(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 September 2016 (22.09.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/146514 A1

(51) International Patent Classification:
A61K 38/28 (2006.01) *A61P 3/10* (2006.01)
A61K 31/155 (2006.01)

(21) International Application Number:
PCT/EP2016/055267

(22) International Filing Date:
11 March 2016 (11.03.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
15159064.3 13 March 2015 (13.03.2015) EP

(71) Applicant: **SANOFI-AVENTIS DEUTSCHLAND GMBH** [DE/DE]; Brüningstrasse 50, 65929 Frankfurt (DE).

(72) Inventors: **ROY, Christine**; c/o SANOFI, 54 rue La Boétie, Département Brevets, 75008 Paris (FR). **SOUHAMI, Elisabeth**; c/o SANOFI, 54 rue La Boétie, Département Brevets, 75008 Paris (FR). **DEMIL, Nacima**; c/o SANOFI, 54 rue La Boétie, Département Brevets, 75008 Paris (FR). **YE, Jenny**; c/o SANOFI US, Mail Code: 55A-505A, 55 Corporate Drive, Bridgewater, New Jersey 08807 (US).

(74) Agent: **WEISS, Wolfgang**; Weickmann & Weickmann, Postfach 860 820, 81635 München (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2016/146514 A1

(54) Title: TREATMENT TYPE 2 DIABETES MELLITUS PATIENTS

(57) Abstract: A pharmaceutical combination for use in glycemic control in a type 2 diabetes mellitus patient, said combination comprising (i) lixisenatide or/and a pharmaceutically acceptable salt thereof, (ii) insulin glargine or/and a pharmaceutically acceptable salt thereof, and (iii) optionally metformin or/and a pharmaceutically acceptable salt thereof.

Treatment type 2 diabetes mellitus patients

Description

Subject of the present invention is a pharmaceutical combination for use in glycemic control, for use in the reduction of the HbA1c value, the fasting plasma glucose or/and the 2 hour postprandial plasma glucose, for use in the prevention of weight gain or/and for inducing weight loss, for use in the reduction of the risk of hypoglycemia, in a type 2 diabetes mellitus patient, said combination comprising

(i) lixisenatide or/and a pharmaceutically acceptable salt thereof,

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

(iii) optionally metformin or/and a pharmaceutically acceptable salt thereof.

In a healthy person the release of insulin by the pancreas is strictly coupled to the concentration of blood glucose. An increased level of blood glucose, as appears after meals, is rapidly counterbalanced by a respective increase in insulin secretion. In fasting condition the plasma insulin level drops to a basal value which is sufficient to ensure the continuous supply of glucose to insulin-sensitive organs and tissues and to keep the hepatic glucose production at a low level at night.

In contrast to type 1 diabetes, there is not generally a lack of insulin in type 2 diabetes mellitus but in many cases, particularly in progressive cases, the treatment with insulin is regarded as the most suitable therapy, if required in combination with orally administered anti-diabetic drugs.

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. It can thus be concluded that an improved therapy of diabetes primarily has to aim keeping blood glucose in the physiological range as close as possible.

A particular risk exists for overweight patients suffering from type 2 diabetes mellitus, e.g. patients with a body mass index (BMI) ≥ 30 kg/m^2. In these patients the risks of diabetes overlap with the risks of overweight, leading e.g. to an increase of cardiovascular diseases compared to type 2 diabetes mellitus patients being of a normal weight.

The compound desPro^{36}Exendin-4(1-39)-Lys_6-NH_2 (AVE0010, lixisenatide) is a derivative of Exendin-4. AVE0010 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. The Exendin analogue 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). In the present invention, "lixisenatide" includes pharmaceutically acceptable salts thereof. The person skilled in the art knows suitable pharmaceutically acceptable salts of lixisenatide.

Insulin glargine is an analogue of human insulin. Insulin glargine is 31^{B}-32^{B}-Di-Arg human insulin with further substitution of asparagine in position A21 by glycine. Insulin glargine is also termed Gly(A21)-Arg(B31)-Arg(B32) human insulin. The CAS number of insulin glargine is 160337-95-1. In the present invention, "insulin glargine" includes pharmaceutically acceptable salts thereof. The person skilled in the art knows suitable pharmaceutically acceptable salts of insulin glargine.

Metformin is the international nonproprietary name of 1,1-dimethylbiguanide (CAS number 657-24-9). 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", as used herein, included pharmaceutically acceptable salts thereof. The person skilled in the art knows suitable pharmaceutically acceptable salts of metformin.

In the examples of the present invention, the effect of the combination of lixisenatide, insulin glargine and optionally metformin has been tested in obese type 2 diabetes mellitus patients poorly controlled with a basal insulin alone or a basal insulin in combination with one to three oral anti-diabetic drugs selected from metformin, sulfonylureas, dipeptidyl-peptidase-4 (DPP-4) inhibitors and glinides. Even by this treatment, the diabetes patients still had a fasting plasma glucose concentration of about 9.2 to 9.5 mmol/L and a HbA1c value of about 8.5 %. The 2 hour postprandial plasma glucose was about 13.8 to 14.5 mmol/L (249 to 262 mg/dL). These values still exceed normoglycemic values.

Surprisingly, a reduction in fasting glucose plasma concentration to about 6.6 mmol/L (119 mg/dL) could be observed by treatment with a combination of lixisenatide, insulin glargine and optionally metformin. Reduction of body weight was statistically superior for lixisenatide in view of the comparative treatment with insulin glulisine once daily or three times daily.

Termination of the above-indicated pre-treatment and titration of insulin glargine (optionally in combination with metformin) for 12 weeks to achieve a glycemic target of 4.4 to 5.6 mmol/L in terms of fasting SMPG without recurrent or severe hypoglycemia before the onset of treatment with the combination of lixisenatide, insulin glargine and optionally metformin resulted in an initial reduction in fasting glucose plasma concentration from 9.16 mmol/L to 6.91 mmol/L and in HbA1c from 8.51 % to 7.87%.

Documented hypoglycemia was numerically and significantly lower with lixisenatide in view of the comparative treatment with insulin glulisine once daily or three times daily.

In conclusion, insulin glargine combined with lixisenatide and optionally metformin may become a preferred option, attaining meaningful glycemic targets with less hypoglycemia and with weight loss compared with prandial insulin (such as insulin glulisine), as basal insulin plus oral anti-diabetic compounds or basal insulin plus prandial insulin (bolus administration) in difficult to control, obese, insulin-treated type 2 diabetes mellitus patients.

A first aspect of the present invention is a pharmaceutical combination for use in glycemic control in a type 2 diabetes mellitus patient, said combination comprising

(i) lixisenatide or/and a pharmaceutically acceptable salt thereof,

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

(iii) optionally metformin or/and a pharmaceutically acceptable salt thereof.

In this aspect, the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone.

As demonstrated by the Example disclosed herein, the combination as described herein can be used for improving glycemic control. In the present invention, "improvement of glycemic control" or "glycemic control" in particular refers to improvement of the 2 hour postprandial plasma glucose concentration, improvement of fasting plasma glucose concentration, or/ and improvement of the HbA_{1c} value.

In particular, "improvement of glycemic control" or "glycemic control" includes the improvement of the 2 hour postprandial plasma glucose concentration.

In particular, "improvement of glycemic control" or "glycemic control" includes the reduction of the 2 hour postprandial plasma glucose concentration. Reduction means in particular that the 2 hour postprandial plasma glucose concentration reaches normoglycemic values or at least approaches these values.

In particular, "improvement of glycemic control" or "glycemic control" includes the improvement of the fasting plasma glucose concentration.

In particular, improvement of fasting plasma glucose concentration includes the reduction of the fasting plasma glucose concentration. Reduction means in particular that the fasting plasma glucose concentration reaches normoglycemic values or at least approaches these values.

In particular, "improvement of glycemic control" or "glycemic control" includes the improvement of the HbA_{1c} value.

In particular, improvement of the HbA_{1c} value includes the reduction of the HbA_{1c} value. Reduction of the HbA_{1c} value in particular means that the HbA_{1c} value is reduced below 6.5 % or 7 %.

Yet another aspect of the present invention is a pharmaceutical combination for use in the improvement of the HbA1c value, the fasting plasma glucose or/and the 2 hour postprandial plasma glucose in a type 2 diabetes mellitus patient, said combination comprising

(i) lixisenatide or/and a pharmaceutically acceptable salt thereof,

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

(iii) optionally metformin or/and a pharmaceutically acceptable salt thereof.

In this aspect, the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone.

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). This range refers in particular to blood glucose concentrations under fasting conditions and postprandial conditions.

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

- 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 or/and postprandial blood glucose levels or/and an oral glucose tolerance test.

According to Craig (Type 2 diabetes mellitus Diabetes 2014: 15(Suppl. 20): 4–17), fasting plasma glucose (FPG) and post challenge (postload) glucose 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)

The corresponding categories when the Oral Glucose Tolerance Test (OGTT) is used, are as follows:

- Two hour postload glucose < 7.8 mmol/L (140 mg/dL) = normal glucose tolerance.

- Two hour postload glucose 7.8 to <11.1mmol/L (140–200 mg/dL) = impaired glucose tolerance.

- Two hour postload glucose ≥ 11.1 mmol/L (200 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 values of fasting plasma glucose are blood glucose concentrations of in particular < 5.6 mmol/L.

In the present invention, normoglycemic values of postprandial plasma glucose, as defined herein, are blood glucose concentrations of in particular <7.8 mmol/L.

In the present invention, "not adequately controlled" by a particular anti-diabetic treatment means that this treatment is not sufficient to remove the symptoms of type 2 diabetes mellitus. In particular, "not adequately controlled" by this treatment means that the patient does not reach normoglycemic values in terms of, for example, 2 hour postprandial plasma glucose concentration, HbA1c value or/and fasting plasma glucose concentration.

The type 2 diabetes mellitus 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 basal insulin monotherapy.

The type 2 diabetes mellitus 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 combination of a basal insulin and metformin alone, for instance with (a) 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 (b) a dose of at the maximum 2.0 g/day metformin for at least 3 months or at the maximum 3.5 g/day metformin for at least 3 months.

The type 2 diabetes mellitus patient to be treated according to the present invention may be a subject suffering from type 2 diabetes mellitus, wherein the type 2 diabetes mellitus to be treated is not adequately controlled with compound (b) and optionally compound (c) alone.

By the treatment according to the present invention, adequate control of type 2 diabetes mellitus may be achieved in type 2 diabetes mellitus patients not adequately controlled by a particular treatment, as described herein.

“Basal insulin”, as used herein, includes insulin glargine, insulin detemir and isophane insulin (NPH insulin). The basal insulin is in particular selected from insulin glargine, insulin detemir and isophane insulin (NPH insulin).

As used herein, "to be treated according to the present invention", "treatment according to the present invention", or “therapy according to the present invention” relates to the treatment of a type 2 diabetes mellitus patient by the pharmaceutical combination comprising

(i) lixisenatide or/and a pharmaceutically acceptable salt thereof,

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

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

as described herein.

A further aspect of the present invention is a pharmaceutical combination for use in the prevention of weight gain or/and for inducing weight loss, in a type 2 diabetes mellitus patient, said combination comprising

(i) lixisenatide or/and a pharmaceutically acceptable salt thereof,

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

(iii) optionally metformin or/and a pharmaceutically acceptable salt thereof.

In this aspect, the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone.

The examples of the present invention demonstrate that the claimed combination can reduce body weight in type 2 diabetes patients, as defined herein, wherein the comparative treatment (insulin glulisine once daily or three times daily) induces a significant weight gain.

Yet another aspect of the present invention is a pharmaceutical combination for use in the reduction of the risk of hypoglycemia, in a type 2 diabetes mellitus patient, said combination comprising

(i) lixisenatide or/and a pharmaceutically acceptable salt thereof,

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

(iii) optionally metformin or/and a pharmaceutically acceptable salt thereof.

In this aspect, the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone.

The examples of the present invention demonstrate that documented hypoglycemia was numerically and significantly lower with the claimed combination in view of the comparative treatment with insulin glulisine once daily or three times daily.

Hypoglycemia is the critical limiting factor in the glycemic management of diabetes in both the short and long term. Despite steady improvements in the glycemic management of diabetes, population-based data indicate that hypoglycemia continues to be a major problem for people with both type 1 and type 2 diabetes (American diabetes association, workgroup on hypoglycemia: Defining and Reporting Hypoglycemia in Diabetes. Diabetes Care 28(5), 2005, 1245-1249).

The combination of the present invention can prevent hypoglycemia when administered to a type 2 diabetes mellitus patient, as described herein. "Prevention of hypoglycemia" includes reduction of the number of hypoglycemic events and/or the severity of hypoglycemia events. The combination as described herein is suitable for use in the prevention of hypoglycemia.

In the present invention, hypoglycemia is a condition wherein a type 2 diabetes mellitus patient experiences a plasma glucose concentration of below 70 mg/dL (or below 3.9 mmol/L), below 60 mg/dL (or below 3.3 mmol/L), below 54 mg/dL (or below 3.0 mmol/L), below 50 mg/dL, below 40 mg/dL, or below 36 mg/dL.

In the present invention, "symptomatic hypoglycemia" or "symptomatic hypoglycemic event" is a condition associated with a clinical symptom that results from the hypoglycemia, wherein the plasma glucose concentration can be below 70 mg/dL (or below 3.9 mmol/L), below 60 mg/dL (or below 3.3 mmol/L), below 54 mg/dL (or below 3.0 mmol/L), below 50 mg/dL, or below 40 mg/dL. A clinical symptom can be, for example, sweating, palpitations, hunger, restlessness, anxiety, fatigue, irritability, headache, loss of concentration, somnolence, psychiatric disorders, visual disorders, transient sensory defects, transient motor defects, confusion, convulsions, and coma. In the present invention, one or more clinical symptoms of symptomatic hypoglycemia, as indicated herein, can be selected. Symptomatic hypoglycemia may be associated with prompt recovery after oral carbohydrate administration. A symptomatic

hypoglycemia event preferably has a plasma glucose concentration of below 60 mg/dL (or below 3.3 mmol/L).

In the present invention, "severe symptomatic hypoglycemia" or "severe symptomatic hypoglycemic event" is a condition with a clinical symptom, as indicated herein, that results from hypoglycemia, wherein the plasma glucose concentration can be below 70 mg/dL (or below 3.9 mmol/L), below 54 mg/dL (or below 3.0 mmol/L) or below 36 mg/dL (or below 2.0 mmol/L). Severe symptomatic hypoglycemia can be associated with acute neurological impairment resulting from the hypoglycemic event. In a severe symptomatic hypoglycemia, the patient may require the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. A severe symptomatic hypoglycemia event preferably has a plasma glucose concentration of below 36 mg/dL (or below 2.0 mmol/L).

The definition of severe symptomatic hypoglycemia may include all episodes in which neurological impairment is severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. The acute neurological impairment may be at least one selected from somnolence, psychiatric disorders, visual disorders, transient sensory defects, transient motor defects, confusion, convulsions, and coma. "Requires assistance" means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a "requires assistance" incident.

Severe symptomatic hypoglycemia may be associated with prompt recovery after oral carbohydrate, intravenous glucose, or/and glucagon administration.

