

TREATMENT OF TYPE 2 DIABETES MELLITUS

Description

- 5 The present invention relates to a pharmaceutical combination, comprising (a) a pharmaceutical formulation comprising (i) lixisenatide or/and a pharmaceutically acceptable salt thereof, and (ii) insulin glargine or/and a pharmaceutically acceptable salt thereof, and (b) an SGLT2 inhibitor, or/and a pharmaceutically acceptable salt thereof.
- 10 Diabetes can be classified into the following general categories (*Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019 - Diabetes Care 2019;42(Suppl. 1):S13–S28*)
1. Type 1 diabetes (due to autoimmune b-cell destruction, usually leading to absolute insulin deficiency)
 - 15 2. Type 2 diabetes (due to a progressive loss of b-cell insulin secretion frequently on the background of insulin resistance)
 3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
 4. Specific types of diabetes due to other causes, e.g., monogenic diabetes
20 syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
- 25 Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or HbA1C criteria

Criteria for the diagnosis of diabetes

- FPG $\geq$ 126 mg/dL (7.0 mmol). Fasting is defined as no caloric intake for at least 8 h.*
- 5 or
- 2-h PG $\geq$ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as describe by the WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.*
- or
- 10 A1C $\geq$ 6.5 % (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
- or
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L).
- 15 *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Type 2 diabetes mellitus is a heterogeneous syndrome characterized by abnormalities in carbohydrate and fat metabolism. The causes of type 2 diabetes are multi-factorial and include both genetic and environmental elements that affect beta-cell function and tissue

20 (muscle, liver, adipose tissue, pancreas) insulin sensitivity (*Acta Clin Belg. 2003 Nov-Dec;58(6):335-41. Pathophysiology of type 2 diabetes. Scheen AJ*). Normal regulation of glucose metabolism is determined by a feedback loop involving the islet β -cell and insulin-sensitive tissues in which tissue sensitivity to insulin determines the magnitude of the β -cell response. When insulin resistance is present, the β -cell maintains normal

25 glucose tolerance by increasing insulin output. It is only when the β -cell is incapable of releasing sufficient insulin in the presence of insulin resistance that glucose levels rise. While β -cell dysfunction has a clear genetic component, environmental changes play a vital role. (*Lancet. 2014 Mar 22; 383(9922): 1068–1083. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present and future Steven E. Kahn, M.B.,*

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People with type 2 diabetes are at increased risk of many complications, which are mainly due to complex and inter-connected mechanisms such as hyperglycemia, insulino-resistance, low-grade inflammation and accelerated athero-genesis. Cardio-cerebrovascular disease are frequently associated to type 2 diabetes and may become life threatening, particularly coronaropathy, stroke and heart failure. Type 2 diabetes must be considered as an independent cardiovascular risk factor. Nephropathy is frequent in type 2 diabetes but has a mixed origin. Now it is the highest cause of end-stage renal disease. Better metabolic and blood pressure control and an improved management of microalbuminuria are able to slowdown the course of the disease. Retinopathy which is paradoxically slightly progressive must however be screened and treated in these rather old patients which are globally at high ophthalmologic risk (*Jean-Louis Schlienger Presse Med. 2013; 42: 839–848*).

A particular risk exists for overweight or obese patients suffering from type 2 diabetes mellitus, e.g. patients with a body mass index (BMI) $\geq 30 \text{ kg/m}^2$. 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.

Type 2 diabetes is a progressive disease that often requires stepwise intensification of treatment to maintain good glycemic control. It is also well established that timely treatment of people with type 2 diabetes has a beneficial effect on outcomes, so tight glycemic control is advocated to reduce the risk of development or progression of micro or macrovascular complications (*Khunti, Diabetes care, 2013*)

Progression occurs despite long-term use of standard-of-care oral antidiabetic therapy . Even with the use of multiple oral antidiabetic drugs (OADs), the majority of patients will eventually require the addition of insulin to achieve and maintain HbA1c targets (*Khunti as above; Levin PA, Wei W, Zhou S, Xie L, Baser O. Outcomes and treatment patterns of adding a third agent to 2 OADs in patients with type 2 diabetes. J Manag Care Spec Pharm. 2014 May;20(5):501-12.*).

Patients with T2DM who are inadequately controlled, generally progress stepwise from monotherapy to dual or triple therapy with oral antidiabetic drugs before initiating injectable therapies.

5 Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are preferred initial injectable therapy in most patients inadequately controlled on oral therapy, with individualized options for incorporation of basal insulin therapy as required.

Multiple studies have demonstrated the effectiveness of combining a GLP-1 RA with basal insulin as separate injectable therapies administered sequentially (*Maiorino MI, Chiodini P, Bellastella G, et al. Free and fixed-ratio combinations of basal insulin and*
10 *GLP-1 receptor agonists versus basal insulin intensification in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab* 2018;20:2309-2313; *Castellana M, Cignarelli A, Brescia F, Laviola L, Giorgino F. GLP-1 receptor agonist added to insulin versus basal-plus or basal-bolus insulin therapy*
15 *in type 2 diabetes: a systematic review and meta-analysis. Diabetes Metab Res Rev* 2019;35:e3082). Fixed-ratio combinations (FRCs) of basal insulin plus a GLP-1 RA represent a further advance to facilitate management, with one single injection offering concomitant administration of two effective injectable therapies with complementary modes of action to treat type 2 diabetes.

20 The compound desPro³⁶Exendin-4(1-39)-Lys₆-NH₂ (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-NH₂

SEQ ID NO: 2: exendin-4 or exenatide (39 amino acids)

25 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-NH₂

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.

- 5 Lixisenatide is also termed des-38-proline-exendin-4(*Heloderma suspectum*)-(1-39)-peptidylpenta-L-lysyl-L-lysineamide (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.

- 10 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. 100 U of insulin glargine
15 correspond to 3.6378 mg of insulin glargine.

- Combination formulations of lixisenatide and insulin glargine are disclosed in WO 2014/202483. These formulations contain a fixed-dose ratio of 100 U/mL of insulin glargine and 50 µg/mL of lixisenatide, or 100 U/mL of insulin glargine and 33 µg/mL of lixisenatide. These formulations are marketed under the tradename "Soliqua" or
20 "Suliqua".

Insulin doses used in Japan are generally lower than those used in Caucasian patients mainly due to lower body mass index (BMI) and insulin resistance of Japanese patients (Møller et al., Diabetes Care. 2014;37(3):796-804).

- Lixisenatide is approved to be used at the same maintenance dose of 20 µg once daily in
25 the EU, the US and Japan.

Lixisenatide pharmacokinetics (PK) and pharmacodynamics in Caucasian and Japanese patients was assessed in the Phase 1 study PDY6797 (Seino et al., Diabetes Obes

Metab. 2014;16(8):739-47). Similarity in terms of safety and tolerability between Caucasian and Japanese patients was shown, with a highly overlapping PK profile between the 2 ethnicities. In addition, optimal efficacy with regard to change in postprandial glucose control was observed at the dose level of 20 µg of lixisenatide for both, Caucasian and Japanese patients.

