, MI: myocardial infarction, CI: confidence interval.

* Only CAC positively adjudicated events are included.

[a] Calculated as time from randomization date to the first event date or censoring date (the end of study date) for patients who had no events.

[b] Calculated as number of patients with an event divided by total patient years for the event and multiplied by 100.

[c] Hazard ratio of lixisenatide versus placebo estimated using Cox proportional hazards model based on ITT population, with treatment (lixisenatide, placebo), and region (North America, South and Central America, Western Europe, Eastern Europe, Africa/Near East, and Asia/Pacific) as covariates, and the associated two-sided 95% CI.

Individual primary endpoints

The results of the analyses of the time to the first occurrence of each individual component of the composite primary endpoint are presented in a forest plot **(Figure 2)**. Overall, these results are concordant with the composite primary endpoint. Numerically more "stroke" events were seen in the lixisenatide group; however, the imbalance in the number of events (67 for lixisenatide versus 60 for placebo) was small and the 95% CI was wide and crossed unity. In addition, fatal strokes were reported less frequently in the lixisenatide group than in the placebo group (Table 13).

3.2.2 Other key efficacy endpoints

3.2.2.1 Secondary CV endpoints

Consistent with the analyses of the primary CV endpoint, the event rates of composite endpoints adding "hospitalization for heart failure" or both "hospitalization for heart failure" and "coronary revascularization" were comparable between treatments. The hazard ratio, 95% CI, and descriptive p-values for each of the composite endpoints are presented in Table 9.

Table 9 - Analysis of the secondary composite cardiovascular endpoints - ITT population

	Placebo (N=3034)	Lixisenatide (N=3034)	Hazard ratio (95% CI)[c]	Log-rank test p-value
Composite of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or hospitalization for heart failure*			0.968 (0.851, 1.102)	0.5823
Number of patients with event (%)	469 (15.5%)	456 (15.0%)	-	-
Total patient years for the event[a]	6209.2	6269.6	-	-
Incidence rate per 100 patient years[b]	7.55	7.27	-	-

	Placebo (N=3034)	Lixisenatide (N=3034)	Hazard ratio (95% CI)[c]	Log-rank test p-value
Composite of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or coronary revascularization procedure*			0.997 (0.895, 1.111)	0.963
Number of patients with event (%)	659 (21.7%)	661 (21.8%)	-	-
Total patient years for the event[a]	5904.5	5946.9	-	-
Incidence rate per 100 patient years[b]	11.16	11.12	-	-

CV: cardiovascular, MI: myocardial infarction, CI: confidence interval.

* Only CAC positively adjudicated events are included.

[a] Calculated as time from randomization date to the first event date or censoring date (the end of study date) for patients who had no events.

[b] Calculated as number of patients with an event divided by total patient years for the event and multiplied by 100.

[c] Hazard ratio of lixisenatide versus placebo estimated using Cox proportional hazards model based on ITT population, with treatment (lixisenatide, placebo), and region (North America, South and Central America, Western Europe, Eastern Europe, Africa/Near East, and Asia/Pacific) as covariates, and the associated two-sided 95% CI.

Individual secondary endpoints

The results of analyses of the time to the first occurrence of each individual component of the composite secondary endpoints are presented in **Figure 3**, including MACE +"hospitalization for heart failure", and MACE + "hospitalization for heart failure" or "coronary revascularization".

The hazard ratios for lixisenatide versus placebo and the associated 2-sided 95% CI suggest that treatment with lixisenatide, as compared to placebo, did not increase or decrease the occurrence of hospitalization for heart failure or both hospitalizations for heart failure and coronary revascularization.

3.2.2.2 Urinary albumin/creatinine ratio

UACR was measured at Weeks 0, 24, 76, 108 and End of Study and percent changes from baseline to Week 108 are summarized (Table 10). Geometric mean values at baseline were similar in the two treatment groups. Geometric mean UACR increased from baseline to Week 108 in both treatment groups, but showed a smaller increase in the lixisenatide group as compared to the placebo group (the difference between lixisenatide versus placebo in the percent change from baseline of UACR was -0.10% with a 95% CI of -0.17 to -0.03).

Table 10 - Analysis of percent change in urinary albumin/creatinine ratio in US units (mg/g) from baseline to Week 108 (LOCF) - ITT population

Urinary albumin/creatinine ratio (mg/g)	Placebo (N=3034)	Lixisenatide (N=3034)

Urinary albumin/creatinine ratio (mg/g)	Placebo (N=3034)	Lixisenatide (N=3034)
Baseline		
Number	2830	2803
Geometric Mean (SD)	17.36 (26.53)	16.04 (23.32)
Median	10.36	10.03
Min : Max	1.24 : 76025.07	1.77 : 155074.87
Week 108 (LOCF)		
Number	2830	2803
Geometric Mean (SD)	22.99 (39.16)	19.90 (31.36)
Median	13.39	11.89
Min : Max	2.15 : 19710.58	1.44 : 16047.83
Percent change from baseline to Week 108 (LOCF[a])		
Based on geometric mean	0.32	0.24
Based on geometric mean estimated from ANCOVA model[b] (SE)	0.34 (0.03)	0.24 (0.03)
Lixisenatide versus placebo[c] (SE)		-0.10 (0.04)
95% CI		(-0.17, -0.03)

SD: standard deviation, LOCF: last observation carried forward, SE: standard error.CI: confidence interval.

[a] In case of missing measurements at Week 108, the LOCF procedure is used by taking the last available post-baseline urinary albumin/creatinine ratio before Week 108 as the value at Week 108, regardless of treatment discontinuation or not.

[b] The urinary albumin/creatinine ratio are first log-transformed. Then the change from baseline is analyzed using ANCOVA model with treatment (lixisenatide, placebo), region, intake of ACE inhibitors at baseline (yes or no) and intake of Angiotensin II Receptor Blockers at baseline (ARB) (yes or no) as fixed effects and using the baseline urinary albumin/creatinine ratio as a covariate. Results in the log scale are back-transformed to provide the estimates of the geometric means.