In the present invention, "documented symptomatic hypoglycemia" or "documented symptomatic hypoglycemic event" is an event during which typical symptoms of

hypoglycemia accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (≤ 3.9 mmol/L), or less than or equal to 54 mg/dL (≤ 3.0 mmol/L). Clinical symptoms that are considered to result from a hypoglycemic episode are, e.g., increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, coma.

In the present invention, "asymptomatic hypoglycemia" or "asymptomatic hypoglycemic event" is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L), or less than or equal to 54 mg/dL (3.0 mmol/L).

In the present invention, "probable symptomatic hypoglycemia" or "probable symptomatic hypoglycemic event" is an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (or less than or equal to 3.9 mmol/L), or less than or equal to 54 mg/dL (or less than or equal to 3.0 mmol/L); symptoms treated with oral carbohydrate without a test of plasma glucose.

In the present invention, "relative hypoglycemia" or "relative hypoglycemic event" is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration greater than 70 mg/dL (or greater than 3.9 mmol/L).

In the present invention, the hypoglycemia can be a symptomatic hypoglycemia, a severe symptomatic hypoglycemia, a documented symptomatic hypoglycemia, a probable symptomatic hypoglycemia, a relative symptomatic hypoglycemia, or an asymptomatic hypoglycemia. Preferred is a symptomatic hypoglycemia, more preferably a severe symptomatic hypoglycemia.

"Reducing the risk of hypoglycemia", as used herein, can include reducing the incidence of hypoglycemia. The incidence of hypoglycemia per patient year can be computed per patient as: 365.25 x (number of episodes of hypoglycemia)/(number of days exposed) and summarized by type of event and treatment group. "Reducing the risk of hypoglycemia", as used herein, can further include prevention of hypoglycemia in a patient, when the formulation described herein is administered to a type 2 diabetes mellitus patient, as described herein. "Reducing the risk of hypoglycemia", as used herein, can further include reduction of the number of hypoglycemic events, and/or the severity of hypoglycemia events.

The type 2 diabetes mellitus 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 type 2 diabetes mellitus patient may have a body mass index of at least 30 kg/m^2. The obese type 2 diabetes mellitus patient may have a body weight of at least 87 kg, at least 88 kg, at least 89 kg or at least 90 kg. The type 2 diabetes mellitus patient may be obese prior to the onset of therapy with the combination according to the present invention.

The patient to be treated may have an age of less than 50 years. The patient may also have an age of at least 50 years, or an age in the range of 50 to 64 years. The patient may also have an age of at least 65 years, or an age in the range of 65 to 74 years. The patient may also have an age of at least 75 years. It is preferred that the patient has an age of at least 65 years.

The type 2 diabetes mellitus to be treated according to the present invention may suffer from a type 2 diabetes mellitus not adequately controlled with a basal insulin monotherapy or a basal insulin and one to three oral anti-diabetics alone selected from the group consisting of metformin, a sulfonylurea, a DPP-4 inhibitor or a glinide alone. In this context, the basal insulin is in particular selected from insulin glargine, insulin detemir and isophane insulin (NPH insulin). In addition, this type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone.

The type 2 diabetes mellitus patient to be treated according to the present invention may have a fasting plasma glucose of at least 9 mmol/L or at least 9.5 mmol/L when treated with a basal insulin monotherapy or a basal insulin and one to three oral anti-diabetics alone selected from the group consisting of metformin, a sulfonylurea, a DPP-4 inhibitor or a glinide alone. In particular, the patient may have this fasting plasma glucose of at least 9 mmol/L L or at least 9.5 mmol/L prior to the onset of therapy with the combination according to the present invention. In this context, the basal insulin is in particular selected from insulin glargine, insulin detemir and isophane insulin (NPH insulin). In addition, this type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone.

Prior to the onset of therapy with the combination according to the present invention, the patient may have a fasting plasma glucose in the range of 5.6 to 6.9 mmol/L when treated with compound (b) and optionally compound (c) alone. This range can be considered to be an impaired fasting plasma glucose concentration.

Prior to the onset of therapy with the combination according to the present invention, the patient may have a fasting plasma glucose of at least 6.6 mmol/L, at least 6.7 mmol/L, at least 6.8 mmol/L or at least 6.9 mmol/L, when treated with compound (b) and optionally compound (c) alone.

The type 2 diabetes mellitus patient to be treated according to the present invention may have a HbA1c of at least 8.5% when treated with a basal insulin monotherapy or a basal insulin and one to three oral anti-diabetics alone selected from the group consisting of metformin, a sulfonylurea, a DPP-4 inhibitor or a glinide alone. In particular, the patient may have this a HbA1c of at least 8.5% prior to the onset of therapy with the combination according to the present invention. In this context, the basal insulin is in particular selected from insulin glargine, insulin detemir and isophane insulin (NPH insulin). In addition, this type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone.

Prior to the onset of therapy with the combination according to the present invention, the patient may have a HbA1c of at least 7.5 % or at least 7.8 % when treated with compound (b) and optionally compound (c) alone.

In particular, the patient to be treated according to the present invention does not receive concomitant treatment with at least one of a sulfonylurea, a DPP-4 inhibitor and a glinide.

In particular, in the patient to be treated according to the present invention, the type 2 diabetes mellitus has been diagnosed for at least 1 year or at least 2 years prior to the onset of a therapy according to the present invention.

The administration of the combination according to the present invention can comprise the steps:

(i) administration of compounds (b) and (c) for at least 4 weeks, and

(ii) continuing treatment by administration of compounds (a), (b) and (c),

wherein the amount of compound (b) to be administered in steps (i) or/and (ii) is adjusted (titrated) so that a predetermined fasting plasma glucose level or/and a predetermined self-monitored plasma glucose level is reached or at least approximated. In particular, adjustment (titration) of compound (b) is performed in steps (i).

In step (i), the compounds (b) and (c) of the pharmaceutical combination of the present invention may be administered for at least 4 weeks, at least 8 weeks, at least 12 weeks, or at least 16 weeks. Preferably, step (i) comprises administration of compounds (b) and (c) for at least about 12 weeks.

Step (i) may be performed for at the maximum about 8 weeks, at the maximum about 12 weeks, at the maximum about 16 weeks, at the maximum about 20 weeks, or at the maximum about 24 weeks. Preferred is a duration of step (i) of about 12 weeks.

Step (i) may be performed with the proviso that compound (a) is not administered. As demonstrated by the Example of the present invention, a treatment with a combination of insulin glargine, lixisenatide and optionally metformin can improve fasting plasma glucose concentration, HbA_{1c} value, body weight and the risk of hypoglycemia if the treatment starts with administration of insulin glargine and optionally metformin alone. By this treatment protocol, the dose of insulin glargine can be reduced.

In the pharmaceutical composition of the present invention, the amount of compound (b) to be administered in steps (i) or/and (ii) is adjusted so that a predetermined fasting plasma glucose level or/and a predetermined self-monitored plasma glucose level is reached or at least approximated. The amount of compound (b) to be administered in steps (i) or/and (ii) may be adjusted on the basis of daily measurements of plasma glucose concentration. In particular the amount of compound (b) to be administered in steps (i) or/and (ii) may adjusted so that

(I) a fasting plasma glucose level or/and a fasting self-monitored plasma glucose level of about 4.4 mmol/l to about 5.6 mmol/l, or/and

(II) a self-monitored plasma glucose level (SMPG) of about 7.8 mmol/l (or about 140 mg/dl) or less

is reached or at least approximated.

"Self-monitored plasma glucose (SMPG)", as used herein, can be the "4-point Self Monitored Plasma Glucose" or the "7-point Self Monitored Plasma Glucose". The 4 point and 7-point Self Monitored Plasma Glucose value are in particular average plasma glucose concentrations including fasting and postprandial conditions.

"4-point Self Monitored Plasma Glucose" in particular refers to the measurement of plasma glucose four times a day and calculation of the average plasma glucose concentration therefrom. In particular, the 4-point Self Monitored Plasma Glucose measurements are performed pre-breakfast, post-breakfast, pre-dinner, and post-dinner.

"7-point Self Monitored Plasma Glucose" in particular refers to the measurement of plasma glucose seven times a day and calculation of the average plasma glucose concentration therefrom. In particular, the 7-point Self Monitored Plasma Glucose measurements are performed pre-breakfast, post-breakfast, pre-lunch, post-lunch, pre-dinner, post-dinner and at bed-time.

The "fasting self-monitored plasma glucose (SMPG)", as used herein, is measured by the patient before breakfast, in particular before insulin glargine or/and lixisenatide injection and optional intake of metformin.

In the present invention, a type 2 diabetes mellitus patient may have a HbA1c value in the range of 7 % to 10%. In particular the type 2 diabetes mellitus patient to be treated may have a HbA_{1c} value of at least about 7 %, at least about 7.5 %, at least about 7.8 %, at least about 8 %, at least about 8.5 %, or at least about 9 %. These values exceed normoglycemic values, indicating that the type 2 diabetes mellitus is not adequately controlled if treated with an antidiabetic compound, as described herein.

The type 2 diabetes mellitus patient to be treated according to the present invention may have a 2 hours postprandial plasma glucose concentration of at least 11.1 mmol/L, at least 12 mmol/L, at least 13 mmol/L, at least 13.5 mmol/L or at least 14 mmol/L. These plasma glucose concentrations exceed normoglycemic concentrations, indicating that the type 2 diabetes mellitus is not adequately controlled if treated with an antidiabetic compound, as described herein.

"Postprandial" is a term that is well known to a person skilled in the art of diabetology. The term "postprandial" describes in particular the phase after an ingestion of a meal or/and exposure to glucose under experimental conditions. In a healthy person this phase is characterised by an increase and subsequent decrease in blood glucose concentration. The postprandial phase typically ends up to 2 h after a meal or/and exposure to glucose (2 h postprandial plasma glucose concentration).

Determination of postprandial plasma glucose is well-known (see, e.g. Crapo et al., Diabetes, 1977, 26(12):1178-1183).

The type 2 diabetes mellitus patient to be treated according to the invention may have a fasting plasma glucose concentration of at least 8 mmol/L, at least 8.5 mmol/L, at least 9 mmol/L, or at least 9.5 mmol/L. These plasma glucose concentrations exceed normoglycemic concentrations, indicating that the type 2 diabetes mellitus is not adequately controlled if treated with an antidiabetic compound, as described herein.

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 before the onset of the therapy as disclosed herein is continued in combination with (a) lixisenatide or/and a pharmaceutically acceptable salt thereof, and (b) insulin glargine 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 type 2 diabetes mellitus 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 or at the maximum of 3.5 g/day. The daily metformin dose can be divided into two 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 insulin glargine and optionally 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 insulin glargine and lixisenatide, and optionally metformin. Metformin, insulin glargine or/and lixisenatide each may be administered in a once-a-day-dosage. Metformin, insulin glargine and

lixisenatide may be administered by different administration routes. Metformin may be administered orally, and lixisenatide and insulin glargine may be administered parenterally.

In particular, "add-on", "add-on treatment" and "add-on therapy" mean that the dose of metformin administered before the onset of the treatment according to the present invention, as disclosed herein, can be continued in the treatment of the present invention.

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 type 2 diabetes mellitus 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 10 µg 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 10 µg 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 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.

In the present invention, insulin glargine 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 insulin glargine.

Surfactants can be added to pharmaceutical formulation comprising insulin glargine, for example, inter alia, non-ionic surfactants. In particular, pharmaceutically customary surfactants are preferred, such as, for example: partial and fatty acid esters and ethers of polyhydric alcohols such as of glycerol, sorbitol and the like (Span®, Tween®, in particular Tween® 20 and Tween® 80, Myrj®, Brij®), Cremophor® or poloxamers. The surfactants are present in the pharmaceutical composition in a concentration of 5 - 200 µg/ml, preferably of 5 – 120 µg/ml and particularly preferably of 20 – 75 µg/ml.

The formulation comprising insulin glargine or/and a pharmaceutically acceptable salt thereof can additionally contain preservatives (e.g. phenol, m-cresol, p-cresol, parabens), isotonic agents (e.g. mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride, glycerol), buffer substances, salts, acids and alkalis and also further excipients. These substances can in each case be present individually or alternatively as mixtures.

Glycerol, dextrose, lactose, sorbitol and mannitol can be present in the pharmaceutical formulation comprising insulin glargine or/and a pharmaceutically acceptable salt thereof in a concentration of 100 – 250 mM, NaCl in a concentration of up to 150 mM. Buffer substances, such as, for example, phosphate, acetate, citrate, arginine, glycylglycine or TRIS (i.e. 2-amino-2-hydroxymethyl-1,3-propanediol) buffer and corresponding salts, can be present in a concentration of 5 – 250 mM, preferably 10 – 100 mM. Further excipients can be, inter alia, salts or arginine.

The zinc concentration of the formulation comprising insulin glargine or/and a pharmaceutically acceptable salt thereof is in the range of the concentration which is reached by the presence of 0 - 1000 µg/mL, preferably 20 – 400 µg/mL zinc, most preferably 90 µg/mL. However, the zinc may be present in form of zinc chloride, but the salt is not limited to be zinc chloride.

In the pharmaceutical formulation comprising insulin glargine or/and a pharmaceutically acceptable salt thereof glycerol and/or mannitol can be present in a concentration of 100 – 250 mmol/L, and/or NaCl is preferably present in a concentration of up to 150 mmol/L.

In the pharmaceutical formulation comprising insulin glargine or/and a pharmaceutically acceptable salt thereof a buffer substance can be present in a concentration of 5 – 250 mmol/L.

Insulin glargine or/and a pharmaceutically acceptable salt thereof can be present in the pharmaceutical formulation in a concentration of 60-6000 nmol/ml, preferably 240-3000 nmol/ml.

The pH of the formulation comprising insulin glargine or/and a pharmaceutically acceptable salt thereof can be in the range of pH 1 – 6,8, preferably pH 3,5 - 6,8, more preferred pH 3,5 – 4,5, even more preferred pH 4,0-4,5.

Yet another aspect of the present invention is the use of a combination comprising

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

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

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

for the manufacture of a medicament for glycemic control in a type 2 diabetes mellitus patient, wherein the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone. In this aspect, the patient may be a patient as defined herein.

Yet another aspect of the present invention is the use of a combination comprising

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

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

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

for the manufacture of a medicament for the improvement of the HbA1c value, the fasting plasma glucose or/and the 2 hour postprandial plasma glucose in a type 2 diabetes mellitus patient, wherein the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone. In this aspect, the patient may be a patient as defined herein.

Yet another aspect of the present invention is the use of a combination comprising

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

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

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

for the manufacture of a medicament for the prevention of weight gain or/and for inducing weight loss in a type 2 diabetes mellitus patient, wherein the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone. In this aspect, the patient may be a patient as defined herein.

Yet another aspect of the present invention is the use of a combination comprising

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

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

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

for the manufacture of a medicament for the reduction of the risk of hypoglycemia in a type 2 diabetes mellitus patient, wherein the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone. In this aspect, the patient may be a patient as defined herein.

Yet another aspect of the present invention is method for glycemic control in a type 2 diabetes mellitus patient, said method comprising administration of a combination comprising

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

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

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

wherein the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone. In this aspect, the patient may be a patient as defined herein.

Yet another aspect of the present invention is method for the improvement of the HbA1c value, the fasting plasma glucose or/and the 2 hour postprandial plasma glucose in a type 2 diabetes mellitus patient, said method comprising administration the use of a combination comprising

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

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

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

wherein the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone. In this aspect, the patient may be a patient as defined herein.