Metformin is the international non-proprietary 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, includes pharmaceutically acceptable salts thereof. The person skilled in the art knows suitable pharmaceutically acceptable salts of metformin.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have a mechanism of action, which is independent of insulin secretion and insulin action. By inhibiting SGLT2 in the renal proximal tubule, they reduce renal glucose reabsorption, causing urinary glucose excretion and thereby lower plasma glucose. This unique mechanism of action, in addition to lowering plasma glucose, corrects a number of metabolic and hemodynamic abnormalities that are risk factors for cardiovascular diseases (Abdul-Ghani MA, *et al.*, Endocr Rev 2011;32:515–531, Abdul-Ghani MA, *et al.*, Diabetes Care 2016;39:717–725). Urinary glucose loss produces negative caloric balance, resulting in weight loss. SGLT2 inhibition decreases sodium reabsorption in the proximal tubule and exerts diuretic/natriuretic effects (Lambers *et al.*, Diabetes Obes Metab 2013; 15:853–862). SGLT2 inhibition also promotes urinary sodium excretion by causing osmotic diuresis. This natriuretic effect, combined with the more long-term reduction in body weight, contributes, in part, to decreases in systolic/ diastolic blood pressure (Abdul-Ghani *et al.*, Am J Physiol Renal Physiol 2015;309:F889–F900).

SGLT2 inhibitors are usually administered orally. However, control of type 2 diabetes mellitus in obese patients by SGLT2 inhibitors may be insufficient. Thus, in these patients, additional measures for controlling type 2 diabetes mellitus may be required.

5 An SGLT2 inhibitor alone may be insufficient to achieve adequate glycemic control. Also an SGLT2 inhibitor, combined with a second antidiabetic, such as metformin or/and a GLP-1 receptor agonist, may be insufficient. Therefore there is a need of a suitable treatment regimen in these patients. The problem of the invention can be seen in the provision of a suitable treatment regimen in these patients.

10 The addition of a second or third anti-diabetic poses the problem that undesired side effects may occur.

In the Examples of the invention, it is demonstrated that in type 2 diabetes patients, receiving an SGLT2 inhibitor, being insufficient to achieve adequate glycemic control, the addition of a fixed-dose ratio formulation of insulin glargine and lixisenatide can improve glycemic control, with an improved side effect profile.

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A first aspect of the present invention is a pharmaceutical combination, comprising

(a) a pharmaceutical formulation comprising

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

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

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and

(b) an SGLT2 inhibitor, or/and a pharmaceutically acceptable salt thereof.

In the present invention, it has been found that the combination of a fixed-dose ratio formulation of lixisenatide and insulin glargine, combined with an SGLT-2 inhibitor, is efficacious and safe in view of a fixed-dose ratio formulation of lixisenatide and insulin glargine not combined with an SGLT2 inhibitor. In the trials described herein, in total 119 type 2 diabetes mellitus patients received an insulin glargine/lixisenatide fixed ratio combination (FRC) and also received an SGLT2 inhibitor.

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As insulin doses used in Japan are generally lower than those used in Caucasian patients mainly due to lower body mass index (BMI) and insulin resistance of Japanese patients (Møller et al., Diabetes Care. 2014;37(3):796-804), in the Examples of the invention, different fixed ratios of the combination are used. In Examples 1 and 4, including patients of 9 countries (Canada, Estonia, Germany, Israel, Italy, Romania, Slovakia, Spain, United States), being considered as "Caucasian" patients, fixed-dose ratio formulations of 2 units insulin glargine U100 (i.e. 100 U/ml) per 1 µg lixisenatide and 3 units insulin glargine U100 per 1 µg lixisenatide are used. In Examples 2, 3, 5 and 6, including Japanese patients, a fixed-dose ratio formulation comprising 1 unit insulin glargine U100 per 1 µg lixisenatide is used. These formulations offer an appropriate dose range, 10 to 60 units in the Examples 1 and 4, and 5 to 20 units in Examples 2, 3, 5 and 6, covering the need of the vast majority of patients in each of the two populations.

Example 1 relates to a study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with Type 2 Diabetes inadequately controlled on GLP-1 receptor agonist and metformin (alone or with pioglitazone and/or SGLT2 inhibitors), followed by a fixed ratio combination single-arm 26-week extension period (Study EFC 13794).

In Example 1, the investigational treatment included a fixed dose ratio formulation comprising 100 U/mL of insulin glargine and 50 µg/mL of lixisenatide, or comprising 100 U/mL of insulin glargine and 33 µg/mL of lixisenatide, on top of metformin with or without the SGLT2 inhibitor. The investigational treatment was compared with the continuation of the GLP-1 receptor agonist as active comparator, on top of metformin with or without an SGLT2 inhibitor.

Example 4 summarizes a sub-group analysis of the data of example 1, comparing patients receiving an SGLT2 inhibitor with patients not receiving an SGLT2 inhibitor. Type 2 diabetes patients were included receiving metformin, a GLP-1 receptor agonist selected from liraglutide, exenatide, an exenatide extended release formulation, albiglutide and dulaglutide, with or without an SGLT2 inhibitor. An improvement was

observed in efficacy results (change from baseline to Week 26 in glycated hemoglobin [HbA1c], fasting plasma glucose [FPG] and 2-hour postprandial plasma glucose [PPG]) in both treatment groups.

- 5 According to Example 4, in patients receiving an SGLT2 inhibitor, the effect of the fixed-ratio formulation was larger than in the comparative treatment, continuing GLP-1 RA, compared with the patient group not receiving an SGLT2 inhibitor.

10 In patients receiving an SGLT2 inhibitor, after 26 weeks improvement in HbA1c was 0.88 % in view of the active comparator, compared with 0.61 % in patients not receiving an SGLT2 inhibitor (Table 3 of Example 4).

15 In patients receiving an SGLT2 inhibitor, after 26 weeks, improvement in fasting plasma glucose was 2.06 mmol/L in view of the active comparator, compared with 1.64 mmol/L in patients not receiving an SGLT2 inhibitor (Table 4 of Example 4).

20 In patients receiving an SGLT2 inhibitor, after 26 weeks, improvement in 2 hour postprandial glucose was 3.26 mmol/L in view of the active comparator, compared with 2.81 mmol/L in patients not receiving an SGLT2 inhibitor (Table 5 of Example 4).

In Example 4 (Table 8) documented symptomatic hypoglycemia (plasma glucose ≤ 3.9 mmol/L [≤ 70 mg/dL]) was reported less frequently in the FRC group using SGLT2i versus non-users (0.72 events per patient year for SGLT2i users versus 1.62 for non-users).

25 In conclusion, Example 4 demonstrates that in patients, using an SGLT2 inhibitor in combination with a fixed-dose ratio formulation of insulin glargine and lixisenatide, an improved glycemic control and an improved side effect profile can be achieved, compared with patients not using an SGLT2 inhibitor.

30 Examples 2 and 3 refer to clinical trials in Japanese patients, receiving a fixed dose ratio formulation comprising 100 U/mL of insulin glargine and 100 μ g/mL of lixisenatide.

Example 2 relates to a study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed-ratio combination to lixisenatide in combination with oral antidiabetic drugs in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs, with a 26-week safety extension period.

Example 3 relates to a study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed-ratio combination to insulin glargine in combination with oral antidiabetic drugs in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs.

In Examples 2 and 3, one or two of the following oral antidiabetic drugs was allowed to be used as background therapy during the study: biguanide (for example metformin), thiazolidinedione (TZD), alpha-glucosidase inhibitor (alpha-GI), SGLT2 inhibitor, glinide, and sulfonylurea (SU).

Example 5 summarizes a sub-group analysis of the data of example 2, comparing patient receiving an SGLT2 inhibitor with patients not receiving an SGLT2 inhibitor. Efficacy results (change from baseline to Week 26 in HbA1c and FPG) in both treatment groups were generally similar in SGLT2i users and non-users (Table 3, Table 4 of Example 5).

With regard to common treatment-emergent adverse events (TEAEs) (Table 6 of Example 5), TEAEs in the gastrointestinal disorder System Organ Class (SOC) were reported less frequently in the FRC treatment group in SGLT2i users when compared to the SGLT2i non-users (17.6% versus 32.3%, respectively). Similarly, documented symptomatic hypoglycemia (plasma glucose ≤ 3.9 mmol/L [≤ 70 mg/dL]) in the FRC group was reported less frequently in SGLT2i users compared to non-users (number of events per patient year: 0.18 and 1.14, respectively) (Table 7 of Example 5).