[c] Calculated based on the estimates from the ANCOVA model.

Region : North America, South and Central America, Western Europe, Eastern Europe, Africa/Near East, and Asia/Pacific.

3.2.2.3 Change from baseline in HbA1c

Patients in both treatment groups had a comparable mean HbA1c at baseline (7.72% for lixisenatide versus 7.64% for placebo). The mean HbA1c was reduced in both treatment groups over the course of the study. A greater reduction was seen in the lixisenatide than in the placebo group at each observation over the entire study period **(Figure 4)**.

3.3 SAFETY

3.3.1 TEAEs

Note: as stated in the statistical section, this table does not include the events reported in the specific CV AE forms for "Myocardial infarction (MI) or hospitalization for unstable angina", "Stroke", "Hospitalization for heart failure", or "Coronary revascularization procedure", regardless of adjudication results, seriousness or drug-relationship, because all these events were reported as endpoints.

The proportion of patients with at least 1 TEAE was numerically higher in the lixisenatide group as compared to the placebo group, while the proportion of patients with a serious TEAE was numerically higher in in the placebo group as compared to the lixisenatide group (Table 11). The percentage of patients with TEAEs leading to death was comparable between treatments.

More patients discontinued IMP due to an AE in the lixisenatide group than in the placebo group. As previously observed in lixisenatide Phase 3 studies, the imbalance was primarily due to the higher frequency of TEAEs of nausea and vomiting, known side effects of GLP-1 receptor agonists.

Table 11 - Overview of on-treatment adverse events - safety population

	Placebo (N=3032)	Lixisenatide (N=3031)
Patients with any on-treatment AE	2321 (76.6%)	2447 (80.7%)
Patients with any serious on-treatment AE	669 (22.1%)	625 (20.6%)
Patients with any on-treatment AE leading to death	64 (2.1%)	74 (2.4%)
Patients with any on-treatment AE leading to permanent treatment discontinuation	217 (7.2%)	347 (11.4%)

AE: adverse event.
On-treatment AE: AEs that developed or worsened (according to the Investigator opinion) or became serious during the on-treatment period.
On-treatment period = the time from the first IMP dose intake until 3 days after treatment discontinuation.
n (%) = number and percentage of patients with at least one on-treatment AE.

3.3.2 Deaths

All deaths were reviewed by the CAC and the primary cause of death was adjudicated by the CAC regardless of the investigators' diagnosis. The incidence of CV and non-CV deaths, or unknown deaths (due to insufficient information for adjudication) according to the CAC adjudication was summarized for on-treatment and on-study periods.

The incidence of all deaths on-treatment and on-study was comparable between lixisenatide and placebo (Table 12), as were the on-study deaths by primary cause of death as adjudicated by the CAC (Table 13).

Table 12 - Number (%) of patients who died by study period (on-study, on-treatment, post-study) and primary cause of death as adjudicated by the CAC - safety population

	Placebo (N=3032)	Lixisenatide (N=3031)
Death on-study[a]	223 (7.4%)	211 (7.0%)
CV death	158 (5.2%)	156 (5.1%)
Non-CV death	58 (1.9%)	46 (1.5%)
Unknown	7 (0.2%)	9 (0.3%)
Death on-treatment[b]	96 (3.2%)	93 (3.1%)
CV death	86 (2.8%)	76 (2.5%)
Non-CV death	10 (0.3%)	13 (0.4%)
Unknown	0	4 (0.1%)
Death post-study[c]	0	1 (<0.1%)

CAC: cardiovascular events adjudication committee, CV: cardiovascular.
[a] On-study period = time from the randomization until the study end date for a patient.
[b] On-treatment period = the time from the first IMP dose intake until 3 days after treatment discontinuation.
[c] Includes deaths that occurred after the end of the study and reported in the database.

Table 13 - Number (%) of patients who died during the on-study period by primary cause of death as adjudicated by the CAC - safety population

Type	Placebo (N=3032)	Lixisenatide (N=3031)
Any death	223 (7.4%)	211 (7.0%)
Cardiovascular death	158 (5.2%)	156 (5.1%)
Fatal Myocardial Infarction	23 (0.8%)	35 (1.2%)
Heart failure	24 (0.8%)	18 (0.6%)
Sudden death	58 (1.9%)	66 (2.2%)
Witnessed or last seen alive LT 1 hr	41 (1.4%)	44 (1.5%)
Last seen alive GE 1 hr and LT 24 hrs	17 (0.6%)	22 (0.7%)
Presumed sudden death	4 (0.1%)	4 (0.1%)
Presumed CV death	25 (0.8%)	12 (0.4%)
Fatal stroke	18 (0.6%)	13 (0.4%)
Ischemic	8 (0.3%)	6 (0.2%)
Ischemic with hemorrhagic conversion	1 (<0.1%)	2 (<0.1%)
Hemorrhagic	8 (0.3%)	3 (<0.1%)
Clinical	1 (<0.1%)	2 (<0.1%)
Fatal pulmonary embolism	1 (<0.1%)	0
CV Procedural	3 (<0.1%)	6 (0.2%)
CABG	1 (<0.1%)	4 (0.1%)
PCI / Stenting	0	1 (<0.1%)
Valvular	0	0
Other CV Procedural	2 (<0.1%)	1 (<0.1%)

Type	Placebo (N=3032)	Lixisenatide (N=3031)
Other cardiovascular death	2 (<0.1%)	2 (<0.1%)
Non Cardiovascular death	58 (1.9%)	46 (1.5%)
Infection	17 (0.6%)	13 (0.4%)
Malignancy	21 (0.7%)	22 (0.7%)
Pulmonary	6 (0.2%)	2 (<0.1%)
Gastro intestinal	10 (0.3%)	3 (<0.1%)
Renal	2 (<0.1%)	1 (<0.1%)
Accidental	0	1 (<0.1%)
Suicide	1 (<0.1%)	1 (<0.1%)
Diabetes-related	1 (<0.1%)	0
Other Non-CV death	0	3 (<0.1%)
Unknown cause of death	7 (0.2%)	9 (0.3%)

CAC: cardiovascular events adjudication committee.