Yet another aspect of the present invention is method for the prevention of weight gain or/and for inducing weight loss in a type 2 diabetes mellitus patient, said method comprising administration the use of a combination comprising

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

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

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

wherein the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone. In this aspect, the patient may be a patient as defined herein.

Yet another aspect of the present invention is method for the reduction of the risk of hypoglycemia in a type 2 diabetes mellitus patient, said method comprising administration the use of a combination comprising

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

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

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

wherein the type 2 diabetes mellitus to be treated preferably is not adequately controlled with compound (b) and optionally compound (c) alone. In this aspect, the patient may be a patient as defined herein.

Subject-matter of the present application is described in the following items:

1. A pharmaceutical combination for use in glycemic control, for use in the reduction of the HbA1c value, the fasting plasma glucose or/and the 2 hour postprandial plasma glucose, for use in the prevention of weight gain or/and for inducing weight loss, for use in the reduction of the risk of hypoglycemia, in a type 2 diabetes mellitus patient, said combination comprising

   (i) lixisenatide or/and a pharmaceutically acceptable salt thereof,

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

(iii) optionally metformin or/and a pharmaceutically acceptable salt thereof.

2. The pharmaceutical combination for use according to item 1, wherein the type 2 diabetes mellitus to be treated is not adequately controlled with compound (b) and optionally compound (c) alone.

3. The pharmaceutical combination for use according to item 1 or 2, wherein the patient to be treated is obese.

4. The pharmaceutical combination for use according to any of the preceding items, wherein the patient to be treated has a body mass index of at least 30 kg/m^2.

5. The pharmaceutical combination for use according to any of the preceding items, wherein the patient to be treated has an age of at least 65 years.

6. The pharmaceutical combination for use according to any of the preceding items, wherein prior to the onset of therapy with the combination according to item 1, the patient has a fasting plasma glucose of at least 9 mmol/L when treated with a basal insulin monotherapy or a basal insulin and one to three oral anti-diabetics alone selected from the group consisting of metformin, a sulfonylurea, a DPP-4 inhibitor or a glinide alone.

7. The pharmaceutical combination for use according to any of the preceding items, wherein prior to the onset of therapy with the combination according to item 1, the patient has a fasting plasma glucose concentration in the range of 5.6 to 6.9 mmol/L or a fasting plasma glucose concentration of at least 6.6 mmol/L when treated with compound (b) and optionally compound (c) alone.

8. The pharmaceutical combination for use according to any of the preceding items, wherein prior to the onset of therapy with the combination according to item 1, the patient has a HbA1c of at least 8.5% when treated with a basal insulin monotherapy or a basal insulin and one to three oral anti-diabetics alone selected from the group consisting of metformin, a sulfonylurea, a DPP-4

inhibitor or a glinide alone.

9. The pharmaceutical combination for use according to any of the preceding items, wherein prior to the onset of therapy with the combination according to item 1, the patient has a HbA1c of at least 7.5 % when treated with compound (b) and optionally compound (c) alone.

10. The pharmaceutical combination for use according to any of the items 6 to 9, wherein the basal insulin is selected from insulin glargine, insulin detemir and isophane insulin (NPH insulin).

11. The pharmaceutical combination for use of any of the preceding items, wherein the patient does not receive concomitant treatment with at least one of a sulfonylurea, a DPP-4 inhibitor and a glinide.

12. The pharmaceutical combination for use of any of the preceding items, wherein in the patient to be treated, type 2 diabetes mellitus has been diagnosed for at least 1 year or at least 2 years prior to the onset of a therapy with compounds (a), (b) and optionally (c).

13. The pharmaceutical combination for use of any of the preceding items, wherein the administration of the combination comprises the steps:

(i) administration of compounds (b) and (c) for at least 4 weeks, and

(ii) continuing treatment by administration of compounds (a), (b) and (c),

wherein the amount of compound (b) to be administered in step (i) is adjusted so that a predetermined fasting plasma glucose level or/and a predetermined self-monitored plasma glucose level is reached or at least approximated.

14. The pharmaceutical combination for use according to item 13, wherein the amount of compound (b) to be administered in step (i) is adjusted so that

(I) a fasting plasma glucose level or/and a fasting self-monitored plasma glucose level of about 4.4 mmol/l to about 5.6 mmol/l, or/and

(II) a self-monitored plasma glucose level (SMPG) of about 7.8 mmol/l (or about 140 mg/dl) or less

is reached or at least approximated.

15. The pharmaceutical combination for use according to item 14, wherein the self-monitored plasma glucose level in (II) is a 4-point self-monitored plasma glucose level or a 7-point self-monitored plasma glucose level.

16. The pharmaceutical combination for use of any of the preceding items, wherein lixisenatide or/and the pharmaceutically acceptable salt thereof is prepared for parenteral administration.

17. The pharmaceutical combination for use according to any of the preceding items, wherein lixisenatide or/and the pharmaceutically acceptable salt thereof is prepared for administration in a daily dose selected from the range of 10 µg to 20 µg.

18. The pharmaceutical combination for use according to any of the preceding items, wherein insulin glargine or/and or/and the pharmaceutically acceptable salt thereof is prepared for parenteral administration.

19. The pharmaceutical combination for use of any of the preceding items, wherein the metformin or/and the pharmaceutically acceptable salt thereof is prepared for oral administration.

20. A method for improving glycemic control, for the reduction of the HbA1c value or/and the fasting plasma glucose, for use in the prevention of weight gain or/and for inducing weight loss, for use in the reduction of the risk of hypoglycemia, said method comprising administering the combination of any one of the items 1 to 18 to a subject in need thereof.

21. The method of item 20, wherein the type 2 diabetes mellitus to be treated is not adequately controlled with compound (b) and optionally compound (c) alone.

22. The method of item 20 or 21, wherein the subject is the subject defined in any one of the items 2 to 15.

The invention is further illustrated by the following examples and figures.

Figure legends

Figure 1 - Plot of mean change in HbA1c(%) from baseline by visit – mITT population

Figure 2 - Plot of mean change in body weight (kg) from baseline by visit – mITT population

Figure 3 - Plot of mean insulin glargine daily dose (U) by visit – mITT population

Figure 4 - Plot of mean daily insulin glulisine dose (U) by visit – mITT population

Figure 5 - Plot of mean total insulin dose (U) by visit – mITT population

Figure 6 - Graphical study design. [1] Insulin glargine should be injected subcutaneously once daily at dinner or breakfast time (according to patient's/investigators' preference). Injection time (dinner or breakfast) should be fixed at V2 and remain the same throughout the study. [2] Injection of lixisenatide should be performed 30-60 minutes prior to dinner or breakfast (the one associated with the highest self-monitored 2h-PPG median value across 3 different days). Meal used for lixisenatide dosing should remain the same throughout the 26-week treatment period. [3] Injection of insulin glulisine should be done 0 to 15 minutes before dinner or breakfast (the one associated with the highest self-monitored 2h-PPG median value across 3 different days). Meal used for insulin glulisine dosing should remain the same throughout the 26-week treatment period. [4] Injection of insulin glulisine prior to breakfast, lunch and dinner.

Example 1

A randomized, open-label, active-controlled, 3-arm parallel-group, 26-week study comparing the efficacy and safety of lixisenatide to that of insulin glulisine once daily and insulin glulisine three times daily in patients with Type 2 diabetes insufficiently controlled with insulin glargine with or without metformin

1 ABBREVIATIONS

AE:	Adverse event
ANCOVA:	Analysis of covariance
BMI:	Body mass index
CI:	Confidence interval
CMH:	Cochran-Mantel-Haenszel
ECG:	Electrocardiogram
FPG:	Fasting plasma glucose
GLP-1:	Glucagon-like peptide-1
IMP:	Investigational medicinal product
LOCF:	Last observation carried forward
LS:	Least square
mITT:	Modified Intent-To-Treat
PG:	Plasma glucose
PT:	Preferred term
QD:	Quaque die (Once a day)
SAE:	Serious adverse event
SMPG:	Self-measured plasma glucose
SOC:	System organ class
TEAE:	Treatment-emergent adverse event
TID:	Ter in die (Three times a day)

2 SYNOPSIS

Title of the study: A randomized, open-label, active-controlled, 3-arm parallel-group, 26-week study comparing the efficacy and safety of lixisenatide to that of insulin glulisine once daily and insulin glulisine three times daily in patients with Type 2 diabetes insufficiently controlled with insulin glargine with or without metformin.

Study center(s): Multicenter (199 centers in 18 countries)

Publications (reference): NA

Graphical study design: Figure 6

Phase of development: Phase 3

Objectives:

Primary Objective

To demonstrate in type 2 diabetic patients not adequately controlled on insulin glargine ± metformin:

- Versus insulin glulisine once daily (QD) non inferiority of lixisenatide in terms of HbA1c reduction at week 26.
- Versus insulin glulisine three times daily (TID) non inferiority of lixisenatide in terms of HbA1c reduction *or* superiority of lixisenatide on body weight change at week 26.

Methodology: open-label, 1:1:1 randomized, active-controlled 3-arm (insulin glargine ± metformin + lixisenatide or insulin glulisine QD or insulin glulisine TID) parallel-group study stratified by V7 (week -1) strata of HbA1c (<8%, ≥8 %) and metformin use (yes, no).

Number of patients:	Planned: 855
	Randomized: 894
	Treated: 893
Evaluated:	Efficacy: 890
	Safety: 893

- **Diagnosis and criteria for inclusion: Inclusion criteria:** Adult patients with type 2 diabetes mellitus diagnosed for at least 1 year, treated with basal insulin for at least 6 months prior to screening visit, and with a stable basal insulin regimen for at least 3 months prior to screening. Patients could be treated with basal insulin alone or in combination with 1 to 3 oral anti-diabetic drugs (OADs) that could be: metformin (≥1.5g/day or maximal tolerated dose), a sulfonylurea (SU), a dipeptidyl-peptidase-4 (DPP-4) inhibitor, a glinide. **Key exclusion criteria at screening**: HbA1c <7.5% or >10.0% for patients treated with basal insulin alone or in combination with metformin only; HbA1c <7.0% and >10.0% for patients treated with basal insulin and a combination of OADs which included a SU and/or a DPP-4 inhibitor and/or a glinide. **Key exclusion criteria for randomization**: HbA1c<7.0% or >9.0%; Mean fasting SMPG>140mg/dL (7.8mmol/L).

Study treatments

Investigational medicinal products (IMPs): Lixisenatide and insulin glulisine

Formulation: Lixisenatide was supplied as a sterile aqueous solution for subcutaneous (s.c.) injection in a 3-mL glass cartridge containing 300 µg of the active ingredient (ie, 100 µg/mL), Glycerol, Sodium acetate trihydrate, Methionine, Metacresol, HCL/NaOH, water for injection.

Insulin glulisine was supplied as Apidra® SoloSTAR®

Route of administration: Lixisenatide was injected subcutaneously using Delta 14 self-injector device

Insulin glulisine was injected subcutaneously using the disposable SoloSTAR® self-injector device.

Dose regimen:

Lixisenatide

Lixisenatide was started with QD injections of 10 µg for 2 weeks then continued at the maintenance dose of 20 µg QD up to the end of the treatment period. If the target maintenance dose of 20 µg was not tolerated, lixisenatide dose could be reduced to 10 µg. Lixisenatide was administered before breakfast or before dinner and remained the same regimen throughout the 26-week treatment period.

Insulin glulisine once daily (Basal Plus regimen)

The starting dose was 3 to 5 U. The dose of insulin glulisine was then titrated to obtain a bedtime (if injected at dinner) or pre-lunch (if injected at breakfast) SMPG value >100 mg/dL (5.6 mmol/L) and ≤140 mg/dL (7.8 mmol/L) while avoiding hypoglycemia. Insulin glulisine QD was administered before breakfast or before dinner and remained the same regimen throughout the 26-week treatment period.

Insulin glulisine three times daily (Basal Bolus regimen)

The starting dose for each meal was 3 to 5 U. The dose of insulin glulisine was then titrated to obtain before the next meal (pre-lunch or pre-dinner) or at bedtime (for the injection performed before dinner) a SMPG value >100 mg/dL (5.6 mmol/L) and ≤140 mg/dL (7.8 mmol/L) while avoiding hypoglycemia.

Stopping Rule:

In case HbA1c was above 8.5% at week 12 or later on, and appropriate corrective action (including appropriate titration of insulin glargine and/or insulin glulisine) failed and if the repeated HbA1c 4 weeks later remained above 8.5%, the assessment planned at visit 19 (final assessment on-treatment visit) and post-treatment follow-up visit was to be performed and the patient was to be discontinued from IMP and from the study.

Noninvestigational medicinal product(s) (background therapy):

Insulin glargine (Lantus®)

- Insulin glargine was supplied as Lantus® SoloSTAR® and was started at V2 (for those patients not already receiving insulin glargine) and injected subcutaneously using the disposable SoloSTAR® self-injector device.
- **Metformin**

  If patients were on metformin, it was to be at a stable dose of at least 1.5 g/day or maximal tolerated dose for at least 3 months prior to screening. This was continued at stable dose throughout the study.

  Sulfonylureas, DPP-4 inhibitors and glinides were stopped at the start of run-in (Visit 2).

  Insulin glargine was injected subcutaneously once daily at breakfast or dinner time according to patients'/ Investigators' preference. The injection time was to remain the same throughout the study.

  Insulin glargine dose was titrated to achieve glycemic targets [fasting SMPG in the range of 80 to 100 mg/dL (4.4 to 5.6 mmol/L) without recurrent or severe hypoglycemia, except during the 4 weeks following randomization when a stable dose should be maintained. Doses could be reduced or modified at any time for recurrent or severe hypoglycemia.

  If HbA1c at visit V7 (week -1) was ≥7% but ≤8.0%, the insulin glargine dose was to be reduced in order to avoid hypoglycemia when starting the IMP (lixisenatide or insulin glulisine).

Duration of treatment: 26 weeks

Duration of observation: Maximum duration was approximately 40 weeks.

Criteria for evaluation:

Primary efficacy endpoints:

The primary efficacy analysis was based on two co-primary endpoints:

- Change in HbA1c from baseline to week 26 (lixisenatide versus each insulin glulisine regimen).
- Change in body weight from baseline to week 26 (lixisenatide versus insulin glulisine TID).

Secondary efficacy endpoints included:

- Change in body weight from baseline to week 26 (lixisenatide versus insulin glulisine QD).
- Change in Fasting Plasma Glucose (FPG) from baseline to week 26
- Change in Insulin glargine dose from baseline to week 26.
- Insulin glulisine dose and total insulin dose at week 26.

Safety endpoints:

- Adverse events, serious adverse events, vital signs.
- Documented (PG <60 mg/dl) symptomatic hypoglycemia, severe hypoglycemia (percentage of subjects with at least one episode, number of events per patient-year).

Statistical methods:

Primary Analysis:

The primary analysis was based on a co-primary endpoint:

1 Non-inferiority of lixisenatide versus insulin glulisine QD on HbA1c change from baseline to Week 26,

2a Non-inferiority of lixisenatide versus insulin glulisine TID on HbA1c change from baseline to Week 26,

2b Superiority of lixisenatide versus Insulin glulisine TID on body weight change from baseline to Week 26.