Example 6 summarizes a sub-group analysis of the data of example 3, comparing patient receiving an SGLT2 inhibitor with patients not receiving an SGLT2 inhibitor. Efficacy

results (change from baseline to Week 26 in HbA1c, FPG and 2-hour PPG) in both treatment groups were generally similar in SGLT2i users and non-users (Table 3, Table 4, Table 5 of Example 6). There was no indication of a decreased efficacy of the FRC in the SGLT2i user subgroup.

- 5 With regard to common TEAEs (Table 7 of Example 6), TEAEs in the gastrointestinal System Organ Class (SOC) were also reported numerically less frequently in the FRC group in SGLT2i users when compared to SGLT2i non-users (22.0% versus 27.4%, respectively). Documented symptomatic hypoglycemia (plasma glucose ≤ 3.9 mmol/L) was reported in similar proportions of SGLT2i users and non-users (Table 8 of Example 6).
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In conclusion, Examples 5 and 6 demonstrate that in patients, using an SGLT2 inhibitor in combination with a fixed-dose ratio formulation of insulin glargine and lixisenatide, an improved side effect profile can be achieved, compared with patients not using an SGLT2 inhibitor.

- 15 „SGLT2 inhibitor”, as used herein, includes pharmaceutically acceptable salts thereof. The person skilled in the art knows suitable pharmaceutically acceptable salts of SGLT2 inhibitors. „SGLT2 inhibitor” are also termed herein as „SGLT-2 inhibitor” or „SGLT2i”.

- In the present invention, the SGLT2 inhibitor can be selected from the group consisting of empagliflozin, canagliflozin, dapagliflozin and ertugliflozin. For example, the SGLT2 inhibitor can be selected from empagliflozin, canagliflozin and dapagliflozin.
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- The skilled person knows suitable doses of the SGLT2 inhibitor to be administered. In the combination of the present invention, canagliflozin can be administered in a daily dose in the range of 100 to 300 mg. In the combination of the present invention, empagliflozin can be administered in a daily dose in the range of 10 to 25 mg. In the combination of the present invention, dapagliflozin can be administered in a daily dose in the range of 5 to 20 mg.
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In the pharmaceutical combination of the present invention the pharmaceutical formulation (a) can comprise insulin glargine in a concentration of 100 to 500 U/mL. For example, the pharmaceutical formulation (a) can comprise insulin glargine in a concentration of 100 U/mL.

In the pharmaceutical combination of the present invention the pharmaceutical formulation (a) can comprise lixisenatide in a concentration of 20 to 150 µg/ml. For example, the pharmaceutical formulation (a) can comprise lixisenatide in a concentration of 33 µg/mL, 50 µg/mL or 100 µg/mL.

In another aspect of the present invention, the pharmaceutical formulation (a) comprises insulin glargine in a concentration of 100 U/mL and lixisenatide in a concentration of 33 µg/mL, 50 µg/mL or 100 µg/mL.

The pharmaceutical combination of the present invention can be used for the treatment of type 2 diabetes mellitus, for example in a human patient.

The patient may be a Caucasian patient, or may be an Asian patient, for example a Chinese or a Japanese patient.

The formulation (a) can comprise insulin glargine in a concentration of 100 U/mL and lixisenatide in a concentration of 33 µg/mL or 50 µg/mL. This formulation is suitable in the treatment of a Caucasian type 2 diabetes mellitus patient, but the use of this formulation is not limited to this patient group.

The formulation (a) may comprise insulin glargine in a concentration of 100 U/mL and lixisenatide in a concentration of 100 µg/mL. This formulation is suitable in the treatment of an Asian type 2 diabetes mellitus patient, for example a Chinese or a Japanese patient, but the use of this formulation is not limited to this patient group.

As demonstrated by the Examples of the invention, the combination as described herein can be used for improving glycemic control in type 2 diabetes mellitus patients. In the present invention, "improvement of glycemic control" or "glycemic control" for example refers to improvement of the 2 hour postprandial plasma glucose concentration, improvement of fasting plasma glucose concentration, improvement of self-monitored plasma glucose (SMPG) or/and improvement of the HbA_{1c} value.

For example, "improvement of glycemic control" or "glycemic control" can include the improvement of the 2 hour postprandial plasma glucose concentration.

For example, "improvement of glycemic control" or "glycemic control" can include the reduction of the 2 hour postprandial plasma glucose concentration. Reduction means for example that the 2 hour postprandial plasma glucose concentration reaches normoglycemic values or at least approaches these values.

For example, "improvement of glycemic control" or "glycemic control" can include the improvement of the fasting plasma glucose concentration.

For example, improvement of fasting plasma glucose concentration can include the reduction of the fasting plasma glucose concentration. Reduction means for example that the fasting plasma glucose concentration reaches normoglycemic values or at least approaches these values.

For example, "improvement of glycemic control" or "glycemic control" can include the improvement of the self-monitored glucose concentration.

For example, improvement of self-monitored glucose concentration can include the reduction of the self-monitored glucose concentration. Reduction means for example that the self-monitored glucose concentration reaches normoglycemic values or at least approaches these values.

For example, "improvement of glycemic control" or "glycemic control" can include the improvement of the HbA_{1c} value.

For example, improvement of the HbA_{1c} value can include the reduction of the HbA_{1c} value. Reduction of the HbA_{1c} value for example means that the HbA_{1c} value is reduced
5 below 6.5 % or 7 %.

In the present invention, normoglycemic values of fasting plasma glucose are blood glucose concentrations of for example < 5.6 mmol/L.

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

10 In the present invention, normoglycemic HbA_{1c} values are for example <6.5% or <7%.

In another aspect of the present invention, the type 2 diabetes mellitus to be treated is not adequately controlled with an SGLT2 inhibitor alone, for example with empagliflozin, canagliflozin, dapagliflozin or ertugliflozin alone.

As used herein, the term "oral anti-diabetic" includes biguanides, thiazolidinediones, alpha-glucosidase inhibitors, glinides, and sulfonylureas, but is not limited to these
15 compounds. For example the biguanide is metformin.

As used herein, the term "GLP-1 receptor agonist" or "GLP-1 RA" includes lixisenatide, exenatide, dulaglutide, liraglutide, and albiglutide, but is not limited to these compounds. Exenatide can also be administered in an extended-release formulation.

20 In another aspect, the type 2 diabetes mellitus to be treated is not adequately controlled with an SGLT2 inhibitor and an oral anti-diabetic alone, or with an SGLT2 inhibitor and a GLP-1 receptor agonist alone. The oral anti-diabetic may be selected from the group of biguanides, thiazolidinediones, alpha-glucosidase inhibitors, glinides, and sulfonylureas. For example the biguanide is metformin.

In another aspect, the type 2 diabetes mellitus to be treated is not adequately controlled (i) with an SGLT2 inhibitor and metformin alone, or (ii) with an SGLT2 inhibitor and a GLP-1 receptor agonist alone.

5 In yet another aspect, the type 2 diabetes mellitus to be treated is not adequately controlled with the SGLT2 inhibitor, metformin and a GLP-1 receptor agonist alone.

In the present invention, "not adequately controlled" by an anti-diabetic treatment means that this treatment is not sufficient to remove the symptoms of type 2 diabetes mellitus. For example, "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, SMPG, HbA1c value or/and fasting plasma glucose concentration. For example, the anti-diabetic pre-treatment is insufficient to achieve adequate glycemic control.