On-study period = time from the randomization until the study end date for a patient.

3.3.3 SAEs

Table 14 is a modified serious TEAE table due to KRM space limitation. It includes serious TEAEs (n/%) by primary system organ class (SOC). Serious TEAEs by HLGT and HLT are displayed only if the incidence was ≥0.4% and was also higher in the lixisenatide than in the placebo group.

The incidence of serious TEAEs was well-balanced between treatment groups. Serious TEAEs were reported in 20.6% and 22.1% of patients in the lixisenatide and placebo groups, respectively (Table 14).

The frequencies of categories of serious TEAEs were generally similar between treatments or numerically lower in the lixisenatide group as compared to the placebo group. An exception was serious TEAEs categorized as gallbladder disorders (32 patients [1.1%] versus 19 [0.6%] for lixisenatide versus placebo), including cholecystitis (acute or chronic) and cholelithiasis.

Table 14 - Number (%) of patients with serious on-treatment adverse events presented by primary SOC, HLGT, HLT, and PT - safety population

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Placebo (N=3032)	Lixisenatide (N=3031)
Any class	669 (22.1%)	625 (20.6%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Placebo (N=3032)	Lixisenatide (N=3031)
INFECTIONS AND INFESTATIONS	186 (6.1%)	173 (5.7%)
HLGT: Infections - pathogen unspecified	154 (5.1%)	150 (4.9%)
HLT: Abdominal and gastrointestinal infections	20 (0.7%)	25 (0.8%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	61 (2.0%)	72 (2.4%)
HLGT: Gastrointestinal neoplasms malignant and unspecified	16 (0.5%)	19 (0.6%)
HLT: Colorectal neoplasms malignant	7 (0.2%)	13 (0.4%)
HLGT: Reproductive neoplasms male malignant and unspecified	9 (0.3%)	12 (0.4%)
HLT: Prostatic neoplasms malignant	8 (0.3%)	12 (0.4%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	14 (0.5%)	14 (0.5%)
ENDOCRINE DISORDERS	3 (<0.1%)	2 (<0.1%)
METABOLISM AND NUTRITION DISORDERS	57 (1.9%)	33 (1.1%)
HLGT: Electrolyte and fluid balance conditions	12 (0.4%)	15 (0.5%)
PSYCHIATRIC DISORDERS	5 (0.2%)	9 (0.3%)
NERVOUS SYSTEM DISORDERS	53 (1.7%)	47 (1.6%)
EYE DISORDERS	13 (0.4%)	9 (0.3%)
EAR AND LABYRINTH DISORDERS	4 (0.1%)	5 (0.2%)
CARDIAC DISORDERS	107 (3.5%)	83 (2.7%)
HLGT: Cardiac arrhythmias	71 (2.3%)	49 (1.6%)
HLT: Ventricular arrhythmias and cardiac arrest	13 (0.4%)	14 (0.5%)
VASCULAR DISORDERS	71 (2.3%)	59 (1.9%)
HLGT: Arteriosclerosis, stenosis, vascular insufficiency and necrosis	19 (0.6%)	19 (0.6%)
HLT: Peripheral vasoconstriction, necrosis and vascular insufficiency	13 (0.4%)	14 (0.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	58 (1.9%)	58 (1.9%)
GASTROINTESTINAL DISORDERS	81 (2.7%)	66 (2.2%)
HEPATOBILIARY DISORDERS	28 (0.9%)	36 (1.2%)
HLGT: Gallbladder disorders	19 (0.6%)	32 (1.1%)
HLT: Cholecystitis and cholelithiasis	19 (0.6%)	31 (1.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	18 (0.6%)	14 (0.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	35 (1.2%)	32 (1.1%)
HLGT: Joint disorders	9 (0.3%)	13 (0.4%)
RENAL AND URINARY DISORDERS	48 (1.6%)	48 (1.6%)
HLGT: Renal disorders (excl nephropathies)	32 (1.1%)	33 (1.1%)
HLT: Renal failure and impairment	31 (1.0%)	32 (1.1%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	5 (0.2%)	13 (0.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	58 (1.9%)	64 (2.1%)
HLGT: General system disorders NEC	51 (1.7%)	54 (1.8%)
HLT: Pain and discomfort NEC	44 (1.5%)	49 (1.6%)
INVESTIGATIONS	19 (0.6%)	10 (0.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	50 (1.6%)	44 (1.5%)
HLGT: Injuries NEC	16 (0.5%)	17 (0.6%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Placebo (N=3032)	Lixisenatide (N=3031)
HLT: Non-site specific injuries NEC	10 (0.3%)	11 (0.4%)
SURGICAL AND MEDICAL PROCEDURES	6 (0.2%)	6 (0.2%)
SOCIAL CIRCUMSTANCES	0	1 (<0.1%)

Note: SOC: system organ class, HLGT: high level group term, HLT: high level term, On-treatment AE: AEs that developed or worsened (according to the Investigator opinion) or became serious during the on-treatment period. On-treatment period = the time from the first IMP dose intake until 3 days after treatment discontinuation. n (%) = number and percentage of patients with at least one on-treatment AE.

3.3.4 Other significant adverse events

3.3.4.1 Pancreatitis

Pancreatitis occurred infrequently in both treatment groups (Table 15), and the percentage of patients with suspected pancreatitis sent for adjudication was similar between lixisenatide and placebo. Fewer patients in the lixisenatide than in the placebo group had TEAEs of any type of pancreatitis as confirmed by the PSAC.