Study was declared positive if both 1 and 2 (at least one of 2a or 2b) were met.

Overall, the statistical assessment was performed at α=0.025 (1-sided) for the co-primary endpoint. Both 1 and 2 (either 2a or 2b) were assessed at α=0.025 (1-sided), and both 1 and 2a were assessed at a non-inferiority margin for HbA1c of 0.4%.

For the co-primary endpoint 1, the non-inferiority was assessed using the upper bound of the 2-sided 95% CI. If the upper bound of the 95% CI was less than 0.4%, the non-inferiority of lixisenatide versus insulin glulisine QD was achieved.

For the co-primary endpoint 2 (2a and 2b), Hochberg procedure was used for these 2 comparisons at α=0.025 (1-sided) in order to control the type 1 error: If non-inferiority of lixisenatide versus insulin glulisine TID on HbA1c and superiority of lixisenatide versus insulin glulisine TID on body weight were both met at α=0.025 (1-sided), then endpoint 2 was met at α=0.025 (1-sided). If only one of them was met, then the one met should be tested at α=0.0125 (1-sided). The non-inferiority on HbA1c was assessed using the upper bound of the 2-sided 95% CI (or 97.5% CI). If the upper bound of the 95% CI (or 97.5% CI) on HbA1c was less than 0.4%, the non-inferiority of lixisenatide versus insulin glulisine TID on HbA1c was met at 1-sided α=0.025 (or α=0.0125). The superiority on body weight was assessed by comparing the p-value with the 1-sided α=0.025 (or α=0.0125).

The primary endpoints were analyzed using an analysis of covariance (ANCOVA) model with treatment (lixisenatide, insulin glulisine QD and insulin glulisine TID), V7 (week -1) strata of HbA1c (<8%, ≥8 %), randomization strata of metformin use (yes, no) and country as fixed effects and using the corresponding baseline value as a covariate. Difference between lixisenatide and insulin glulisine QD and the associated two sided 95% confidence interval were estimated. Similarly, difference between lixisenatide and insulin glulisine TID and the associated 2-sided 95% confidence interval (or 97.5% confidence interval if either 2a or 2b was not met) were estimated for HbA1c and body weight.

Analysis of secondary endpoints:

All continuous secondary efficacy endpoints (except for insulin glulisine and total daily insulin doses) were analyzed using the same ANCOVA model as described for the primary endpoint. Differences between treatment groups and confidence intervals were estimated. Insulin glulisine and total daily insulin doses were summarized by treatment group.

All categorical efficacy parameters were analyzed using the Cochran-Mantel-Haenszel (CMH) method stratified by V7 (week -1) strata of HbA1c (<8%, ≥8 %), and randomization strata of metformin use (Y, N). Missing efficacy endpoint values including that of primary endpoints were imputed using LOCF method.

Safety analyses:

Safety analyses for the 26-week open-label treatment period were descriptive, based on the safety population.

Summary:

Population characteristics: A total of 894 patients were randomized to one of the three treatment groups (298 patients each): lixisenatide, insulin glulisine QD and insulin glulisine TID. One patient randomized to insulin glulisine TID group was not exposed to the IMP, and 890 patients were included in the mITT population. Four patients randomized to the insulin glulisine TID arm were included in the insulin glulisine QD arm of the safety population since they injected insulin glulisine once a day more than 50% of the time. One patient randomized to the insulin glulisine QD arm was included in the insulin glulisine TID arm of safety population since he injected insulin glulisine three times a day more than 50% of the time. (Table 1). Demographics and baseline characteristics were generally similar across the treatment groups. The median age was 60 years. The study population was primarily Caucasian (92.6%), and 54.7% of the population were female patients (Table 2).

Efficacy results:

Primary analysis

Change in HbA1c from baseline to Week 26: lixisenatide versus insulin glulisine QD

Mean changes in HbA1c were -0.63% for the lixisenatide group and -0.58% for the insulin glulisine QD group (Difference = -0.05%, 95% CI: -0.170% to 0.064%). The non-inferiority of lixisenatide compared to insulin glulisine QD was demonstrated, as the upper bound of the two-sided 95% CI of the treatment difference was less than the predefined non-inferiority margin of 0.4% (Table 6).

Change in HbA1c from baseline to Week 26: lixisenatide versus insulin glulisine TID

Mean changes in HbA1c were -0.63% for the lixisenatide group and -0.84% for the insulin glulisine TID group (Difference = 0.21%, 95% CI: 0.095% to 0.328%). The non-inferiority of lixisenatide compared to the insulin glulisine TID was demonstrated, as the upper bound of the two-sided 95% CI of the treatment difference was less than the predefined non-inferiority margin of 0.4% (Table 6).

Change in body weight from baseline to Week 26: lixisenatide versus insulin glulisine TID

Mean changes body weight were -0.63 kg for the lixisenatide group and 1.37 kg for the insulin glulisine TID group (Difference = -1.99 kg, p-value<0.0001). The superiority of lixisenatide compared to insulin glulisine TID in body weight was demonstrated at α=0.025 one-sided (Table 7).

Secondary efficacy endpoints:

Mean changes from baseline to Week 26 in body weight were -0.63 kg for the lixisenatide group and 1.03 kg for the insulin glulisine QD group (Difference = -1.66 kg, 95% CI: -2.257 to -1.062 kg) (Table 7).

Mean changes in FPG were -0.23 mmol/L in the lixisenatide group, -0.21 mmol/L in the glulisine QD group and -0.06 mmol/L in the glulisine TID group (Differences: lixisenatide versus glulisine QD = -0.01 mmol/L, 95% CI: [-0.319 to 0.298]; lixisenatide versus glulisine TID = -0.17 mmol/L, 95% CI: [-0.475 to 0.143]) (Table 8).

Changes in insulin glargine dose were 0.70 U in the lixisenatide group, -0.06 U in the glulisine QD group and -3.13 U in the glulisine TID group (Table 9).

Mean daily insulin glulisine dose at Week 26 was 9.97 U in the insulin glulisine QD group and 20.24 U in the insulin glulisine TID group (Figure 4). Mean total daily insulin dose at Week 26 was 73.61 U in the insulin glulisine QD group and 81.05 U in the insulin glulisine TID group (Figure 5).

Safety results:

The percentages of patients with any TEAEs were: lixisenatide 74.2%, insulin glulisine QD 73.8% and insulin glulisine TID 80.3%. The two most frequent TEAEs were "hypoglycemia" which were reported in 107 patients (35.9%) in the lixisenatide group, 140 patients (46.5%) in the insulin glulisine QD group, and 154 patients (52.4%) in the insulin glulisine TID group, and "blood glucose decreased" (events not accompanied by typical symptoms of hypoglycemia) which were reported in 60 patients (20.1%) in the lixisenatide group, 67 patients (22.3%) in the insulin glulisine QD group, and 82 patients (27.9%) in the insulin glulisine TID group. Nausea was reported in 75 patients (25.2%) in lixisenatide group, 5 patients (1.7%) in the insulin glulisine QD group and 3 patients (1.0%) in the insulin glulisine TID group (Table 11).

Serious TEAEs were reported by a similar number of patients in all treatment groups (lixisenatide: 11/298 [3.7%], glulisine QD: 11/301 [3.7%] and glulisine TID: 14/294 [4.8%]) (Table 12). Three patients died during the study due to a TEAE, one from the lixisenatide group and two from the insulin glulisine TID group:

- lixisenatide group: metastatic pancreatic cancer. A 67 year-old male patient was diagnosed with metastatic pancreatic cancer 35 days after the first administration of the IMP. The patient permanently discontinued lixisenatide. Further evaluation showed a tumor classified T4N+M1 of the corpus part of the pancreatic gland with infiltration into the vein of the left kidney and into the left adrenal gland with multiple metastases in the liver, intra-abdominal lymphadenopathy, peritoneal dissemination, and ascites. The patient underwent palliative care and died on study day 52. The event was adjudicated by PSAC as probable malignant pancreatic neoplasm unrelated to IMP.
- glulisine TID: skin ulcer haemorrhage. A 75 year-old male patient died of exsanguination due to severe bleeding from a skin ulcer 155 days after the first intake of insulin glulisine.
- glulisine TID: cardiac failure chronic. A 59 year-old male was found dead on study day 145. Autopsy was performed and the reason of death was reported as exacerbation of chronic heart insufficiency.

None of the deaths were considered related to IMP.

One additional patient died during the run-in period due to worsening of chronic obstructive pulmonary disease (pre-treatment AE).

More patients in the lixisenatide group experienced at least one TEAE leading to permanent treatment discontinuation compared to the insulin glulisine groups (lixisenatide: 15/298 [5.0%], glulisine QD: 2/301 [0.7%] and glulisine TID: 3/294 [1.0%]), mainly due to gastrointestinal disorders (3.7% in the lixisenatide group versus none in glulisine QD or TID group) including nausea and vomiting in four patients (1.3%) each. (Table 13).

Protocol defined TEAEs of symptomatic hypoglycemia (either accompanied by plasma glucose < 60 mg/dL [3.3 mmol/L] or associated with prompt recovery after countermeasures if no plasma glucose was available) were experienced by more patients in the insulin glulisine groups compared to the lixisenatide group (lixisenatide: 98/298 [32.9%]; glulisine QD: 117/301 [38.9%]; glulisine TID: 132/294 [44.9%]). Similarly, more TEAEs of symptomatic hypoglycemia per 100 patient years occurred in the insulin glulisine QD group and insulin glulisine TID group (266.4 and 410.4, respectively) than in the lixisenatide group (229.6) (Table 14). Two patients (both from the insulin glulisine QD group) experienced TEAEs defined as severe symptomatic hypoglycemia per protocol. Thirteen patients in the insulin glulisine QD group and 20 patients in the insulin glulisine TID group reported symptomatic or asymptomatic accidental overdose with IMP versus none in lixisenatide group.

Three lixisenatide-treated patients (1.0%) and 1 (0.3%) patient in the glulisine TID group had a TEAE adjudicated as allergic reaction by ARAC, however none were adjudicated as possibly related to IMP (Table 15).

One patient (0.3%) in the lixisenatide group had one TEAE adjudicated by PSAC as acute pancreatitis of mild intensity (Table 16):

- A 57-year old female patient had a TEAE of suspected pancreatitis of moderate intensity 89 days after first lixisenatide administration. Four days before the onset of the event routine laboratory results revealed lipase 3.37 x ULN. The investigator reported that the event consisted of epigastric pain of mild intensity, nausea and diarrhea. Abdominal US performed on Day 90 revealed steatohepatitis, which was reported as a new TEAE; no signs consistent with pancreatitis were observed. Lipase retested on Day 90 was within the normal range. The IMP was temporarily discontinued from Day 91 and was resumed on Day 102. The subject was considered recovered from the event on Day 92 without sequelae and completed the study treatment with lixisenatide as per protocol. Further scheduled central laboratory test showed pancreatic enzymes within normal ranges. The investigator considered the event as related to lixisenatide.

Two patients in the lixisenatide group and one patient in the insulin glulisine TID group had a TEAE of increased calcitonin (≥20 pg/mL) that were reported on the specific AE form (Table 17).

Preliminary Conclusions:

This study in 894 patients with T2DM not adequately controlled on insulin glargine ± metformin met its primary objective, demonstrating non-inferiority of lixisenatide versus insulin glulisine QD as well as insulin glulisine TID in reducing HbA1c levels, and demonstrating superiority of lixisenatide versus insulin glulisine TID in body weight change.

The study medication was well tolerated by patients in all three treatment groups, more patients in the insulin glulisine groups reported protocol defined events of symptomatic hypoglycemia. More patients in the lixisenatide group discontinued the study prematurely mostly due to gastrointestinal TEAEs. In the lixisenatide group, 1 event was adjudicated by PSAC as probable malignant pancreatic neoplasm unrelated to IMP, and 1 event was adjudicated by PSAC as acute pancreatitis of mild intensity.

3 RESULTS

3.1 STUDY PATIENTS

3.1.1 Patient accountability

Table 1 - Analysis populations

	Lixisenatide	Insulin Glulisine QD	Insulin Glulisine TID	All
Randomized population	298 (100%)	298 (100%)	298 (100%)	894 (100%)
Efficacy population				
Modified Intent-to-Treat (mITT)	297 (99.7%)	298 (100%)	295 (99.0%)	890 (99.6%)
Safety population	298	301	294	893

Note: The safety population patients are tabulated according to treatment actually received (as treated).
For the other populations, patients are tabulated according to their randomized treatment.

3.1.2 Study disposition

Table 2 - Patient disposition – Randomized population

	Lixisenatide (N=298)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=298)
Randomized and not treated	0	0	1 (0.3%)
Randomized and treated	298 (100%)	298 (100%)	297 (99.7%)
Completed study treatment period	268 (89.9%)	281 (94.3%)	285 (95.6%)
Did not complete study treatment period	30 (10.1%)	17 (5.7%)	12 (4.0%)
Subject's decision for treatment discontinuation	18 (6.0%)	11 (3.7%)	8 (2.7%)
Reason for treatment discontinuation			
Adverse event	14 (4.7%)	2 (0.7%)	5 (1.7%)
Lack of efficacy[a]	6 (2.0%)	4 (1.3%)	0
Poor compliance to protocol	0	3 (1.0%)	2 (0.7%)
Lost to follow-up	0	0	0
Other reasons	9 (3.0%)	8 (2.7%)	5 (1.7%)

[a]: No rescue therapy was planned for the study, instead discontinuation was recommended if HbA1c value is above 8.5% at Week 12 or later on, and if appropriate corrective action fails and the repeated HbA1c 4 weeks later remains above 8.5%.
Note: Percentages are calculated using the number of patients randomized as denominator.