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In the present invention, "pre-treatment", "treatment prior to administration of the combination of the invention", or treatment of "the patient to be treated according to the invention" relates to the anti-diabetic treatment which the patient receives before receiving the combination of the invention, for example within one, two, three months or within a longer period, before receiving the combination of the invention.

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20 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 of the invention.

Metformin being used in the treatment prior to administration of the combination of the invention can be administered for instance in 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 in 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

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3 months. The daily dose may also be in the range of 500 to 3000 mg, for example 1000 to 2600 mg.

The GLP-1 receptor agonist being used in the treatment prior to administration of the combination of the invention can be selected from lixisenatide, exenatide, dulaglutide, liraglutide, and albiglutide. Exenatide can also be administered in an extended-release formulation.

For example, the GLP-1 receptor agonist being used in the treatment prior to administration of the combination of the invention can be selected from lixisenatide, exenatide, dulaglutide, and liraglutide.

Formulations comprising a GLP-1 receptor agonist, such as selected from lixisenatide, exenatide, dulaglutide, liraglutide and albiglutide are known to the skilled person.

Typical doses of GLP-1 receptor agonists are known to the skilled person. In the present invention, the daily dose of exenatide can be in the range of 10 - 20 µg. The weekly dose of exenatide in an extended-release formulation can be 2 mg. The daily dose of dulaglutide can be in the range of 0.75 - 1.5 mg. The daily dose of liraglutide can be in the range of 1.2 - 1.8 mg. The daily dose of albiglutide can be in the range of 30 to 50 mg. The daily dose of lixisenatide can be in the range of 10 - 20 µg.

A typical daily dose of insulin glargine, to be administered with the pharmaceutical formulation (a) of the present invention, is 5 to 60 U, and the corresponding dose of lixisenatide. For example, in a formulation comprising 100 U/mL of insulin glargine and 50 µg/mL of lixisenatide, this dosage range corresponds to a daily dose of lixisenatide of 2.5 to 30 µg. For example, in a formulation comprising 100 U/mL of insulin glargine and 33 µg/mL of lixisenatide, this dosage range corresponds to a daily dose of lixisenatide of about 1.6 to 20 µg.

For example, a dose of 10 to 60 U can be administered. This dosage range is suitable in the treatment of a Caucasian type 2 diabetes mellitus patient, but the use of this dosage is not limited to this patient group. For example, in a formulation comprising 100 U/mL of insulin glargine and 50 µg/mL of lixisenatide, this dosage range corresponds to a daily
5 dose of lixisenatide of 5 to 30 µg. For example, in a formulation comprising 100 U/mL of insulin glargine and 33 µg/mL of lixisenatide, this dosage range corresponds to a daily dose of lixisenatide of about 3.3 to 20 µg.

For example, a dose of 5 to 20 U can be administered. This dosage range is suitable in the treatment of an Asian type 2 diabetes mellitus patient, for example a Japanese or
10 Chinese patient, but the use of this dosage is not limited to this patient group. For example, in a formulation comprising 100 U/mL of insulin glargine and 100 µg/mL of lixisenatide, this dosage range corresponds to a daily dose of lixisenatide of 5 to 20 µg.

The pre-treatment, being insufficient to adequately control the type 2 diabetes, as
15 described herein, may also include the treatment with pioglitazone. Formulations comprising pioglitazone being used in the treatment prior to administration of the combination of the invention are known to the skilled person.

In the present invention, the daily dose of pioglitazone can be in the range of 15 to 45
20 mg, for example 30 mg.

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/m² (Caucasian patient) or at least 25 kg/m²
25 (Asian patient, for example a Chinese or a Japanese patient).

In the present invention, an obese type 2 diabetes mellitus patient may have a body mass index of at least 30 kg/m² at least 31 kg/m² or at least 32 kg/m², which for example is a Caucasian patient. If the patient is an Asian patient, for example a Chinese or a Japanese patient, the patient may have a body mass index of at least 25 kg/m² or at

least 26 kg/m². 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.

- 5 In the present invention, the type 2 diabetes mellitus patient may have a HbA1c value in the range of 7 % to 9%, in the range of 7.5 % to 9.5 %, or in the range of 7.5 % to 10 %. The type 2 diabetes mellitus patient may have a HbA1c of at least 7.5 %, at least 7.8 %, or at least 8%. These HbA1c values exceed normoglycemic values, indicating that the type 2 diabetes mellitus is not adequately controlled if treated with an antidiabetic compound.
- 10

Prior to the onset of therapy with the combination according to the present invention, the patient may have a HbA1c as described herein, for example of at least 7.5 %, at least 7.8 %, or at least 8% when treated with

- (a) an SGLT2 inhibitor alone,
- 15 (b) an SGLT2 inhibitor in combination with an oral antidiabetic, as described herein,
- (c) an SGLT2 inhibitor in combination with metformin, or
- (d) an SGLT2 inhibitor in combination with metformin and a GLP-1 receptor agonist, as described herein.

- The oral anti-diabetic treatment may be selected from the group of biguanides, thiazolidinediones, alpha-glucosidase inhibitors, glinides, and sulfonylureas. For example
- 20 the biguanide is metformin, as described herein. The GLP-1 receptor agonist may be selected from liraglutide, lixisenatide, exenatide, an exenatide extended release formulation, albiglutide and dulaglutide, as described herein.

- The type 2 diabetes mellitus patient to be treated according to the invention may have a
- 25 fasting plasma glucose concentration of at least 8 mmol/L, at least 8.5 mmol/L, or at least 9 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.

Prior to the onset of therapy with the combination according to the present invention, the patient may have a fasting plasma glucose of HbA1c of at least 8 mmol/L, at least 8.5 mmol/L, or at least 9 mmol/L when treated with

- (a) an SGLT2 inhibitor alone,
- 5 (b) an SGLT2 inhibitor in combination with an oral antidiabetic, as described herein,
- (c) an SGLT2 inhibitor in combination with metformin, or
- (d) an SGLT2 inhibitor in combination with metformin and a GLP-1 receptor agonist, as described herein.

The oral anti-diabetic treatment may be selected from the group of biguanides, thiazolidinediones, alpha-glucosidase inhibitors, glinides, and sulfonylureas. For
10 example, the biguanide is metformin. The GLP-1 receptor agonist may be selected from liraglutide, lixisenatide, exenatide, an exenatide extended release formulation, albiglutide and dulaglutide, as described herein.

For example, in the patient to be treated according to the present invention, the type 2
15 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.

"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 for example average plasma
20 glucose concentrations including fasting and postprandial conditions.

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

25 "7-point Self Monitored Plasma Glucose" for example refers to the measurement of plasma glucose seven times a day and calculation of the average plasma glucose concentration therefrom. For example, 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, for example before insulin glargine or/and lixisenatide
5 injection and optional intake of metformin.

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. These plasma glucose concentrations exceed normoglycemic concentrations, indicating that the type 2 diabetes mellitus is not adequately controlled if treated with an
10 antidiabetic compound.

"Postprandial" is a term that is well known to a person skilled in the art of diabetology. The term "postprandial" describes for example 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
15 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).

As disclosed herein the patient can be an Asian patient, for example a Chinese or a
20 Japanese patient. For example, the Asian patient, for example a Chinese or a Japanese patient, may be obese. The Asian patient, for example a Chinese or a Japanese patient may have a body mass index of at least 25 kg/m² or at least 26 kg/m². The Asian patient, for example a Chinese or a Japanese patient may be obese prior to the onset of therapy with the combination according to the present invention.

The formulation (a) of the present invention may comprise insulin glargine in a concentration of 100 U/mL and lixisenatide in a concentration of 100 µg/mL, when used in an Asian patient, for example a Chinese or a Japanese patient.