Table 15 - Summary of events sent to PSAC for pancreatitis adjudication during the on-treatment period - safety population

Type	Placebo (N=3032)	Lixisenatide (N=3031)
Total patient years of exposure	5942.69	5757.09
Events sent to PSAC for adjudication		
Number of patients with events	32 (1.1%)	36 (1.2%)
Number of events	34	47
Events adjudicated as "Yes" for pancreatitis by PSAC		
Number of patients with events	8 (0.3%)	5 (0.2%)
Number of events	8	5
Events adjudicated as "Yes" for acute pancreatitis by PSAC		
Number of patients with events	7 (0.2%)	2 (<0.1%)
Number of events	7	2
Events adjudicated as "Yes" for acute on chronic pancreatitis by PSAC		
Number of patients with events	0	1 (<0.1%)
Number of events	0	1
Events adjudicated as "Yes" for chronic pancreatitis by PSAC		

Type	Placebo (N=3032)	Lixisenatide (N=3031)
Number of patients with events	1 (<0.1%)	2 (<0.1%)
Number of events	1	2
Events adjudicated as "Yes" for unknown pancreatitis by PSAC		
Number of patients with events	0	0
Number of events	0	0
Events adjudicated as "No" for pancreatitis by PSAC		
Number of patients with events	24 (0.8%)	32 (1.1%)
Number of events	25	42
Events adjudicated as Insufficient documentation for event determination by PSAC		
Number of patients with events	1 (<0.1%)	0
Number of events	1	0

PSAC: pancreatic safety assessment committee.
On-treatment period = the time from the first IMP dose intake until 3 days after treatment discontinuation.
Patient years of exposure is calculated as time from the first to the last injection of IMP plus 3 days.

3.3.4.2 Pancreatic cancer

Pancreatic cancer occurred infrequently during the combined on-treatment and post-treatment periods (Table 16). The incidence of observed pancreatic malignancy confirmed by the PSAC was lower in the lixisenatide than in the placebo group (3 patients [<0.1%] versus 9 [0.3%], respectively).

No patients in the lixisenatide and two in the placebo group had pancreatic cancers that were considered as possibly related to study treatment by the PSAC (Table 17).

Table 16 - Summary of events sent to PSAC for pancreatic neoplasms adjudication during the combined on-treatment and post-treatment periods - safety population

Type	Placebo (N=3032)	Lixisenatide (N=3031)
Total patient years of follow up	6690.75	6730.22
Events sent to PSAC for adjudication		
Number of patients with events	11 (0.4%)	5 (0.2%)
Number of events	11	5
Events adjudicated as malignant pancreatic neoplasms by PSAC		
Number of patients with events	9 (0.3%)	3 (<0.1%)
Number of events	9	3
Events adjudicated as benign pancreatic neoplasms by PSAC		

Type	Placebo (N=3032)	Lixisenatide (N=3031)
Number of patients with events	0	1 (<0.1%)
Number of events	0	1
Events adjudicated as Insufficient documentation for event determination by PSAC		
Number of patients with events	1 (<0.1%)	1 (<0.1%)
Number of events	1	1

PSAC: pancreatic safety assessment committee.
On-treatment period = the time from the first IMP dose intake until 3 days after treatment discontinuation.
Post-treatment period = the time starting 4 days after the last administration of IMP (after the on-treatment period).
Patient years of follow up is calculated as time from the first dosing to the last contact date or death.

Table 17 - Number (%) of patients with events adjudicated as malignant pancreatic neoplasms by PSAC by causal relationship during the combined on-treatment and post-treatment periods - safety population

	Placebo (N=3032)	Lixisenatide (N=3031)
Number of patients with events adjudicated as malignant pancreatic neoplasms by PSAC		
Related	0	0
Possibly related	2 (<0.1%)	0
Unlikely related	3 (<0.1%)	2 (<0.1%)
Not related	4 (0.1%)	1 (<0.1%)

PSAC: pancreatic safety assessment committee.
On-treatment period = the time from the first IMP dose intake until 3 days after treatment discontinuation.
Post-treatment period = the time starting 4 days after the last administration of IMP (after the on-treatment period).

3.3.4.3 Other malignancy events and unspecified tumors

Using a standardized MedDRA Query, the SMQ "Malignant or unspecified tumors" was used for the analyses. The presented AEs include cancers and unspecified neoplasm (eg, nodules and neoplasms). Five pre-specified categories of malignancies are summarized in the table.

A numerically greater incidence of any type of malignancy was noted for lixisenatide treatment (3.5%) as compared to placebo (2.9%) (Table 18). For the individual categories, reported events were balanced for thyroid, lung, and breast cancers. Numerically more events of colorectal and prostate cancers were reported in the lixisenatide as compared to the placebo group.

No event of thyroid C-cell tumor or hyperplasia was reported in the study.

Table 18 - Number (%) of malignancies during the combined on-treatment and post-treatment periods - safety population

	Placebo (N=3032)	Lixisenatide (N=3031)
Any patients with malignancy event	89/3032 (2.9%)	105/3031 (3.5%)

	Placebo (N=3032)	Lixisenatide (N=3031)
Thyroid	8/3032 (0.3%)	11/3031 (0.4%)
Lung	12/3032 (0.4%)	8/3031 (0.3%)
Colorectal	11/3032 (0.4%)	17/3031 (0.6%)
Breast[a]	3/937 (0.3%)	3/920 (0.3%)
Prostate[b]	8/2095 (0.4%)	14/2111 (0.7%)

On-treatment period = the time from the first IMP dose intake until 3 days after treatment discontinuation.
Post-treatment period = the time starting 4 days after the last administration of IMP (after the on-treatment period).
The overall malignancy will be defined by preferred terms in the MedDRA SMQ of Malignant orunspecified tumors (#20000091). Additional classifications by subcategories (thyroid, lung, colorectal, breast, and prostate) will be done based on this SMQ.
[a] Events of breast cancer/malignancy will be summarized for females only.
[b] Events of prostate cancer/malignancy for males only.