3.1.3 Demographics and baseline characteristics

Table 3 - Demographics and patient characteristics at screening or baseline – Randomized population

	Lixisenatide (N=298)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=298)	All (N=894)
Age (years)				
Number	298	298	298	894
Mean (SD)	59.8 (8.6)	60.2 (8.6)	59.4 (9.5)	59.8 (8.9)
Median	60.0	60.0	60.0	60.0
Min : Max	35 : 79	35 : 78	32 : 87	32 : 87
Age group (years) [n (%)]				
Number	298	298	298	894
< 50	39 (13.1%)	33 (11.1%)	48 (16.1%)	120 (13.4%)
≥ 50 to < 65	170 (57.0%)	172 (57.7%)	154 (51.7%)	496 (55.5%)
≥ 65 to < 75	76 (25.5%)	76 (25.5%)	85 (28.5%)	237 (26.5%)
≥ 75	13 (4.4%)	17 (5.7%)	11 (3.7%)	41 (4.6%)
Gender [n (%)]				
Number	298	298	298	894
Male	138 (46.3%)	135 (45.3%)	132 (44.3%)	405 (45.3%)
Female	160 (53.7%)	163 (54.7%)	166 (55.7%)	489 (54.7%)
Race [n (%)]				
Number	298	298	298	894
Caucasian/White	276 (92.6%)	280 (94.0%)	272 (91.3%)	828 (92.6%)
Black	13 (4.4%)	11 (3.7%)	12 (4.0%)	36 (4.0%)
Asian/Oriental	9 (3.0%)	7 (2.3%)	13 (4.4%)	29 (3.2%)
Other	0	0	1 (0.3%)	1 (0.1%)
V1 (Week -14) HbA1c (%)				
Number	297	298	298	893
Mean (SD)	8.51 (0.72)	8.49 (0.72)	8.51 (0.78)	8.50 (0.74)
Median	8.50	8.40	8.50	8.50
Min : Max	7.1 : 10.0	7.0 : 10.0	7.0 : 10.0	7.0 : 10.0
V7 (Week -1) HbA1c(%)				
Number	298	297	298	893
Mean (SD)	7.87 (0.53)	7.82 (0.52)	7.89 (0.54)	7.86 (0.53)
Median	7.80	7.80	7.90	7.80
Min : Max	7.0 : 9.0	7.0 : 8.9	7.0 : 9.0	7.0 : 9.0
Randomization strata of HbA1c category (%) [n (%)]				
Number	298	298	298	894
<8%	172 (57.7%)	171 (57.4%)	172 (57.7%)	515 (57.6%)
≥ 8%	126 (42.3%)	127 (42.6%)	126 (42.3%)	379 (42.4%)
Randomization strata of metformin use (%) [n (%)]				
Number	298	298	298	894
Yes	257 (86.2%)	258 (86.6%)	257 (86.2%)	772 (86.4%)
No	41 (13.8%)	40 (13.4%)	41 (13.8%)	122 (13.6%)

	Lixisenatide (N=298)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=298)	All (N=894)
V2 (Week -12) FPG (mmol/L)				
Number	296	293	297	886
Mean (SD)	9.16 (2.94)	9.28 (2.88)	9.51 (2.96)	9.32 (2.93)
Median	9.05	9.10	9.30	9.10
Min : Max	3.6 : 20.5	2.9 : 20.2	3.4 : 22.6	2.9 : 22.6
V7 (Week -1) FPG (mmol/L)				
Number	289	291	289	869
Mean (SD)	6.91 (2.07)	6.75 (1.80)	6.65 (1.86)	6.77 (1.91)
Median	6.60	6.50	6.40	6.50
Min : Max	2.8 : 13.6	2.9 : 13.6	3.0 : 14.1	2.8 : 14.1
V2 (Week -12) Body Weight (kg)				
Number	298	298	298	894
Mean (SD)	89.75 (17.37)	87.93 (15.84)	89.66 (17.28)	89.11 (16.85)
Median	88.20	87.55	87.75	88.00
Min : Max	54.1 : 155.8	51.0 : 132.8	46.4 : 152.0	46.4 : 155.8
Meal for IMP injection[a]				
Number	298	298		
Breakfast	90 (30.2%)	88 (29.5%)		
Dinner	207 (69.5%)	208 (69.8%)		
Missing	1 (0.3%)	2 (0.7%)		

BMI = Body Mass Index.
[a]: Meal for IMP injection as determined by 4-point SMPG, only presented for lixisenatide and insulin glulisine QD groups.

Table 4 - Disease characteristics at screening or baseline – Randomized population

	Lixisenatide (N=298)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=298)	All (N=894)
Duration of diabetes (years)				
Number	298	298	298	894
Mean (SD)	11.89 (6.43)	12.33 (6.75)	12.41 (6.80)	12.21 (6.66)
Median	11.03	11.44	11.45	11.34
Min : Max	1.3 : 37.9	1.1 : 50.2	1.0 : 37.1	1.0 : 50.2
Duration of treatment with basal insulin treatment (years)				
Number	298	298	298	894
Mean (SD)	3.07 (2.64)	3.26 (3.46)	3.19 (3.13)	3.17 (3.09)
Median	2.32	2.28	2.01	2.15
Min : Max	0.1 : 16.9	0.2 : 35.8	0.3 : 20.1	0.1 : 35.8
Daily dose of basal insulin by types at screening (U)				
Glargine				
Number	199	203	191	593
Mean (SD)	41.70 (23.23)	41.36 (23.35)	40.23 (22.73)	41.11 (23.08)
Median	35.00	34.00	33.00	34.00
Min : Max	12.0 : 140.0	16.0 : 160.0	12.0 : 160.0	12.0 : 160.0

	Lixisenatide (N=298)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=298)	All (N=894)
Detemir				
Number	25	32	30	87
Mean (SD)	41.00 (29.69)	39.59 (25.27)	39.43 (21.59)	39.94 (25.18)
Median	32.00	30.00	35.00	32.00
Min : Max	20.0 : 160.0	18.0 : 120.0	20.0 : 125.0	18.0 : 160.0
NPH				
Number	74	63	77	214
Mean (SD)	40.61 (20.43)	38.97 (18.20)	40.92 (20.26)	40.24 (19.66)
Median	33.00	36.00	36.00	34.50
Min : Max	20.0 : 116.0	16.0 : 100.0	16.0 : 116.0	16.0 : 116.0
Daily dose of insulin glargine at V2 (Week -12) (U)				
Number	298	298	298	894
Mean (SD)	40.92 (21.78)	39.83 (22.04)	39.46 (21.00)	40.07 (21.60)
Median	34.00	34.00	34.50	34.00
Min : Max	16.0 : 134.0	16.0 : 160.0	12.0 : 160.0	12.0 : 160.0
Daily dose of insulin glargine at V8 (Week 0) (U)				
Number	292	295	296	883
Mean (SD)	67.88 (31.90)	64.72 (32.12)	65.14 (26.90)	65.91 (30.39)
Median	62.00	58.00	60.83	60.00
Min : Max	13.0 : 192.0	14.0 : 205.3	18.0 : 204.0	13.0 : 205.3
Metformin use at screening [n (%)]				
Number	298	298	298	894
Yes	262 (87.9%)	260 (87.2%)	259 (86.9%)	781 (87.4%)
No	36 (12.1%)	38 (12.8%)	39 (13.1%)	113 (12.6%)
Daily dose of metformin at baseline (mg)				
Number	262	260	258	780
Mean (SD)	2069.37 (486.66)	2089.13 (477.03)	2114.15 (446.74)	2090.77 (470.31)
Median	2000.00	2000.00	2000.00	2000.00
Min : Max	500.0 : 3000.0	750.0 : 3400.0	850.0 : 3000.0	500.0 : 3400.0

GLP-1 = Glucagon like peptide-1.

3.1.4 Dosage and treatment compliance

Table 5 - Treatment compliance – Safety population

	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
Compliance rate (%)			
Number	297	301	294
Mean (SD)	99.34 (2.69)	98.72 (6.00)	97.12 (15.97)
Median	100.00	100.00	100.00
Min : Max	68.2 : 102.7	44.4 : 113.3	0.0 : 298.4
Overall compliance [n (%)]			
Number	297	301	294
Patients with <60%	0	3 (1.0%)	4 (1.4%)
Patients with ≥60% to <80%	2 (0.7%)	1 (0.3%)	12 (4.1%)
Patients with ≥80% to ≤100%	294 (99.0%)	296 (98.3%)	273 (92.9%)
Patients with >100%	1 (0.3%)	1 (0.3%)	5 (1.7%)
Missing	1	0	0

IMP: Investigational Medicinal Product

Note: Compliance rate (%) = (Total number of actual IMP injections for the dosing interval / Total number of expected IMP injections for the dosing interval)×100.

3.2 EFFICACY

3.2.1 Primary efficacy endpoint

Table 6 - Mean change in HbA1c (%) from baseline to Week 26 – mITT population

HbA1c (%)	Lixisenatide (N=297)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=295)
Baseline			
Number	292	292	295
Mean (SD)	7.76 (0.56)	7.72 (0.58)	7.79 (0.60)
Median	7.70	7.70	7.70
Min : Max	6.4 : 9.8	6.5 : 9.5	6.5 : 12.1
Week 26 (LOCF)			
Number	292	292	295
Mean (SD)	7.17 (0.77)	7.21 (0.79)	6.96 (0.73)
Median	7.10	7.10	7.00
Min : Max	5.1 : 9.8	5.2 : 10.5	5.1 : 9.1
Change from baseline to Week 26 (LOCF)			
Number	292	292	295
Mean (SD)	-0.59 (0.79)	-0.51 (0.80)	-0.82 (0.78)
Median	-0.60	-0.50	-0.90
Min : Max	-3.4 : 2.0	-2.6 : 2.5	-5.6 : 1.7
LS Mean (SE) [a]	-0.63 (0.054)	-0.58 (0.054)	-0.84 (0.053)
LS Mean difference (SE) of Lixisenatide vs. [ab]	-	-0.05 (0.059)	0.21 (0.059)
95% CI	-	(-0.170 to 0.064)	(0.095 to 0.328)

LOCF = Last observation carried forward.
[a]Analysis of covariance (ANCOVA) model with treatment groups (lixisenatide, insulin glulisine QD, and insulin glulisine TID), Visit 7 (Week -1) strata of HbA1c [<8.0, ≥8.0%], randomization strata of metformin use, and country as fixed effects and baseline HbA1c value as a covariate.
[b]Difference in LS Mean between lixisenatide vs. insulin glulisine QD, or lixisenatide vs. insulin glulisine TID.
The analysis included measurements obtained up to 14 days after the last injection of the investigational medicinal product.
Patients with both baseline and Week 26 (LOCF) measurements are included.

Table 7 - Mean change in body weight (kg) from baseline to Week 26 – mITT population

Body weight (kg)	Lixisenatide (N=297)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=295)
Baseline			
Number	295	295	295
Mean (SD)	90.10 (17.39)	88.37 (15.88)	90.00 (17.21)
Median	88.00	88.00	88.70
Min : Max	54.2 : 158.4	53.6 : 132.8	49.0 : 154.2
Week 26 (LOCF)			
Number	295	295	295
Mean (SD)	89.37 (18.14)	89.31 (16.27)	91.29 (17.27)
Median	87.30	88.40	90.50
Min : Max	54.2 : 191.1	55.0 : 134.8	50.3 : 155.0
Change from baseline to Week 26 (LOCF)			
Number	295	295	295
Mean (SD)	-0.72 (5.16)	0.94 (2.50)	1.29 (2.80)
Median	-0.50	0.90	1.20
Min : Max	-16.4 : 72.5	-8.2 : 10.9	-9.5 : 12.4
LS Mean (SE) [a]	-0.63 (0.276)	1.03 (0.276)	1.37 (0.271)
LS Mean difference (SE) of Lixisenatide vs. [ab]	-	-1.66 (0.305)	-1.99 (0.305)
95% CI	-	(-2.257 to -1.062)	(-2.593 to -1.396)
p-value		<.0001	<.0001

LOCF = Last observation carried forward.
[a]Analysis of covariance (ANCOVA) model with treatment groups (lixisenatide, insulin glulisine QD, and insulin glulisine TID), Visit 7 (Week -1) strata of HbA1c [<8.0, ≥8.0%], randomization strata of metformin use, and country as fixed effects and baseline body weight as a covariate.
[b]Difference in LS Mean between lixisenatide vs. insulin glulisine QD, or lixisenatide vs. insulin glulisine TID.
The analysis included measurements obtained up to 3 days after the last injection of the investigational medicinal product.
Patients with both baseline and Week 26 (LOCF) measurements are included.

Figure 1 shows the mean change in HbA1c(%) from baseline by visit in the mITT population. **Figure 2** shows the mean change in body weight (kg) from baseline by visit in the mITT population.

3.2.2 Other key efficacy endpoints

Table 8 - Mean change in fasting plasma glucose (mmol/L) from baseline to Week 26 – mITT population

Fasting plasma glucose (mmol/L)	Lixisenatide (N=297)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=295)
Baseline			
Number	295	295	294
Mean (SD)	6.58 (1.83)	6.85 (1.99)	6.65 (1.89)
Median	6.40	6.50	6.40
Min : Max	2.9 : 16.1	2.9 : 13.8	2.9 : 13.4
Week 26 (LOCF)			
Number	295	295	294
Mean (SD)	6.59 (1.96)	6.66 (1.94)	6.71 (2.02)
Median	6.20	6.40	6.50
Min : Max	2.9 : 15.3	2.9 : 16.1	2.7 : 16.2
Change from baseline to Week 26 (LOCF)			
Number	295	295	294
Mean (SD)	0.01 (2.15)	-0.19 (2.52)	0.05 (2.47)
Median	-0.15	-0.10	-0.20
Min : Max	-7.0 : 7.9	-8.4 : 7.5	-7.5 : 10.7
LS Mean (SE) [a]	-0.23 (0.143)	-0.21 (0.142)	-0.06 (0.140)
LS Mean difference (SE) of Lixisenatide vs. [ab]	-	-0.01 (0.157)	-0.17 (0.158)
95% CI	-	(-0.319 to 0.298)	(-0.475 to 0.143)

LOCF = Last observation carried forward.
[a]Analysis of covariance (ANCOVA) model with treatment groups (lixisenatide, insulin glulisine QD, insulin glulisine TID), Visit 7 (Week -1) strata of HbA1c [<8.0, ≥8.0%], randomization strata of metformin use, and country as fixed effects and baseline fasting plasma glucose as a covariate
[b]Difference in LS Mean between lixisenatide vs. insulin glulisine QD, or lixisenatide vs. insulin glulisine TID.
The analysis included measurements obtained up to one day after the last injection of the investigational medicinal product.
Patients with both baseline and Week 26 (LOCF) measurements are included.

Table 9 - Mean change in insulin glargine dose (U) from baseline to Week 26 – mITT population

Insulin glargine dose (Units)	Lixisenatide (N=297)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=295)
Baseline			
Number	292	294	294
Mean (SD)	67.45 (31.68)	64.79 (32.09)	65.05 (27.01)
Median	62.00	58.00	60.67
Min : Max	13.0 : 192.0	14.0 : 205.3	18.0 : 204.0
Week 26 (LOCF)			
Number	292	294	294
Mean (SD)	67.22 (36.22)	63.89 (35.67)	61.16 (29.33)
Median	60.00	54.00	57.00
Min : Max	14.0 : 224.7	9.3 : 254.0	14.0 : 230.0
Change from baseline to Week 26 (LOCF)			
Number	292	294	294
Mean (SD)	-0.22 (13.59)	-0.91 (13.41)	-3.89 (13.28)
Median	-1.00	-1.33	-4.00
Min : Max	-36.0 : 60.0	-72.7 : 76.0	-56.0 : 35.3
LS Mean (SE) [a]	0.70 (1.002)	-0.06 (0.999)	-3.13 (0.982)
LS Mean difference (SE) of Lixisenatide vs. [ab]	-	0.76 (1.104)	3.83 (1.106)
95% CI	-	(-1.410 to 2.923)	(1.658 to 6.001)

LOCF = Last observation carried forward.
[a]Analysis of covariance (ANCOVA) model with treatment groups (lixisenatide, insulin glulisine QD, insulin glulisine TID), Visit 7 (Week -1) strata of HbA1c [<8.0, ≥8.0%], randomization strata of metformin use, and country as fixed effects and baseline insulin glargine dose as a covariate.
[b]Difference in LS Mean between lixisenatide vs. insulin glulisine QD, or lixisenatide vs. insulin glulisine TID.
The analysis included measurements obtained up to the date of the last injection of the investigational medicinal product.
Patients with both baseline and Week 26 (LOCF) measurements are included.