5 In another aspect of the invention, in the Asian patient, for example a Chinese or a Japanese patient, the type 2 diabetes mellitus to be treated is not adequately controlled with an SGLT2 inhibitor and an oral anti-diabetic alone. The oral anti-diabetic may be selected from the group of biguanides, thiazolidinediones, alpha-glucosidase inhibitors, glinides, and sulfonylureas. For example the biguanide is metformin.

10 In the present invention, metformin can be administered according to commonly known administration protocols of metformin in accordance with the terms of marketing authorization. The skilled person knows suitable dosage forms. For example, metformin can be administered once daily, twice daily or three times a day. For example, the metformin dose applied before the onset of the therapy as disclosed herein is continued with the treatment of the invention, as disclosed herein.

15 In the present invention, metformin may be administered orally. 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.

20 In the present invention, the SGLT-2 inhibitor can be administered according to commonly known administration protocols of the SGLT-2 inhibitor in accordance with the terms of marketing authorization. The skilled person knows suitable dosage forms. For example, the SGLT-2 inhibitor can be administered once daily, twice daily or three times a day. For example, the SGLT-2 inhibitor dose applied before the onset of the therapy as disclosed herein is continued with the treatment of the invention, as disclosed herein.

25 In the present invention, the SGLT-2 inhibitor may be administered orally. For oral administration, the SGLT-2 inhibitor may be formulated in a solid dosage form, such as a

tablet or pill. The SGLT-2 inhibitor may be formulated with suitable pharmaceutically acceptable carriers, adjuvants, or/and auxiliary substances.

The pharmaceutical combination of the invention allows a simultaneous, separate or sequential administration of (a) the pharmaceutical formulation comprising lixisenatide
5 or/and a pharmaceutically acceptable salt thereof and insulin glargine or/and a pharmaceutically acceptable salt thereof, and (b) of the SGLT2 inhibitor or/and a pharmaceutically acceptable salt thereof and, optionally, (c) of metformin or/and a pharmaceutically acceptable salt thereof.

In the present invention "separate administration" means that the pharmaceutical
10 combination according to the invention may be administered in separate pharmaceutical formulations, wherein one pharmaceutical formulation (a) comprises lixisenatide or/and a pharmaceutically acceptable salt thereof, and insulin glargine or/and a pharmaceutically acceptable salt thereof, and the second pharmaceutical formulation (b) comprises an SGLT2 inhibitor, or/and a pharmaceutically acceptable salt thereof. Optionally, a third
15 pharmaceutical formulation (c) comprising metformin, or/and a pharmaceutically acceptable salt thereof, may be administered.

The pharmaceutical formulations can be administered simultaneously or successively in any sequence. The invention thus relates, for example, to a pharmaceutical combination comprising an injectable pharmaceutical formulation comprising lixisenatide or/and a
20 pharmaceutically acceptable salt thereof and insulin glargine or/and a pharmaceutically acceptable salt thereof, and an oral pharmaceutical formulation comprising an SGLT2 inhibitor, or/and a pharmaceutically acceptable salt thereof, and optionally an oral pharmaceutical formulation comprising metformin or/and a pharmaceutically acceptable salt thereof by simultaneous, separate or sequential administration, in particular for use
25 in the treatment of a type 2 diabetes mellitus patient.

In the present invention, simultaneous administration may include administration of the formulations of the invention at the same time, or within a time interval necessary to administer the compositions of the invention, for example within 5 min, 10 min, or 15 min.

In the present invention, sequential administration may include administration of the formulations of the invention at intervals of at least 15 min, at least 1 h, or at least 2 h, or at intervals of up to 3 h. If optionally a formulation comprising metformin or/and a pharmaceutically acceptable salt thereof, is administered, the intervals between administration of the formulations may be selected independently. Any sequence of administration may be selected. For example, administration can start with (a) the pharmaceutical formulation comprising lixisenatide or/and a pharmaceutically acceptable salt thereof and insulin glargine or/and a pharmaceutically acceptable salt thereof, and can continue with the formulation (b) comprising the SGLT2 inhibitor or/and a pharmaceutically acceptable salt thereof, or vice versa. If optionally a formulation (c) comprising metformin or/and a pharmaceutically acceptable salt thereof, is administered, this formulation may be administered before, in between or after formulations (a) and (b). For example, administration may start with the formulation (c) comprising metformin or/and the pharmaceutically acceptable salt thereof, and may continue with (a) the pharmaceutical formulation comprising lixisenatide or/and a pharmaceutically acceptable salt thereof and insulin glargine or/and a pharmaceutically acceptable salt thereof, and then may continue with the formulation (b) comprising the SGLT2 inhibitor or/and a pharmaceutically acceptable salt thereof, or vice versa.

As disclosed herein the formulation comprising lixisenatide or/and a pharmaceutically acceptable salt thereof and insulin glargine or/and a pharmaceutically acceptable salt thereof, may be administered by one injection per day. If, for example, the oral formulation comprising the SGLT2 inhibitor or/and a pharmaceutically acceptable salt thereof, is administered more than once daily, for example twice daily or three times daily, one of the doses can be administered simultaneously with the formulation comprising lixisenatide or/and a pharmaceutically acceptable salt thereof and insulin glargine or/and a pharmaceutically acceptable salt thereof. If, for example, the optional oral formulation comprising metformin or/and a pharmaceutically acceptable salt thereof, is administered more than once daily, for example twice daily or three times daily, one of the doses can be administered simultaneously with the formulation comprising

lixisenatide or/and a pharmaceutically acceptable salt thereof and insulin glargine or/and a pharmaceutically acceptable salt thereof.

In the present invention, the pharmaceutical combination, as described herein, may be administered in an add-on therapy.

5 In the present invention, the terms "add-on", "add-on treatment" and "add-on therapy" relate to treatment according to the present invention, wherein the pre-treatment with at least one anti-diabetic is continued. "Add-on", "add-on treatment" and "add-on therapy" for example mean that the dose of the at least one anti-diabetic administered before the onset of the treatment according to the present invention, as disclosed herein, can be
10 continued in the treatment of the present invention. If the pre-treatment includes the administration of an SGLT2 inhibitor, in an add-on therapy, the treatment with the SGLT2 inhibitor is continued, for example with the same dose. If necessary, the dose or the doses of one or more of the at least one anti-diabetic administered in the pre-treatment regimen can be adapted.

15 In the present invention, lixisenatide, as used herein, includes pharmaceutically acceptable salts thereof. The person skilled in the art knows suitable pharmaceutically acceptable salts of lixisenatide. An exemplary pharmaceutically acceptable salt of lixisenatide employed in the present invention is the acetate salt of lixisenatide.

In the present invention, insulin glargine, as used herein includes pharmaceutically
20 acceptable salts thereof. The person skilled in the art knows suitable pharmaceutically acceptable salts of insulin glargine.

The formulation (a), as described herein, may be provided as a liquid composition, for example as an aqueous formulation.

The formulation (a), as described herein, can contain a preservative (e.g. phenol, m-
25 cresol, p-cresol, a paraben), an isotonic agent (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.

The formulation (a), as described herein, may comprise a buffer substance. Buffer substances, such as, for example, phosphate, acetate, citrate, arginine, glycylglycine or
5 TRIS (i.e. 2-amino-2-hydroxymethyl-1,3-propanediol) buffer and corresponding salts, can be present in a concentration of 5 – 250 mM, for example 10 – 100 mM. Further excipients can be, inter alia, salts or arginine.

The formulation (a), as described herein, may comprise a surfactant, for example, a non-ionic surfactant. For example, the surfactant can be a pharmaceutically customary
10 surfactants such as, for example: partial and fatty acid esters and ethers of polyhydric alcohols such as of glycerol, sorbitol and the like (Span[®], Tween[®], for example Tween[®] 20 and Tween[®] 80, Myrj[®], Brij[®]), Cremophor[®] or poloxamers. The surfactants are present in the pharmaceutical formulation (a) in a concentration of 5 - 200 µg/ml, for example of 5 – 120 µg/ml or 20 – 75 µg/ml.