3.3.4.4 Severe Hypoglycemia

The incidence of severe symptomatic hypoglycemia was low in both treatment groups as assessed by either the event-rate per 100 patient-years or the percentage of patients with events (Table 19). Fewer patients treated with lixisenatide than with placebo experienced severe symptomatic hypoglycemia; event rates per 100-patient years were 0.3 and 0.6 in the lixisenatide and placebo group, respectively.

Table 19 - Summary of severe symptomatic hypoglycemia during the on-treatment period - safety population

Type	Placebo (N=3032)	Lixisenatide (N=3031)
Total patient years	5942.69	5757.09
Any severe symptomatic hypoglycemia		
Number of patients with events[a]	24 (0.8%)	14 (0.5%)
Number of patients with events per 100 patient years[b]	0.4	0.2
Number of events	37	16
Number of events per 100 patient years[c]	0.6	0.3
Blood glucose <36 mg/dL		
Number of patients with events[a]	14 (0.5%)	4 (0.1%)
Number of patients with events per 100 patient years[b]	0.2	0.1
Number of events	25	5
Number of events per 100 patient years[c]	0.4	0.1

Type	Placebo (N=3032)	Lixisenatide (N=3031)
No blood glucose reported[d]		
Number of patients with events[a]	12 (0.4%)	10 (0.3%)
Number of patients with events per 100 patient years[b]	0.2	0.2
Number of events	12	11
Number of events per 100 patient years[c]	0.2	0.2

Symptomatic hypoglycemia = symptomatic hypoglycemia as defined per protocol.
On-treatment period = the time from the first IMP dose intake until 3 days after treatment discontinuation.
[a]: Percentages are calculated using the safety population as the denominator.
[b]: Number of patients with events per 100 patient years = number of patients with events * 100 / total exposure + 3 days in patient years.
[c]: Number of events per 100 patient years = number of events * 100 / total exposure + 3 days in patient years.
[d]: Events associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration, if plasma glucose measurement is not available or obtained after the event was treated.

Claims

1. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use in the reduction of progression of urinary albumin excretion in a type 2 diabetes mellitus patient.

2. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use in the reduction of urinary albumin excretion in a type 2 diabetes mellitus patient.

3. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to claim 1 or 2, wherein the patient has experienced at least one acute coronary syndrome event.

4. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any of the claims 1 to 3, wherein the patient suffers from microalbuminuria with an urinary albumin to creatinine ratio of ≥30 to <300 mg/g.

5. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any of the claims 1 to 3, wherein the patient suffers from macroalbuminuria with an urinary albumin to creatinine ratio of ≥300 mg/g.

6. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 1 to 5, wherein the patient suffers from mild renal impairment with a glomerular filtration rate of ≥60 to <90 mL/min/1.73 m^2.

7. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 1 to 5, wherein the patient suffers from a

moderate renal impairment with a glomerular filtration rate of ≥30 to <60 mL/min/1.73 m^2.

8. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 1 to 7, wherein the patient suffers from a severe renal impairment with a glomerular filtration rate of ≥15 to <30 mL/min/1.73 m^2.

9. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use in the reduction of cardiovascular morbidity or/and cardiovascular mortality in a type 2 diabetes mellitus patient who experienced at least one acute coronary syndrome event.

10. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to claim 9, wherein the 30-day or/and the 6-months mortality is reduced.

11. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to claim 9 or 10, wherein reduction of cardiovascular morbidity or/and cardiovascular mortality includes reduction of the risk of a cardiovascular event.

12. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to claim 11, wherein reduction of cardiovascular morbidity or/and cardiovascular mortality includes reduction of the risk of a cardiovascular event within one year after the at least one acute coronary syndrome event.

13. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to claim 11 or 12, wherein the cardiovascular event includes death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalization for unstable angina, non-fatal heart failure, hospitalization for heart failure or/and coronary revascularization procedure.

14. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 9 to 13, wherein the patient experienced the at least one acute coronary syndrome event within 1, within 2, within 3, within 4, within 5 or within 6 months prior to the onset of treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof.

15. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 9 to 14, wherein the at least one acute coronary syndrome event has been diagnosed within 1, within 2, within 3, within 4, within 5 or within 6 months prior to the onset of treatment with lixisenatide treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof.

16. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 3 to 15, wherein the at least one acute coronary syndrome event is a spontaneous acute coronary syndrome event.

17. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 3 to 16, wherein the at least one acute coronary syndrome event includes an ST-segment elevation myocardial infarction.

18. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 3 to 16, wherein the at least one acute coronary syndrome event includes a non-ST-segment elevation myocardial infarction.

19. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 3 to 18, wherein the at least one acute coronary syndrome event includes an unstable angina.

20. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 1 to 19, wherein the patient has a risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalization for unstable angina, non-fatal heart failure, hospitalization for heart failure or/and coronary revascularization procedure.

21. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 1 to 20, wherein the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalization for unstable angina, non-fatal heart failure, hospitalization for heart failure or/and revascularization procedure is treated.

22. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to claim 20 or 21, wherein the revascularization procedure is percutaneous coronary intervention or coronary artery bypass grafting.

23. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 1 to 22, wherein the blood plasma concentration of hs-CRP, BNP or/and NT-proBNP is reduced by the treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof.

24. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 1 to 23, wherein the type 2 diabetes mellitus patient has a cardiovascular disease history prior to the at least one acute coronary syndrome.

25. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to claim 24, wherein the cardiovascular disease history includes at least one of coronary heart disease, cerebrovascular disease, peripheral artery disease, and cardiac arrhythmia.

26. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the claims 3 to 25, wherein the type 2 diabetes mellitus patient has been diagnosed with a cardiovascular disease prior to the at least one acute coronary syndrome.

27. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to claim 26, wherein the cardiovascular disease includes at least one of coronary heart disease, cerebrovascular disease, peripheral artery disease, and cardiac arrhythmia.

28. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the preceding claims, wherein the patient receives lixisenatide or/and the pharmaceutically acceptable salt thereof in combination with

(a) metformin or/and a pharmaceutically acceptable salt thereof,

(b) insulin or/and a pharmaceutically acceptable salt thereof,

(c) a glinide or/and a pharmaceutically acceptable salt thereof,

or/and

(d) a sulfonylurea or/and a pharmaceutically acceptable salt thereof.

29. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to claim 28, wherein the insulin is a premixed, rapid-acting, or regular insulin.

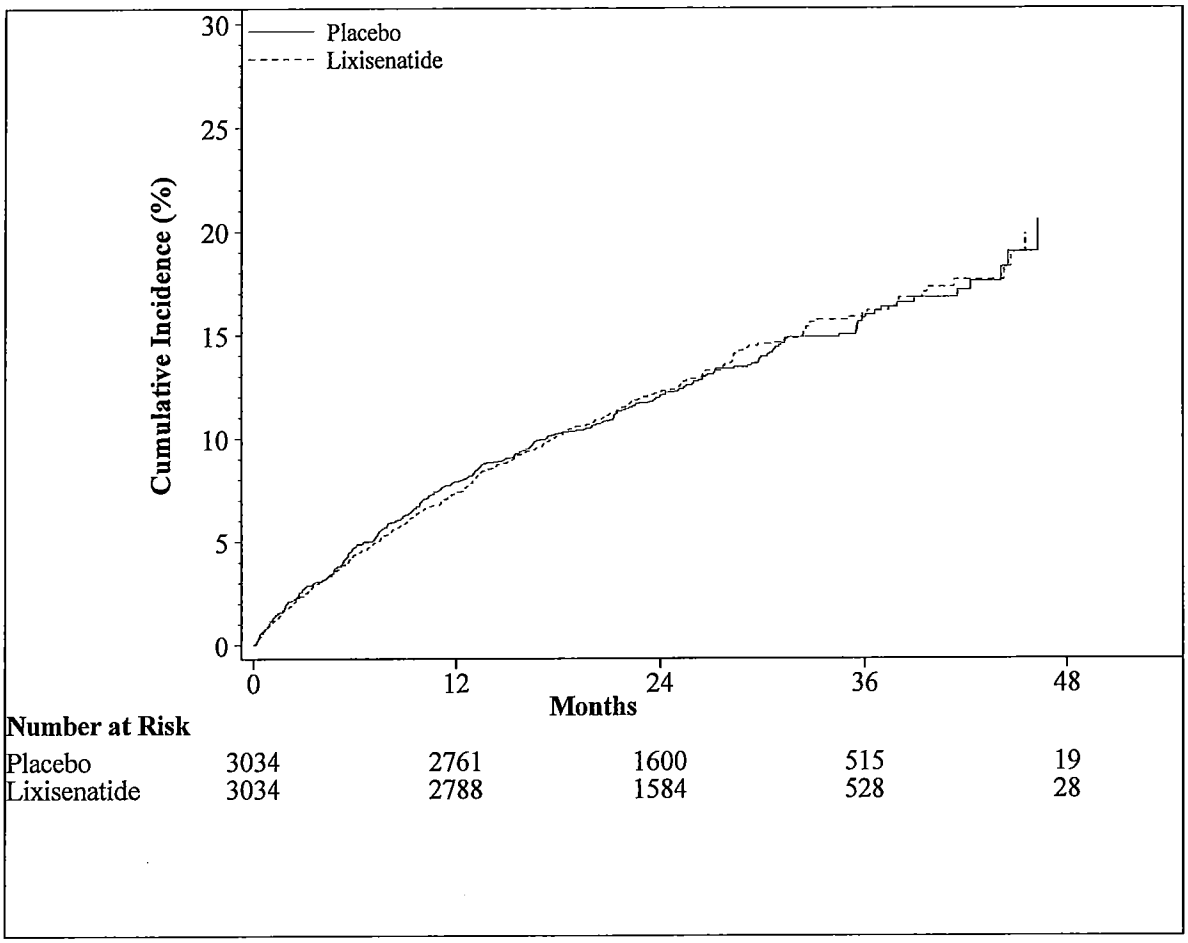
30. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the preceding claims, wherein the patient in need of the treatment has a body mass index of at least 30 kg/m^2 or at least 31 kg/m^2.

31. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the preceding claims, wherein prior to the onset of

treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof, the patient has a fasting plasma glucose concentration of at least 8 mmol/L or at least 8.5 mmol/L.

32. Lixisenatide or/and a pharmaceutically acceptable salt thereof, for use according to any one of the preceding claims, wherein prior to the onset of treatment with lixisenatide or/and the pharmaceutically acceptable salt thereof, the patient has a HbA1c value of at least about 7 %, at least about 7.5 %, at least about 8 %, at least about 8.5 %, or at least about 9 %.

Figure 1



Number at Risk					
Placebo	3034	2761	1600	515	19
Lixisenatide	3034	2788	1584	528	28