Figure 3 shows the mean insulin glargine daily dose (U) by visit in the mITT population. **Figure 4** shows the mean daily insulin glulisine dose (U) by visit in the mITT population. **Figure 5** shows the mean total insulin dose (U) by visit in the mITT population

3.3 SAFETY

3.3.1 Treatment-emergent adverse events

Table 10 - Overview of adverse event profile: treatment emergent adverse events – Safety

	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
Patients with any TEAE	221 (74.2%)	222 (73.8%)	236 (80.3%)
Patients with any treatment emergent SAE	11 (3.7%)	11 (3.7%)	14 (4.8%)
Patients with any TEAE leading to death	1 (0.3%)	0	2 (0.7%)
Patients with any TEAE leading to permanent treatment discontinuation	15 (5.0%)	2 (0.7%)	3 (1.0%)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event
n (%) = number and percentage of patients with at least one TEAE

Table 11 - Number (%) of patients with TEAE(s) that occurred with PT≥3% in any treatment group by primary SOC and PT – Safety

Primary System Organ Class Preferred Term n(%)	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
Any class	221 (74.2%)	222 (73.8%)	236 (80.3%)
Infections and infestations	70 (23.5%)	70 (23.3%)	81 (27.6%)
Nasopharyngitis	14 (4.7%)	21 (7.0%)	18 (6.1%)
Upper respiratory tract infection	8 (2.7%)	5 (1.7%)	11 (3.7%)
Influenza	5 (1.7%)	8 (2.7%)	14 (4.8%)
Metabolism and nutrition disorders	111 (37.2%)	143 (47.5%)	157 (53.4%)
Hypoglycaemia	107 (35.9%)	140 (46.5%)	154 (52.4%)
Nervous system disorders	32 (10.7%)	22 (7.3%)	29 (9.9%)
Headache	20 (6.7%)	8 (2.7%)	12 (4.1%)
Gastrointestinal disorders	105 (35.2%)	26 (8.6%)	22 (7.5%)
Nausea	75 (25.2%)	5 (1.7%)	3 (1.0%)
Vomiting	26 (8.7%)	5 (1.7%)	6 (2.0%)
Diarrhoea	20 (6.7%)	10 (3.3%)	4 (1.4%)
Investigations	69 (23.2%)	76 (25.2%)	92 (31.3%)
Blood glucose decreased	60 (20.1%)	67 (22.3%)	82 (27.9%)
Injury, poisoning and procedural complications	14 (4.7%)	20 (6.6%)	28 (9.5%)
Accidental overdose	0	13 (4.3%)	20 (6.8%)

TEAE: Treatment emergent adverse event, SOC: System organ class
MedDRA 17.1
n (%) = number and percentage of patients with at least one TEAE
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT in Lixisenatide main meal group.

3.3.2 Serious treatment-emergent adverse events

Table 12 - Number (%) of patients with treatment emergent SAE presented by primary SOC and PT – Safety population

Primary System Organ Class Preferred Term n(%)	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
Any class	11 (3.7%)	11 (3.7%)	14 (4.8%)
Infections and infestations	3 (1.0%)	1 (0.3%)	1 (0.3%)
Cellulitis	0	1 (0.3%)	1 (0.3%)
Erysipelas	1 (0.3%)	0	0
Penile infection	1 (0.3%)	0	0
Septic arthritis staphylococcal	1 (0.3%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0%)	0	3 (1.0%)
Invasive ductal breast carcinoma	1 (0.3%)	0	1 (0.3%)
Pancreatic carcinoma metastatic	1 (0.3%)	0	0
Uterine cancer	1 (0.3%)	0	0
Basal cell carcinoma	0	0	1 (0.3%)
Neoplasm malignant [a]	0	0	1 (0.3%)
Metabolism and nutrition disorders	1 (0.3%)	2 (0.7%)	0
Hypoglycaemia	0	1 (0.3%)	0
Decreased appetite	1 (0.3%)	0	0
Dehydration	1 (0.3%)	1 (0.3%)	0
Nervous system disorders	1 (0.3%)	3 (1.0%)	2 (0.7%)
Cerebrovascular accident	1 (0.3%)	0	2 (0.7%)
Hypoglycaemic unconsciousness	0	2 (0.7%)	0
Neuritis cranial	0	1 (0.3%)	0
Cardiac disorders	1 (0.3%)	3 (1.0%)	5 (1.7%)
Angina pectoris	1 (0.3%)	0	1 (0.3%)
Cardiac failure chronic	0	0	1 (0.3%)
Cardiac failure congestive	0	0	1 (0.3%)
Myocardial ischaemia	0	0	1 (0.3%)
Angina unstable	0	1 (0.3%)	0
Atrial fibrillation	0	1 (0.3%)	0
Atrioventricular block complete	0	0	1 (0.3%)
Myocardial infarction	0	1 (0.3%)	0
Vascular disorders	0	0	1 (0.3%)
Hypertension	0	0	1 (0.3%)
Gastrointestinal disorders	2 (0.7%)	0	0
Abdominal pain	1 (0.3%)	0	0
Epigastric discomfort	1 (0.3%)	0	0
Gastric ulcer haemorrhage	1 (0.3%)	0	0
Hepatobiliary disorders	1 (0.3%)	0	0
Hepatic mass	1 (0.3%)	0	0
Skin and subcutaneous tissue disorders	1 (0.3%)	0	1 (0.3%)
Diabetic bullosis	1 (0.3%)	0	0
Skin ulcer haemorrhage	0	0	1 (0.3%)

Primary System Organ Class Preferred Term n(%)	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
Renal and urinary disorders	2 (0.7%)	0	0
Renal failure	1 (0.3%)	0	0
Renal failure acute	1 (0.3%)	0	0
Injury, poisoning and procedural complications	0	4 (1.3%)	1 (0.3%)
Accidental overdose	0	2 (0.7%)	1 (0.3%)
Ankle fracture	0	1 (0.3%)	0
Incisional hernia	0	1 (0.3%)	0

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 17.1
[a] basal cell cancer reported as "carcinoma on left side above hairline"
n (%) = number and percentage of patients with at least one treatment emergent SAE.
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT in Lixisenatide main meal group.

3.3.3 Adverse events leading to permanent IMP discontinuation

Table 13 - Number (%) of patients experiencing TEAE(s) leading to permanent treatment discontinuation by primary SOC and PT during on-treatment period – Safety population

Primary System Organ Class Preferred Term n(%)	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
Any class	15 (5.0%)	2 (0.7%)	3 (1.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7%)	0	0
Invasive ductal breast carcinoma	1 (0.3%)	0	0
Metastases to liver	1 (0.3%)	0	0
Metastases to peritoneum	1 (0.3%)	0	0
Pancreatic carcinoma metastatic	1 (0.3%)	0	0
Blood and lymphatic system disorders	1 (0.3%)	0	0
Lymphadenopathy	1 (0.3%)	0	0
Immune system disorders	0	0	1 (0.3%)
Seasonal allergy	0	0	1 (0.3%)
Metabolism and nutrition disorders	2 (0.7%)	0	0
Hypoglycaemia	1 (0.3%)	0	0
Decreased appetite	1 (0.3%)	0	0
Dehydration	1 (0.3%)	0	0
Nervous system disorders	1 (0.3%)	1 (0.3%)	0
Headache	1 (0.3%)	0	0
Tremor	0	1 (0.3%)	0

Primary System Organ Class Preferred Term n(%)	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
Cardiac disorders	0	0	1 (0.3%)
Cardiac failure chronic	0	0	1 (0.3%)
Vascular disorders	2 (0.7%)	0	0
Hot flush	1 (0.3%)	0	0
Thrombosis	1 (0.3%)	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.7%)	0	0
Cough	1 (0.3%)	0	0
Nasal congestion	1 (0.3%)	0	0
Gastrointestinal disorders	11 (3.7%)	0	0
Nausea	4 (1.3%)	0	0
Vomiting	4 (1.3%)	0	0
Diarrhoea	1 (0.3%)	0	0
Abdominal pain	1 (0.3%)	0	0
Dyspepsia	1 (0.3%)	0	0
Ascites	2 (0.7%)	0	0
Epigastric discomfort	1 (0.3%)	0	0
Gastric ulcer haemorrhage	1 (0.3%)	0	0
Hepatobiliary disorders	1 (0.3%)	0	0
Hepatic mass	1 (0.3%)	0	0
Skin and subcutaneous tissue disorders	1 (0.3%)	0	1 (0.3%)
Diabetic bullosis	1 (0.3%)	0	0
Skin ulcer haemorrhage	0	0	1 (0.3%)
Renal and urinary disorders	1 (0.3%)	0	0
Renal failure	1 (0.3%)	0	0
Investigations	0	1 (0.3%)	0
Blood glucose decreased	0	1 (0.3%)	0

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 17.1
n (%) = number and percentage of patients with at least one TEAE leading to permanent treatment discontinuation
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT in Lixisenatide group.

3.3.4 Other significant adverse events

Symptomatic hypoglycemia

Table 14 - Summary of symptomatic hypoglycemia meeting the protocol definition during the TEAE period – Safety population

Type	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
Total patient years	144.6	148.3	146.2
Any symptomatic hypoglycemia			
Number of patients with events, n (%)	98 (32.9%)	117 (38.9%)	132 (44.9%)
Number of patients with events per 100 patient years[1]	67.8	78.9	90.3
Number of events	332	395	600
Number of events per 100 patient years[2]	229.6	266.4	410.4

Symptomatic hypoglycemia = symptomatic hypoglycemia as defined per protocol (accompanied by plasma glucose < 60 mg/dL [3.3 mmol/L] or associated with prompt recovery to countermeasures if no plasma glucose was available).
On-treatment period = the time from the first injection of the investigational medicinal product up to 3 days after the last injection of the investigational medicinal product.
[1]: Calculated as (number of patients with events*100 divided by total exposure + 3 days in patient years).
[2]: Calculated as (number of events*100 divided by total exposure + 3 days in patient years).

Allergic reaction

Table 15 - Number (%) of patients with events adjudicated as allergic reaction by ARAC during the TEAE period – Safety population

Relationship to study treatment (by ARAC)	ARAC diagnosis category	MedDRA coded term (PT) for ARAC diagnosis	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
All	Any category	Any event	3 (1.0%)	0	1 (0.3%)
	URTICARIA (HIVES)	Urticaria	1 (0.3%)	0	0
	OTHER ALLERGIC REACTION	Rhinitis allergic	2 (0.7%)	0	1 (0.3%)
Possibly Related to IMP	Any category	Any event	0	0	0

ARAC = Allergic Reaction Assessment Committee. IMP=Investigational medicinal product.

Pancreatitis

Table 16 - Number (%) of patients with any event adjudicated as pancreatitis by PSAC during the TEAE period – Safety population

	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
Total number of patients with any event adjudicated as pancreatitis by PSAC	1 (0.3%)	0	0
Acute pancreatitis	1 (0.3%)	0	0
Acute on chronic pancreatitis	0	0	0
Chronic pancreatitis	0	0	0
Unknown pancreatitis	0	0	0

PSAC=Pancreas Safety Assessment Committee.

Calcitonin

Table 17 - Number (%) of patients with TEAE reported on the specific adverse event form for increased calcitonin (>=20 ng/L) – Safety population

Preferred Term	Lixisenatide (N=298)	Insulin Glulisine QD (N=301)	Insulin Glulisine TID (N=294)
Any	2 (0.7%)	0	1 (0.3%)
Blood calcitonin increased	2 (0.7%)	0	1 (0.3%)

TEAE: Treatment emergent adverse event

Example 2

Advancing Basal Insulin Glargine with Prandial Lixisenatide QD vs Insulin Glulisine QD or TID in Obese T2DM: The GetGoal-Duo2 Evidence-Based Trial

To provide evidence on how to advance basal insulin (BI), we explored treatment options in poorly controlled BI-treated (≥6 mo ± 1–3 OADs) obese adults with T2DM randomized to lixisenatide 20 µg QD (LIXI), insulin glulisine QD (GLU-1), or GLU TID (GLU-3), all added to insulin glargine (IG) ± metformin, if HbA_{1c} remained >7–9% after a 12-week IG optimization run-in period stopping other OADs. Co-primary endpoints at 26 weeks were (1) non-inferiority (95% CI upper bound <0.4%) in HbA_{1c} reduction with LIXI vs GLU-1 and (2) for LIXI vs GLU-3, either non-inferiority in HbA_{1c} reduction (2a) OR superiority (one-sided $\alpha \leq 0.025$) in body weight change (2b). FPG, PPG, IG dose, composite outcomes, AEs, and hypoglycemia were assessed. Each arm randomized 298 pts (T2DM duration 12 yrs, BI duration 3 yrs, weight ~90 kg). All co-primary endpoints were met as LIXI was non-inferior to GLU-1 and GLU-3 for HbA_{1c} reductions and statistically superior to both for body weight loss (Table). Documented hypoglycemia was numerically and significantly lower with LIXI than with GLU-1 and GLU-3, respectively. In conclusion, BI plus LIXI, if tolerated, may become a preferred option to advance BI, attaining meaningful glycemic targets with less hypoglycemia and with weight loss compared with prandial insulin as Basal Plus or Basal/Bolus for difficult to control, obese, insulin-treated T2DM.

Table

Outcomes	Lixisenatide 20 µg QD + Insulin Glargine (n=297)	Insulin Glulisine QD + Insulin Glargine (n=298)	Insulin Glulisine TID + Insulin Glargine (n=295)
FPG, mg/dL			
Screening (start run-in) mean ± SD	165 ± 53	167 ± 52	171 ± 53
BL (end run-in) mean ± SD	119 ± 33	123 ± 36	120 ± 34
Week 26 (LOCF) mean ± SD	119 ± 35	120 ± 35	121 ± 36
LS mean ± SE change from BL	–4 ± 3	–4 ± 3	–1 ± 3
LS mean [95% CI] treatment difference	–	0 [–6, 5]	–3 [–9, 3]
2-h PPG post test meal, mg/dL*			
BL (end run-in) mean ± SD	254 ± 65	249 ± 63	262 ± 63
Week 26 (LOCF) mean ± SD	184 ± 70	220 ± 60	229 ± 69
LS mean ± SE change from BL	–66 ± 11	–28 ± 11	–25 ± 11
LS mean [95% CI] treatment difference	–	–37 [–59, –15]	–40 [–61, –19]
HbA_{1c},%			
Screening (start run-in) mean ± SD	8.5 ± 0.7	8.5 ± 0.7	8.5 ± 0.8
BL (end run-in) mean ± SD	7.8 ± 0.6	7.7 ± 0.6	7.8 ± 0.6
Week 26 (LOCF) mean ± SD	7.2 ± 0.8	7.2 ± 0.8	7.0 ± 0.7
LS mean ± SE change from BL	–0.6 ± 0.1	–0.6 ± 0.1	–0.8 ± 0.1
LS mean [95% CI] treatment difference	–	**–0.1† [–0.2, 0.1]**	**0.2† [0.1, 0.3]**
Insulin Glargine dose, U/day			
Screening (start run-in) mean ± SD	41 ± 22	40 ± 22	39 ± 2
BL (end run-in) mean ± SD	67 ± 32	65 ± 32	65 ± 27
Week 26 (LOCF) mean ± SD	67± 36	64 ± 36	61 ± 29
LS mean ± SE change from BL	0.7 ± 1.0	–0.1 ± 1.0	–3.1 ± 1.0
LS mean [95% CI] treatment difference	–	0.8 [–1.4, 2.9]	3.9 [1.7, 6.0]
Insulin Glulisine dose, U/day			
Week 26 (LOCF) mean	–	10	20
Body Weight, kg			
BL mean ± SD	90.1 ± 17.4	88.4 ± 15.9	90.0 ± 17.2
Week 26 (LOCF) mean ± SD	89.4 ± 18.1	89.3 ± 16.3	91.3 ± 17.3
LS mean ± SE change from BL	–0.6 ± 0.3	1.0 ± 0.3	1.4 ± 0.3
LS mean [95% CI] treatment difference	–	–1.7 [–2.3, –1.1]	**–2.0 [–2.6, –1.4]**
(p-value vs Lixisenatide)	–	(p<0.0001)	**(p<0.0001)†**
Documented Symptomatic Hypoglycemia at Week 26			
% pts (p-value vs Lixisenatide)	31.5	37.5 (p=0.144)	44.6 (p=0.001)
No. of events	325	384	595
No. of events/pt years	2.2	2.6	4.1
Estimated rate ratio	–	0.8	0.5
Lixisenatide:Glulisine [95% CI] (p-value vs Lixisenatide)	–	[0.5, 1.1] (p=0.123)	[0.3, 0.7] (p<0.0001)
Severe Hypoglycemia, no. of pts with events	0	2	0
Gastrointestinal AEs, n (%)‡			
Nausea	75 (25)	5 (2)	3 (1)
Diarrhea	20 (7)	10 (3)	4 (1)
Vomiting	26 (9)	5 (2)	6 (2)

*Subset of the mITT population treated with lixisenatide or insulin glulisine before breakfast; †**co-primary endpoints**; ‡safety population. AEs, adverse events; BL, baseline; CI, confidence interval; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; LOCF, last observation carried forward; LS, least squares; mITT, modified intent-to-treat; PPG, postprandial glucose; QD, once daily; SD, standard deviation; SE, standard error; TID, thrice daily.
n numbers are for the mITT population (all pts who received ≥1 dose of study medication, with both a baseline assessment and ≥1 post-baseline assessment).