15 The formulation (a), as described herein, may comprise a tonicity agent. A suitable tonicity agent may be selected from glycerol, dextrose, lactose, sorbitol, mannitol, glucose, NaCl, calcium or magnesium containing compounds such as CaCl₂. 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.

20 An exemplary tonicity agent is glycerol. Glycerol 85% can be present in an amount of 10-30 mg/mL, for example 20 mg/mL.

The pharmaceutical formulation (a), as described herein, may comprise methionine in a concentration selected from 0.3 mg/mL to 20 mg/mL, for example from 1 mg/ml to 5 mg/ml. An exemplary concentration of methionine is 3 mg/mL. For example, the liquid
25 composition comprises L-methionine.

The pharmaceutical formulation (a), as described herein, may comprise a suitable preservative. A suitable preservative may be selected from phenol, m-cresol, benzyl alcohol and p-hydroxybenzoic acid ester. An exemplary preservative is m-cresol. The preservative, for example m-cresol, may be present in a concentration of up to 3 mg/mL, for example 1-3 mg/mL. For example, the concentration is 2.7 mg/mL.

The pharmaceutical formulation (a), as described herein, may comprise zinc. The zinc concentration may be in the range of 0 - 1000 µg/mL, for example 20 – 400 µg/mL zinc. An exemplary zinc concentration is 30 µg/mL. The zinc may be present in form of zinc chloride, but the salt is not limited to be zinc chloride.

10 The pH of the pharmaceutical formulation (a), as described herein, can be adjusted by hydrochloric acid or/and sodium hydroxide. The pH can be in the range of pH 1 – 6.8, pH 3.5 – 6.8, or pH 3.5 – 4.5. For example, the pH is in the range of 4.0-4.5. Exemplary pH values are 4.0 and 4.5.

15 In the present invention, the pharmaceutical formulation (a) may be administered to a type 2 diabetes mellitus patient in need thereof, in an amount sufficient to induce a therapeutic effect.

The pharmaceutical formulation (a), as described herein, may be administered parenterally. For example the pharmaceutical formulation (a), as described herein, may be administered by injection, such as, for example, by subcutaneous injection.

20 The pharmaceutical formulation (a) as described herein, may be an injectable formulation. Suitable injection devices, for instance the so-called "pens" comprising a cartridge comprising the formulation, and an injection needle, are known.

The formulation (a) may be administered by one injection per day. For example, the formulation (a) may be administered before breakfast, such as about 30 min before breakfast.

For example, 1 mL of the pharmaceutical formulation (a), comprising 50 µg/mL of lixisenatide, can contain:

Ingredient	Quantity	Standard
<i>Active ingredient</i>		
Insulin glargine	3.6378 mg [100 U]	Ph. Eur., USP
Lixisenatide	50 µg	
<i>Excipients</i>		
Glycerol (85%)	20.0 mg	Ph. Eur.
Methionine (L-methionine)	3.0 mg	Ph. Eur., USP
Metacresol (m-cresol)	2.7 mg	Ph. Eur., USP
Zinc chloride	0.0626 mg, corresponds to 0.03 mg of zinc	Ph. Eur., USP
Hydrochloric acid	Up to pH = 4.5	Ph. Eur., USP-NF
Sodium hydroxide	Up to pH = 4.5	Ph. Eur., USP-NF
Water for injection	q.s. to 1.0 mL	Ph. Eur., USP

This formulation is suitable for subcutaneous injection. In this formulation, the amount of zinc chloride reflects the total amount in the drug composition, including zinc (calculated as zinc chloride) from pharmaceutical substance insulin glargine and zinc chloride introduced during manufacture of the drug product.

For example, 1 mL of the pharmaceutical formulation (a), comprising 33 µg/mL of lixisenatide, can contain:

Ingredient	Quantity	Standard
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<i>Active ingredient</i>		
Insulin glargine	3.6378 mg [100 U]	Ph. Eur., USP
Lixisenatide	33 µg	
<i>Excipients</i>		
Glycerol (85%)	20.0 mg	Ph. Eur.
Methionine (L-methionine)	3.0 mg	Ph. Eur., USP
Metacresol (m-cresol)	2.7 mg	Ph. Eur., USP
Zinc chloride	0.0626 mg, corresponds to 0.03 mg of zinc	Ph. Eur., USP
Hydrochloric acid	Up to pH = 4.5	Ph. Eur., USP-NF
Sodium hydroxide	Up to pH = 4.5	Ph. Eur., USP-NF
Water for injection	q.s. to 1.0 mL	Ph. Eur., USP

This formulation is suitable for subcutaneous injection. In this formulation, the amount of zinc chloride reflects the total amount in the drug composition, including zinc (calculated as zinc chloride) from pharmaceutical substance insulin glargine and zinc chloride introduced during manufacture of the drug product.

- 5 The pharmaceutical formulation (a), comprising 100 µg/mL of lixisenatide and 100 U/ml of insulin glargine, can contain the same excipients in the same concentrations of the formulations comprising 50 µg/mL of lixisenatide and 100 U/ml of insulin glargine, or 33 µg/mL of lixisenatide and 100 U/ml of insulin glargine.
- 10 Yet another aspect of the present invention relates to the use of a pharmaceutical combination, comprising

- (a) a pharmaceutical formulation comprising
- (i) lixisenatide or/and a pharmaceutically acceptable salt thereof, and
 - (ii) insulin glargine or/and a pharmaceutically acceptable salt thereof,
- and
- 5 (b) an SGLT2 inhibitor, or/and a pharmaceutically acceptable salt thereof,
- in the manufacture of a medicament for the treatment of type 2 diabetes mellitus. The patient may be any patient as described herein. The pharmaceutical formulation (a) may be any pharmaceutical formulation as described herein. The SGLT2 inhibitor (b) may be any SGLT2 inhibitor as described herein.

10

Yet another aspect of the present invention relates to a method of treatment of a type 2 diabetes mellitus patient in need thereof, the method comprising administering a pharmaceutical combination, comprising

- (a) a pharmaceutical formulation comprising
- 15 (i) lixisenatide or/and a pharmaceutically acceptable salt thereof, and
- (ii) insulin glargine or/and a pharmaceutically acceptable salt thereof,
- and
- (b) an SGLT2 inhibitor, or/and a pharmaceutically acceptable salt thereof.
- The patient may be any patient as described herein. The pharmaceutical formulation (a)
- 20 may be any pharmaceutical formulation as described herein. The SGLT2 inhibitor (b) may be any SGLT2 inhibitor as described herein.

The following aspects are also subject of the present invention

25

Item 1. A pharmaceutical combination, comprising

- (a) a pharmaceutical formulation comprising
- (i) lixisenatide or/and a pharmaceutically acceptable salt thereof, and
 - (ii) insulin glargine or/and a pharmaceutically acceptable salt thereof,
- 30 and
- (b) an SGLT2 inhibitor, or/and a pharmaceutically acceptable salt thereof.