Figure 2

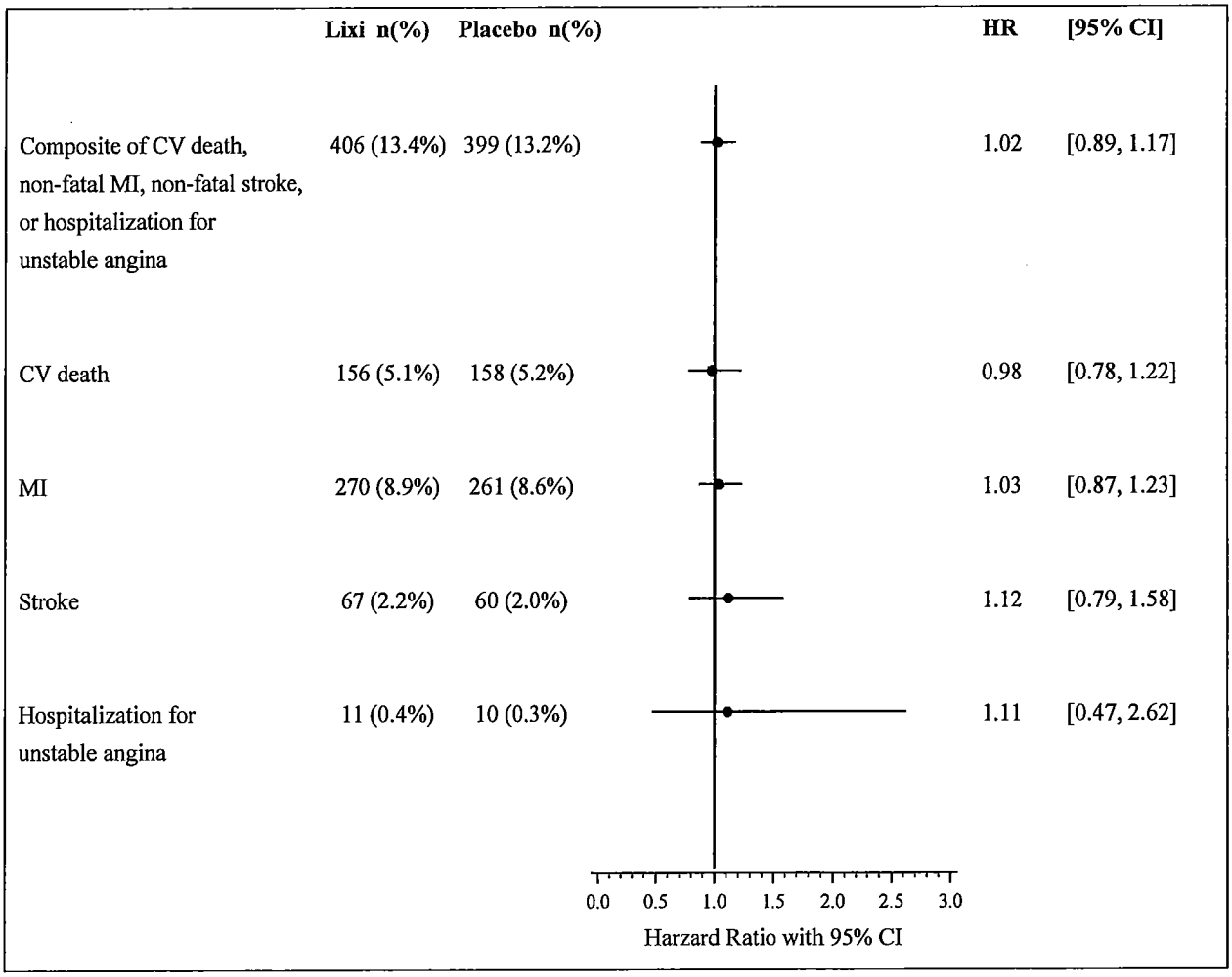

Lixi n(%)
Placebo n(%)
HR
[95% CI]
Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina
406 (13.4%)
399 (13.2%)
1.02
[0.89, 1.17]
CV death
156 (5.1%)
158 (5.2%)
0.98
[0.78, 1.22]
MI
270 (8.9%)
261 (8.6%)
1.03
[0.87, 1.23]
Stroke
67 (2.2%)
60 (2.0%)
1.12
[0.79, 1.58]
Hospitalization for unstable angina
11 (0.4%)
10 (0.3%)
1.11
[0.47, 2.62]
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Harzard Ratio with 95% CI