Claims

1. A pharmaceutical combination for use in glycemic control in a type 2 diabetes mellitus patient, said combination comprising

   (i) lixisenatide or/and a pharmaceutically acceptable salt thereof,

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

   (iii) optionally metformin or/and a pharmaceutically acceptable salt thereof.

2. The pharmaceutical combination for use according to claim 1, wherein the type 2 diabetes mellitus to be treated is not adequately controlled with compound (b) and optionally compound (c) alone.

3. The pharmaceutical combination for use according to claim 1 or 2, wherein the patient to be treated is obese.

4. The pharmaceutical combination for use according to any of the preceding claims, wherein the patient to be treated has an age of at least 65 years.

5. The pharmaceutical combination for use according to any of the preceding claims, wherein prior to the onset of therapy with the combination according to claim 1, the patient has a fasting plasma glucose of at least 9 mmol/L when treated with a basal insulin monotherapy or a basal insulin and one to three oral anti-diabetics alone selected from the group consisting of metformin, a sulfonylurea, a DPP-4 inhibitor or a glinide alone.

6. The pharmaceutical combination for use according to any of the preceding claims, wherein prior to the onset of therapy with the combination according to claim 1, the patient has a fasting plasma glucose concentration in the

range of 5.6 to 6.9 mmol/L or a fasting plasma glucose concentration of at least 6.6 mmol/L when treated with compound (b) and optionally compound (c) alone.

7. The pharmaceutical combination for use according to any of the preceding claims, wherein prior to the onset of therapy with the combination according to claim 1, the patient has a HbA1c of at least 8.5% when treated with a basal insulin monotherapy or a basal insulin and one to three oral anti-diabetics alone selected from the group consisting of metformin, a sulfonylurea, a DPP-4 inhibitor or a glinide alone.

8. The pharmaceutical combination for use according to any of the preceding claims, wherein prior to the onset of therapy with the combination according to claim 1, the patient has a HbA1c of at least 7.5 % when treated with compound (b) and optionally compound (c) alone.

9. The pharmaceutical combination for use according to any of the claims 5 to 8, wherein the basal insulin is selected from insulin glargine, insulin detemir and isophane insulin (NPH insulin).

10. The pharmaceutical combination for use of any of the preceding claims, wherein the patient does not receive concomitant treatment with at least one of a sulfonylurea, a DPP-4 inhibitor and a glinide.

11. The pharmaceutical combination for use of any of the preceding claims, wherein in the patient to be treated, type 2 diabetes mellitus has been diagnosed for at least 1 year or at least 2 years prior to the onset of a therapy with compounds (a), (b) and optionally (c).

12. The pharmaceutical combination for use of any of the preceding claims, wherein the administration of the combination comprises the steps:

(i) administration of compounds (b) and (c) for at least 4 weeks, and

(ii) continuing treatment by administration of compounds (a), (b) and (c),

wherein the amount of compound (b) to be administered in step (i) is adjusted so that a predetermined fasting plasma glucose level or/and a predetermined self-monitored plasma glucose level is reached or at least approximated.

13. The pharmaceutical combination for use according to claim 12, wherein the amount of compound (b) to be administered in step (i) is adjusted so that

(I) a fasting plasma glucose level or/and a fasting self-monitored plasma glucose level of about 4.4 mmol/l to about 5.6 mmol/l, or/and

(II) a self-monitored plasma glucose level (SMPG) of about 7.8 mmol/l (or about 140 mg/dl) or less

is reached or at least approximated.

14. The pharmaceutical combination for use according to claim 13, wherein the self-monitored plasma glucose level in (II) is a 4-point self-monitored plasma glucose level or a 7-point self-monitored plasma glucose level.

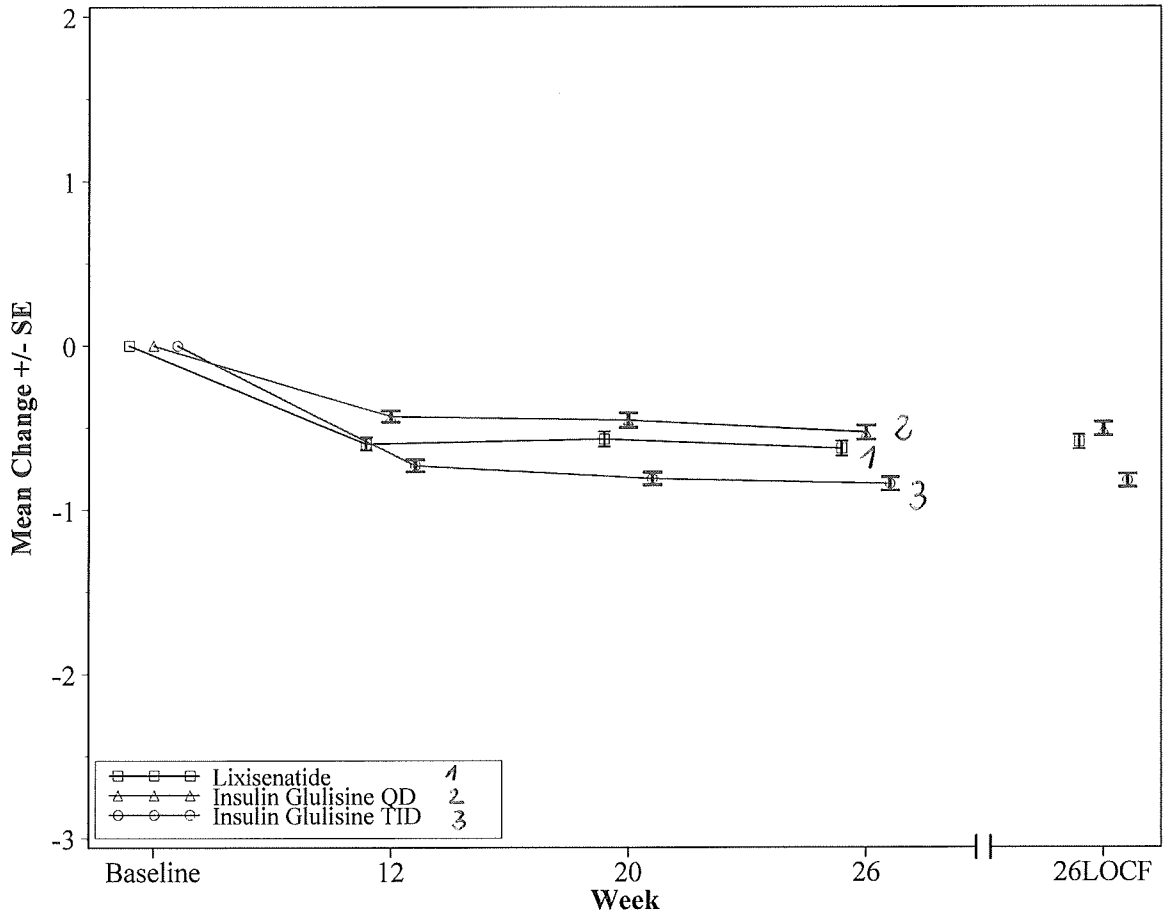
15. The pharmaceutical combination for use of any of the preceding claims, wherein

(a) lixisenatide or/and the pharmaceutically acceptable salt thereof is prepared for parenteral administration,

(b) insulin glargine or/and or/and the pharmaceutically acceptable salt thereof is prepared for parenteral administration, or/and

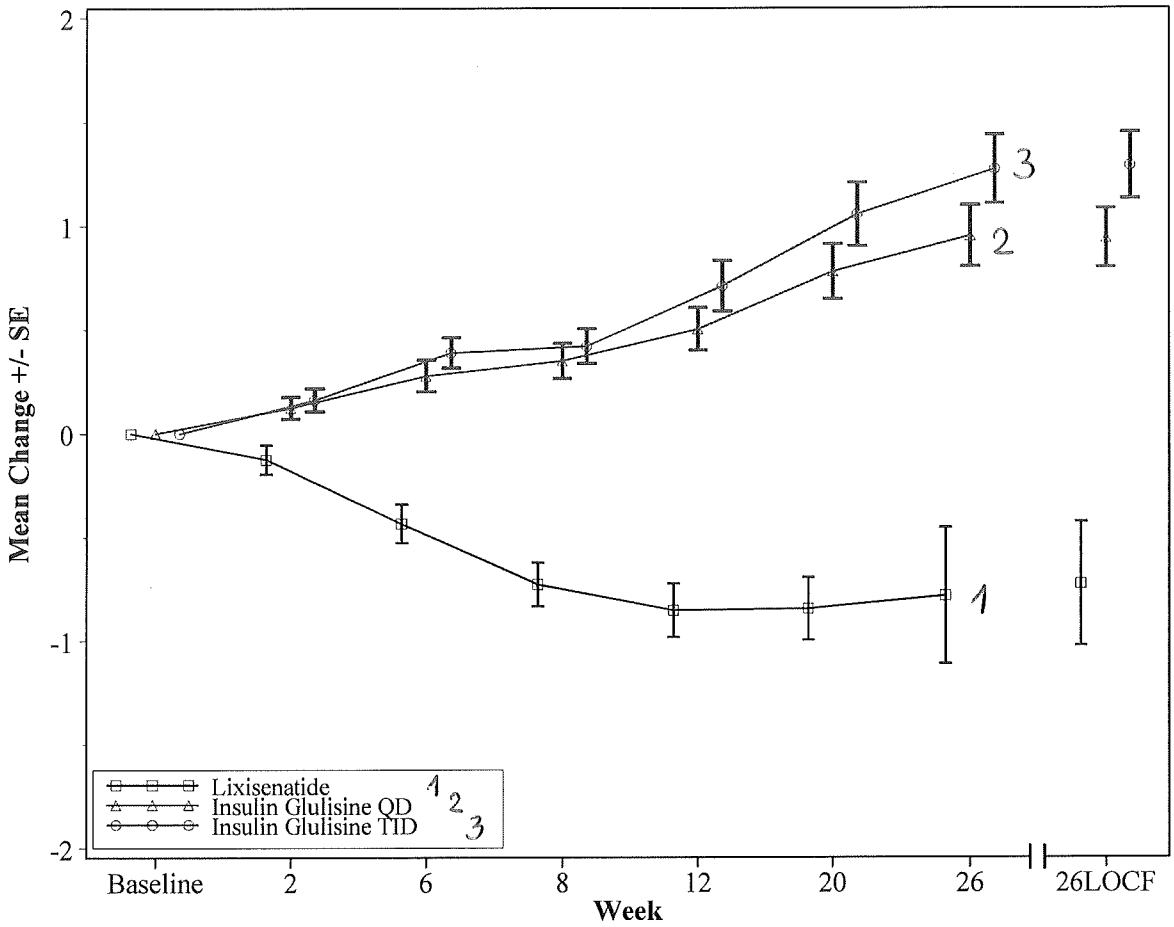
(c) metformin or/and the pharmaceutically acceptable salt thereof is prepared for oral administration.

Figure 1 - mean change in HbA1c(%) from baseline by visit – mITT population



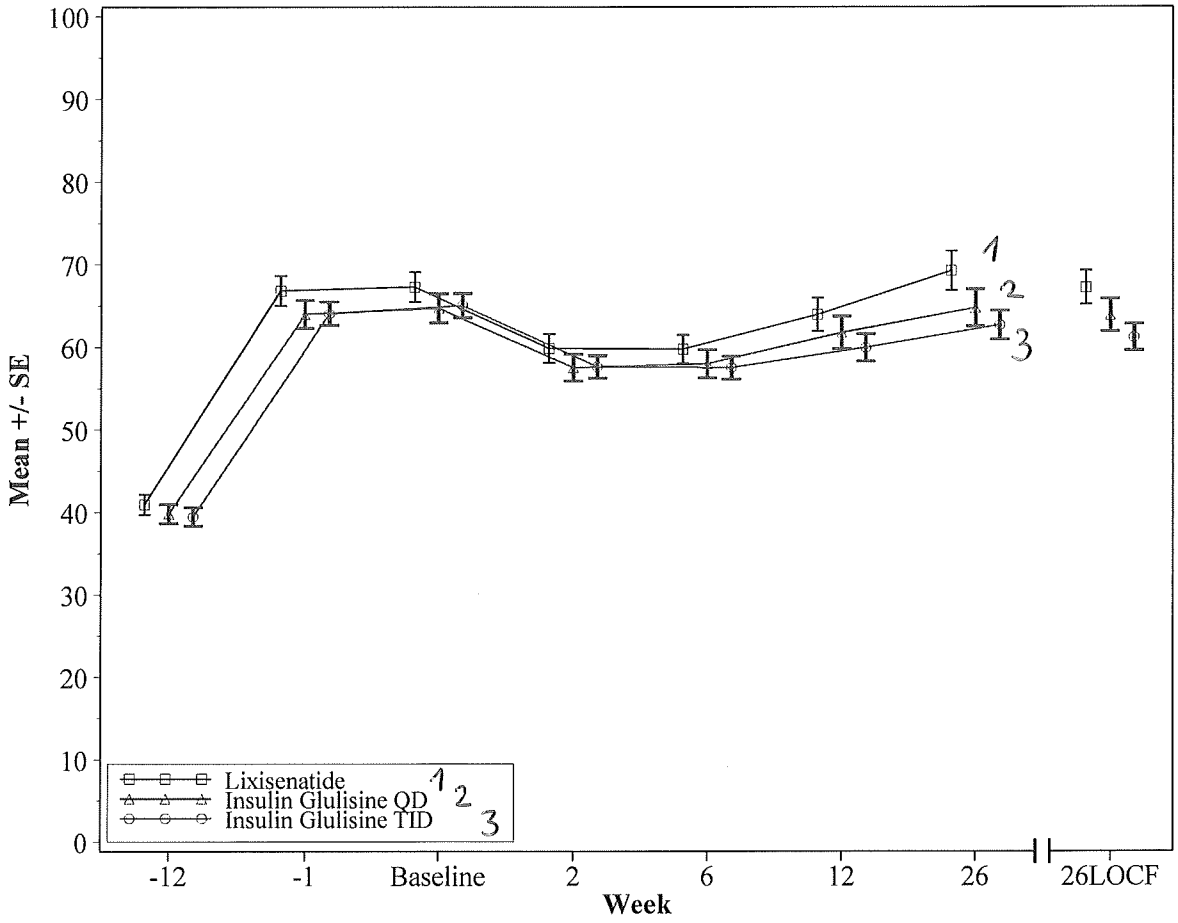
LOCF = Last observation carried forward.
Note: The plot included measurements obtained up to 14 days after the last injection of the investigational medicinal product.