- Item 2. The pharmaceutical combination according to item 1, further comprising (c) metformin or/and pharmaceutically acceptable salt thereof.
- 5 Item 3. The pharmaceutical combination according to item 1 or 2, wherein the SGLT2 inhibitor is selected from the group consisting of empagliflozin, canagliflozin, dapagliflozin and ertugliflozin.
- Item 4. The pharmaceutical combination according to any one of the items 1 to 3,
10 wherein the SGLT2 inhibitor is selected from the group consisting of empagliflozin, canagliflozin and dapagliflozin.
- Item 5. The pharmaceutical combination according to any one of the preceding items, wherein the pharmaceutical formulation (a) comprises insulin glargine in a concentration
15 of 100 to 500 U/mL.
- Item 6. The pharmaceutical combination according to any one of the preceding items, wherein the pharmaceutical formulation (a) comprises insulin glargine in a concentration
20 of 100 U/mL.
- Item 7. The pharmaceutical combination according to any one of the preceding items, wherein the pharmaceutical formulation (a) comprises lixisenatide in a concentration of 20 to 150 µg/ml.
- 25 Item 8. The pharmaceutical combination according to any one of the preceding items, wherein the pharmaceutical formulation (a) comprises lixisenatide in a concentration of 33 µg/mL, 50 µg/mL or 100 µg/mL.
- Item 9. The pharmaceutical combination according to any one of the items 1 to 8,
30 wherein the pharmaceutical formulation comprises lixisenatide in a concentration of 33

µg/mL or 50 µg/mL.

Item 10. The pharmaceutical combination according to any one of the items 1 to 8, wherein the pharmaceutical formulation comprises lixisenatide in a concentration of 100
5 µg/mL.

Item 11. The pharmaceutical combination according to any one of the items 1 to 8, wherein the pharmaceutical formulation (a) comprises insulin glargine in a concentration of 100 U/ml, and lixisenatide in a concentration of 33 µg/mL, 50 µg/mL or 100 µg/mL.
10

Item 12. The pharmaceutical combination according to any one of the items 1 to 8 and 11, wherein the pharmaceutical formulation comprises insulin glargine in a concentration of 100 U/ml, and lixisenatide in a concentration of 33 µg/mL or 50 µg/mL.

15 Item 13. The pharmaceutical combination according to any one of the items 1 to 8 and 11, wherein the pharmaceutical formulation comprises insulin glargine in a concentration of 100 U/ml, and lixisenatide in a concentration of 100 µg/mL.

Item 14. The pharmaceutical combination according to any one of the preceding items,
20 for use in the treatment of a type 2 diabetes mellitus patient.

Item 15. The pharmaceutical combination for use according to item 14, wherein the patient is a human patient.

25 Item 16. The pharmaceutical combination for use according to item 14 or 15, wherein the patient is an Asian patient.

Item 17. The pharmaceutical combination for use according to any one of the items 14 to 16, wherein the patient is a Chinese or a Japanese patient.

Item 18. The pharmaceutical combination for use according to item 14 or 15, wherein the patient is a Caucasian patient.

Item 19. The pharmaceutical combination for use according to any one of the items 14-
5 18, wherein the type 2 diabetes mellitus to be treated is not adequately controlled with the SGLT2 inhibitor alone.

Item 20. The pharmaceutical combination for use according to any one of the items 14-
18, wherein the type 2 diabetes mellitus to be treated is not adequately controlled with an
10 SGLT2 inhibitor selected from empagliflozin, canagliflozin, dapagliflozin and ertugliflozin, or from the group consisting of empagliflozin, canagliflozin and dapagliflozin.

Item 21. The pharmaceutical combination for use according to any one of the items 14-
18, wherein the type 2 diabetes mellitus to be treated is not adequately controlled with an
15 SGLT2 inhibitor and an oral anti-diabetic alone.

Item 22. The pharmaceutical combination for use according to item 21, wherein the type
2 diabetes mellitus to be treated is not adequately controlled alone with
(a) an SGLT2 inhibitor selected from the group consisting of empagliflozin,
20 canagliflozin, dapagliflozin and ertugliflozin, or from the group consisting of empagliflozin, canagliflozin and dapagliflozin, and
(b) an oral anti-diabetic selected from the group consisting of biguanides, thiazolidinediones, alpha-glucosidase inhibitors, glinides, and sulfonylureas,
wherein the biguanide can be metformin.

25

Item 23. The pharmaceutical combination for use according to any one of the items 14-
18, wherein the type 2 diabetes mellitus to be treated is not adequately controlled with
the SGLT2 inhibitor and metformin alone, or with an SGLT2 inhibitor and a GLP-1
receptor agonist alone.

30

Item 24. The pharmaceutical combination for use according to item 23, wherein the type

2 diabetes mellitus to be treated is not adequately controlled alone with

- (a) (i) an SGLT2 inhibitor selected from the group consisting of empagliflozin, canagliflozin, dapagliflozin and ertugliflozin, or from the group consisting of empagliflozin, canagliflozin and dapagliflozin, and (ii) metformin, or
- 5 (b) (i) an SGLT2 inhibitor selected from the group consisting of empagliflozin, canagliflozin, dapagliflozin and ertugliflozin, or from the group consisting of empagliflozin, canagliflozin and dapagliflozin, and (ii) a GLP-1 receptor agonist selected from the liraglutide, lixisenatide, exenatide, albiglutide and dulaglutide.

10

Item 25. The pharmaceutical combination for use according to any one of the items 14-18, wherein the type 2 diabetes mellitus to be treated is not adequately controlled with the SGLT2 inhibitor, metformin and a GLP-1 receptor agonist alone.

- 15 Item 26. The pharmaceutical combination for use according to item 25, wherein the type 2 diabetes mellitus to be treated is not adequately controlled alone with

- (a) an SGLT2 inhibitor selected from the group consisting of empagliflozin, canagliflozin, dapagliflozin and ertugliflozin, or from the group consisting of empagliflozin, canagliflozin and dapagliflozin,
- 20 (b) an oral anti-diabetic selected from the group consisting of biguanides, thiazolidinediones, alpha-glucosidase inhibitors, glinides, and sulfonylureas, wherein the biguanide can be metformin, and
- (c) GLP-1 receptor agonist selected from the liraglutide, lixisenatide, exenatide, albiglutide and dulaglutide.

25

Item 27. The pharmaceutical combination for use according to any one of the items 23 to 26, wherein the GLP-1 receptor agonist is selected from lixisenatide, exenatide, dulaglutide, and liraglutide.

- 30 Item 28. The pharmaceutical combination for use according to any one of the items 14-

27, wherein the patient to be treated is obese.

Item 29. The pharmaceutical combination for use according to any one of the items 14-28, wherein the patient has a Body Mass Index (BMI) of at least 30 kg/m², at least 31
5 kg/m² or at least 32 kg/m².

Item 30. The pharmaceutical combination for use according to item 29, wherein the patient is a Caucasian patient.

10 Item 31. The pharmaceutical combination for use according to any one of the items 14 to 28, wherein the patient has a Body Mass Index (BMI) of at least 25 kg/m², or at least 26 kg/m².

Item 32. The pharmaceutical combination for use according to item 31, wherein the
15 patient is an Asian patient, for example a Chinese or a Japanese patient.

Item 33. The pharmaceutical combination for use according to any one of the items 14 to 32, wherein prior to the onset of therapy with the combination according to any one of the items 1 to 8 the patient to be treated has a HbA1c of at least 7.5%.
20

Item 34. The pharmaceutical combination for use according to any one of the items 14 to 33, wherein prior to the onset of therapy with the combination according to any one of the items 1 to 8 the patient to be treated has a fasting plasma glucose concentration of at least 8 mmol/L.

25 The invention is further illustrated by the following examples.

Figure 1 describes the Graphical Study Design:

* Additional titration phone calls-only for FRC arm

** Insulin glargine/lixisenatide fixed ratio combination (FRC) treatment will be initiated with the Peach Pen. The initial daily dose to be administered will be 10 U: this corresponds to an initial associated dose of
 5 insulin glargine 10 U and lixisenatide 5 µg according to the 2/U µg fixed ratio used in the Peach Pen. Afterwards, doses will be individually titrated throughout the study to reach and maintain testing SMPG: 80-100mg/dL(4.4-6.6 mmol/L) avoiding hypoglycemia.