Figure 3

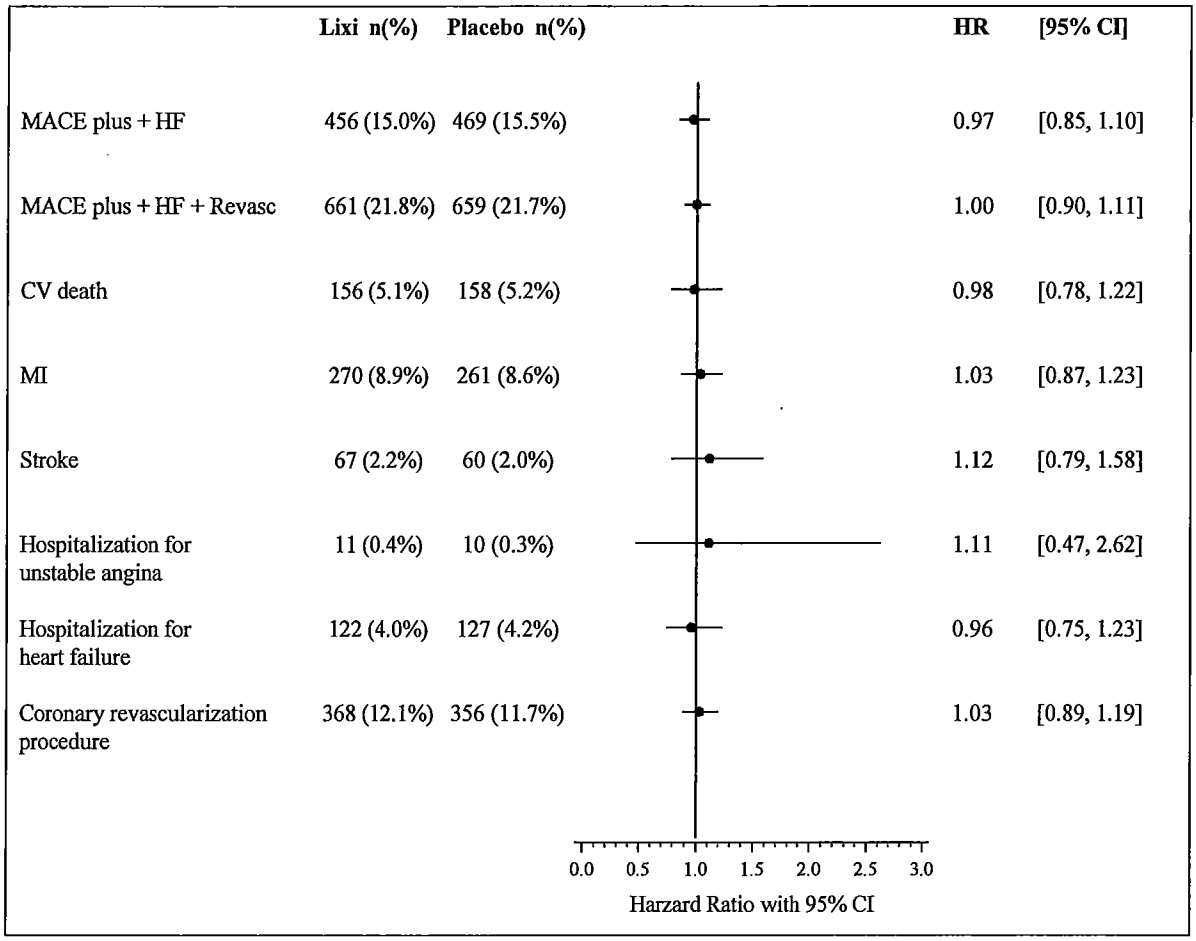
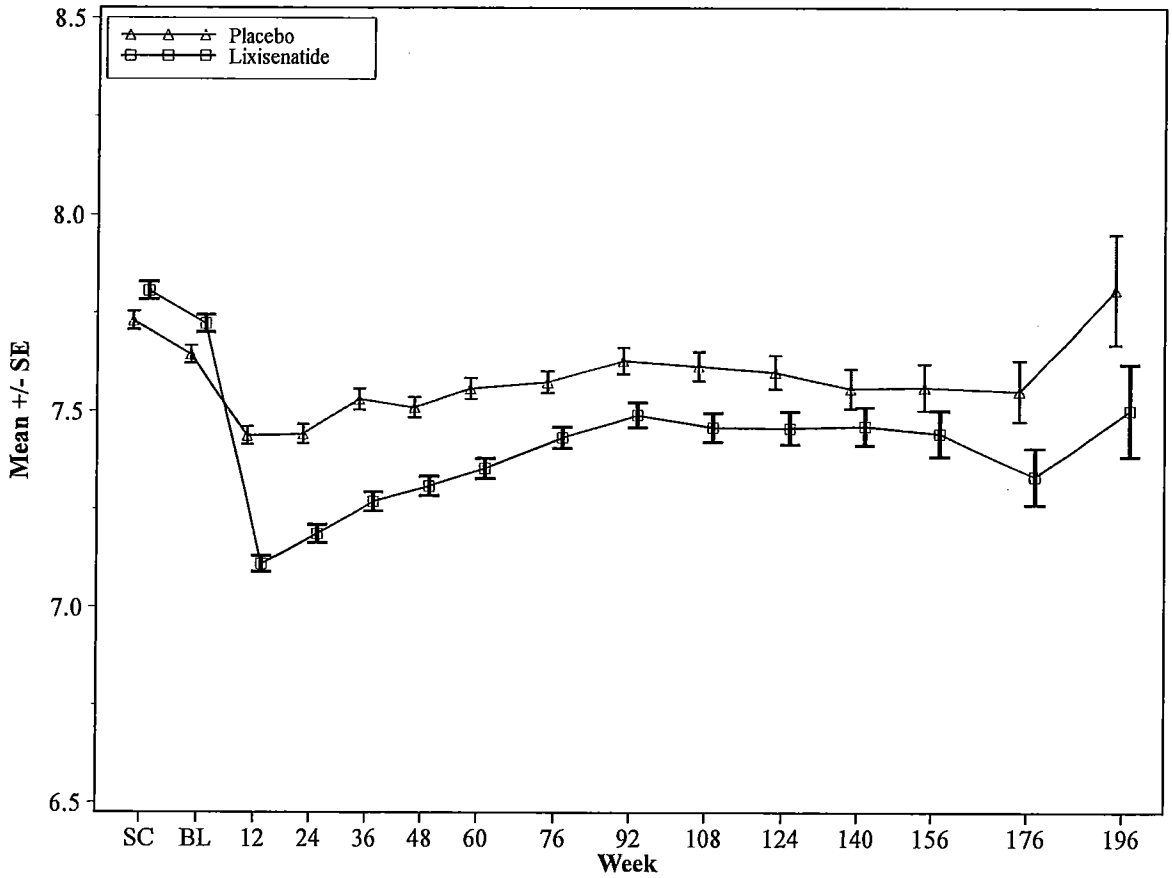

Lixi n(%)
Placebo n(%)
HR
[95% CI]
MACE plus + HF
456 (15.0%)
469 (15.5%)
0.97
[0.85, 1.10]
MACE plus + HF + Revasc
661 (21.8%)
659 (21.7%)
1.00
[0.90, 1.11]
CV death
156 (5.1%)
158 (5.2%)
0.98
[0.78, 1.22]
MI
270 (8.9%)
261 (8.6%)
1.03
[0.87, 1.23]
Stroke
67 (2.2%)
60 (2.0%)
1.12
[0.79, 1.58]
Hospitalization for unstable angina
11 (0.4%)
10 (0.3%)
1.11
[0.47, 2.62]
Hospitalization for heart failure
122 (4.0%)
127 (4.2%)
0.96
[0.75, 1.23]
Coronary revascularization procedure
368 (12.1%)
356 (11.7%)
1.03
[0.89, 1.19]
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Harzard Ratio with 95% CI

Figure 4



# subjects															
Placebo	3030	3033	2877	2791	2726	2681	2642	2523	1906	1510	1136	799	518	302	118
Lixisenatide	3031	3034	2839	2773	2713	2661	2620	2481	1872	1493	1108	780	526	295	122