Figure 2 - mean change in body weight (kg) from baseline by visit – mITT population



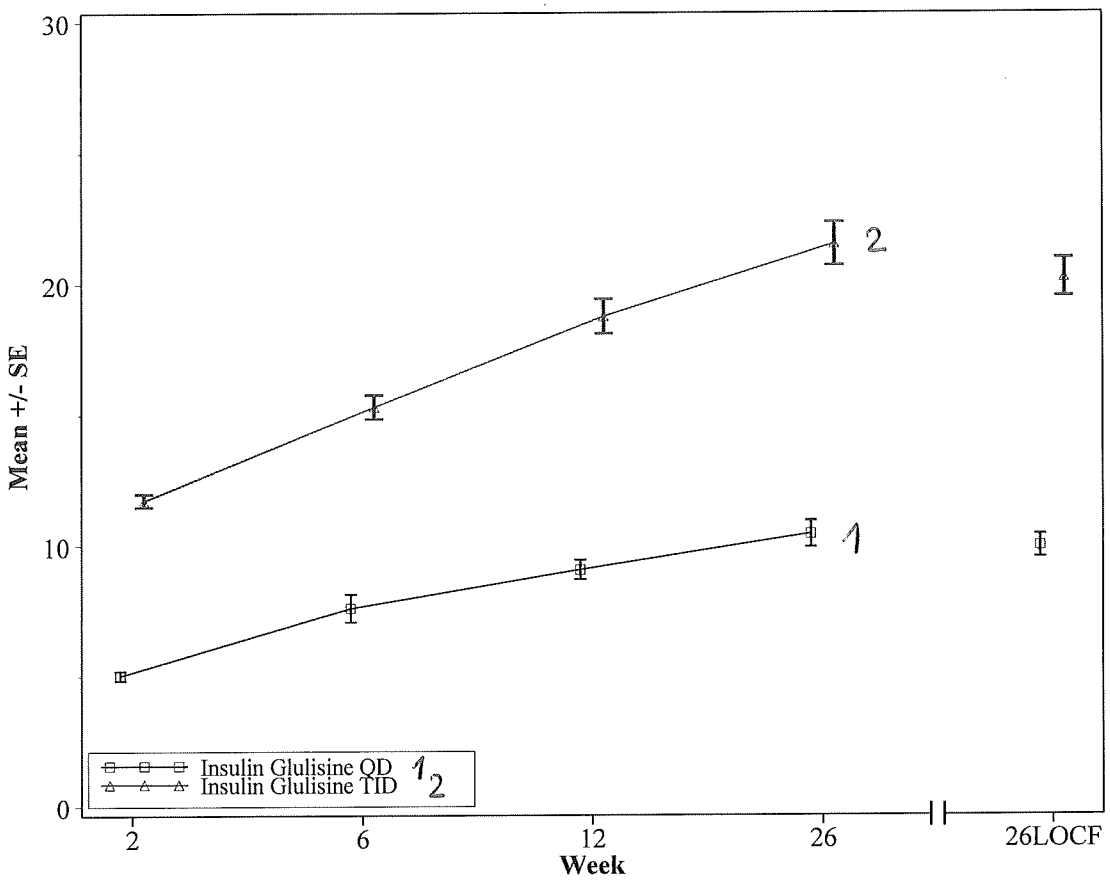
LOCF = Last observation carried forward.
The analysis included measurements obtained up to 3 days after the last injection of the investigational medicinal product.

Figure 3 - mean insulin glargine daily dose (U) by visit – mITT population



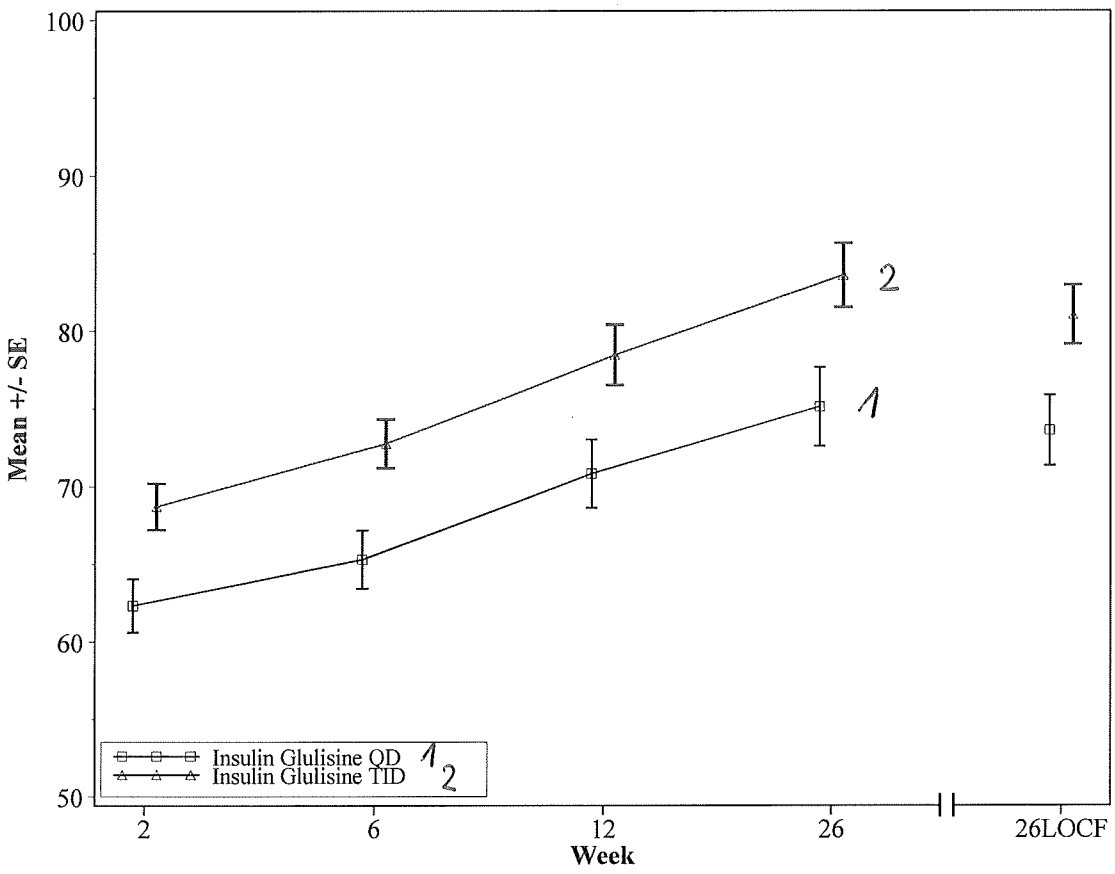
LOCF = Last observation carried forward.
The analysis included measurements obtained up to the date of last injection of the investigational medicinal product.
The dose of insulin glargine are collected on 3 different days during the week prior to the visit and the values presented are the average of the collected doses except for Week -12 when the dose was collected only once for the visit.

Figure 4 - mean daily insulin glulisine dose (U) by visit – mITT population



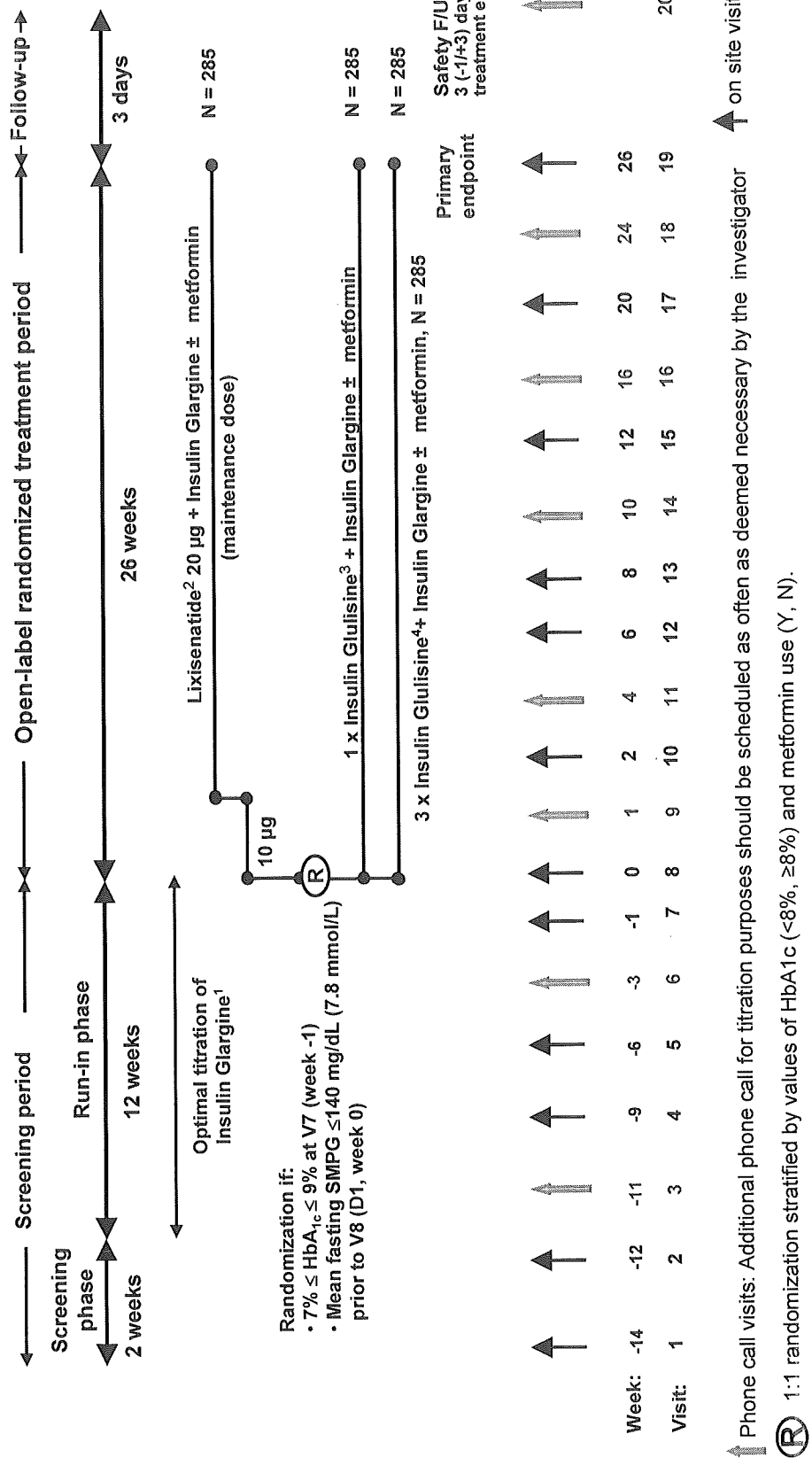
LOCF = Last observation carried forward.
The analysis included measurements obtained up to the date of last injection of the investigational medicinal product.
The insulin glulisine doses were collected on 3 different days during the week prior to the visit and the values presented are the average of the collected doses.

Figure 5 - mean total insulin dose (U) by visit – mITT population



LOCF = Last observation carried forward.
The analysis included measurements obtained up to the date of last injection of the investigational medicinal product.
Total insulin dose is the sum of average insulin glargine dose and average insulin glulisine dose for the visit.

Figure 6 - graphical study design



INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/055267

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/055267

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/28 A61K31/155 A61P3/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/060850 A1 (SANOFI AVENTIS DEUTSCHLAND [DE]) 2 May 2013 (2013-05-02) page 7, lines 28-33; claims 1,8,9,15,19,24,25,27 page 10, line 21 - line 24 page 12, line 1 - line 4; tables 19,11 page 8, line 16 - line 20 page 36, lines 6-8 ----- -/--	1-15

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 May 2016	07/06/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Allnutt, Sarah

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MATTHEW C RIDDLE ET AL: "Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1)", DIABETES CARE, AMERICAN DIABETES ASSOCIATION, INC, US , vol. 36, no. 9 1 September 2013 (2013-09-01), pages 2497-2503, XP002729330, ISSN: 1935-5548, DOI: 10.2337/DC12-2462 Retrieved from the Internet: URL:http://care.diabetesjournals.org/content/36/9/2497.full.pdf+html [retrieved on 2013-04-05] the whole document	1-15
X	"Evidence summary: new medicine Key points from the evidence", , 24 September 2013 (2013-09-24), XP055219047, Retrieved from the Internet: URL:https://www.nice.org.uk/advice/esnm26/resources/type-2-diabetes-lixisenatide-1502680866716869 [retrieved on 2015-10-07] page 17 - page 18	1,7,10
Y	WO 2012/156299 A1 (SANOFI AVENTIS DEUTSCHLAND [DE]; NIEMOELLER ELISABETH [DE]; SILVESTRE) 22 November 2012 (2012-11-22) the whole document	1-15
Y	M. C. RIDDLE ET AL: "Adding Once-Daily Lixisenatide for Type 2 Diabetes Inadequately Controlled by Established Basal Insulin: A 24-week, randomized, placebo-controlled comparison (GetGoal-L)", DIABETES CARE, vol. 36, no. 9, 1 September 2013 (2013-09-01), pages 2489-2496, XP055219024, US ISSN: 0149-5992, DOI: 10.2337/dc12-2454 the whole document	1-15

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/055267

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013060850 A1	02-05-2013	AU 2012328388 A1	15-05-2014
		CA 2851690 A1	02-05-2013
		CN 104066441 A	24-09-2014
		EP 2771024 A1	03-09-2014
		HK 1198577 A1	30-04-2015
		JP 2015501314 A	15-01-2015
		KR 20140093935 A	29-07-2014
		RU 2014121386 A	10-12-2015
		SG 11201401175S A	26-09-2014
		US 2013296236 A1	07-11-2013
		WO 2013060850 A1	02-05-2013
WO 2012156299 A1	22-11-2012	AU 2012257850 A1	28-11-2013
		CA 2835265 A1	22-11-2012
		CN 103717232 A	09-04-2014
		EP 2707015 A1	19-03-2014
		JP 2014514357 A	19-06-2014
		KR 20140038410 A	28-03-2014
		RU 2013155481 A	20-06-2015
		US 2013005649 A1	03-01-2013
		WO 2012156299 A1	22-11-2012