† Liraglutide, exenatide, albiglutide, or dulaglutide is discontinued at visit 3 for patients randomized to the FRC treatment. Any patient treated with a once weekly GLP-1 RA upon entering the study who is
 10 assigned to receive the FRC treatment should not receive their first dose until at least 1 week after their last dose of GLP-1 RA.

Figure 2 describes the plot of mean HbA1c (%) by visit during the 26-week randomized treatment period - mITT population:

S = Screening (Week -2), B = Baseline

15 FRC = Fixed Ratio Combination, GLP-1RA = GLP-1 Receptor Agonist

The plot included all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue medication.

Figure 3 describes the plot of mean fasting plasma glucose (mmol/L[mg/dL]) by visit during the 26-week randomized treatment period - mITT population:

20 S = Screening (Week -2), B = Baseline

FRC = Fixed Ratio Combination, GLP-1 RA = GLP-1 Receptor Agonist

The analysis included all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue medication.

25 **Figure 4** describes the plot of mean 7-point SMPG (mmol/L[mg/dL]) at baseline and Week 26 during the on-treatment period - mITT population:

SMPG = Self-monitored plasma glucose.

FRC = Fixed Ratio Combination, GLP-1 RA=GLP-1 Receptor Agonist

30 The analysis included all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy.

Example 1

5 **A 26-week randomized, open-label, active controlled, parallel-group, study assessing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination in adults with Type 2 Diabetes inadequately controlled on GLP-1 receptor agonist and metformin (alone or with pioglitazone and/or SGLT2 inhibitors), followed by a fixed ratio combination single-arm 26-week extension period (EFC13794)**

1 SYNOPSIS

Study center(s): 111 centers in 9 participating countries (Canada, Estonia, Germany, Israel, Italy, Romania, Slovakia, Spain, United States)
Objectives: Primary Objective: To demonstrate the superiority of the insulin glargine/lixisenatide fixed-ratio combination (FRC) versus GLP-1 receptor agonist (RA) in glycated hemoglobin A1c (HbA1c) change from baseline to Week 26 Secondary Objectives: To assess the effects of FRC in comparison with GLP-1 RA over 26 weeks on: • Percentage of patients reaching HbA1c targets <7% or ≤6.5%. • Fasting plasma glucose (FPG) • 7 point self-monitored plasma glucose (SMPG) profile • Glycemic control in relation to a meal as evaluated by 2 hour postprandial plasma glucose (PPG) and glucose excursion during a standardized meal test. • Body weight. To assess the safety and tolerability in each treatment group. Other Objectives: To assess GLP-1 RA and lixisenatide doses in the FRC group To assess the development of anti-lixisenatide and/or anti-insulin antibodies (FRC group) To assess the total plasma concentration of lixisenatide before and following injection (FRC group)
Methodology: This was an open-label, 1:1 randomized, active-controlled, 2-arm, parallel group, multinational and multicenter Phase 3 study. Patients were stratified by values of HbA1c at screening (<8%, ≥8%) and GLP-1 RA subtype at screening (once/twice daily [QD/BID] formulations, once weekly [QW] formulations). The study comprised 4 periods: • An up to 2 week screening period. • A 26-week open label randomized treatment period. • A 26-week single-arm extension period, only for eligible patients treated with the FRC during the randomization period • A 3-day post-treatment safety follow-up period. There were 2 amendments to the clinical study protocol. The major change in the amendment 1 was to add a single-arm FRC 26-weeks extension period and PK and antibody assessments. The major change in the amendment 2 was to allow enrollment of patients with a background anti-diabetic treatment including a sodium-glucose co-transporter 2(SGLT 2) inhibitor. This key results memo is describing the results for the first 26-week randomized comparative treatment period. The FRC single-arm extension period is still ongoing. Results for the whole study period (including the extension period) will be presented in a separate study report.

Diagnosis and criteria for inclusion: Major Inclusion Criteria: Patients with type 2 diabetes mellitus (T2DM) diagnosed for at least 1 year before the screening visit who have been treated with one of following: - For at least 4 months with stable dose for at least 3 months prior to screening visit with one of the following GLP-1 RAs: liraglutide QD (1.8mg QD or 1.2mg QD, if 1.8mg QD was not well tolerated according to investigator's judgment) or exenatide BID (10µg BID or 5µg BID, if 10µg BID was not well tolerated according to investigator's judgment) - For at least 6 months prior to screening with stable dose of one of following GLP-1 RAs: exenatide extended-release (2mg QW) or albiglutide (50mg QW or 30mg QW, if 50mg QW was not well tolerated according to investigator's judgment) or dulaglutide (1.5mg QW or 0.75mg QW, if 1.5mg QW was not well tolerated according to investigator's judgment) , In combination with metformin with or without pioglitazone, with or without SGLT2 inhibitor, all at stable dose for at least 3 months. Major Exclusion Criteria: under legal age of adulthood; HbA1c <7% or >9%; body mass index (BMI) ≤20 or >40 kg/m²; use of anti-diabetic drugs within 3 months prior to screening visit other than those described in inclusion criteria; previous treatment with insulin in the year prior to screening visit (except for short-term treatment due to intercurrent illness including gestational diabetes) Dose Regimen FRC treatment was self-administered once daily in the hour (0 to 60 minutes) before breakfast. FRC treatment was initiated with the Peach (2U:1µg ratio) Pen at a dose of 10 U (10 U insulin glargine/5µg lixisenatide) and then titrated to reach and maintain a fasting SMPG target between 80 and 100 mg/dL. Patients randomized to the GLP-1 RA group continued the same daily dose and regimen of GLP-1 RA as prior to randomization.
Primary and main secondary key endpoints: Efficacy: <u>Primary efficacy endpoint:</u> - Change in HbA1c from baseline to Week 26. <u>Secondary efficacy endpoints:</u> - Percentage of patients reaching HbA1c <7% or ≤6.5% at Week 26 - Change in FPG from baseline to Week 26 - Change in 7 point SMPG profiles from baseline to Week 26 (each time point and average daily value) - Change in 2 hour PPG and in blood glucose excursion during standardized meal test from baseline to Week 26 - Change in body weight from baseline to Week 26 - Insulin glargine and lixisenatide dose at Week 26 in the FRC group Safety: - Symptomatic hypoglycemia - Adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESI), AEs requiring specific monitoring, safety laboratory values, vital signs, and electrocardiogram (ECG)
Statistical methods: <u>Efficacy analysis:</u> Efficacy analysis was based on the modified Intent-to-treat (mITT) population using efficacy assessment collected during the study, including those obtained after investigational medicinal product (IMP) discontinuation or introduction of rescue therapy. The mITT population consisted of all randomized patients who had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures. <u>Primary efficacy endpoint analysis:</u> The primary efficacy endpoint was analyzed using a mixed-effect model with repeated measures (MMRM) under the missing at random framework. The MMRM model included treatment group (FRC or GLP-1 RA), randomization strata of HbA1c (<8%, ≥8%) at V1 (Week -2), randomization strata of GLP-1 RA subtype (once/twice daily formulations, once weekly formulations) at screening, visit (Week 8, Week 12, Week 18, Week 22 and Week 26), treatment by-visit interaction and world region as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. The adjusted mean change in HbA1c from baseline to Week

26 for each treatment group was estimated in the framework of this model, as well as the between group difference in least square (LS) means and the corresponding 95% confidence interval (CI). The statistical test was 2-sided at the significance level of 5%.

Secondary efficacy endpoint analysis:

Except for 2-hour PPG and glucose excursion, all continuous secondary efficacy endpoints were analyzed using the same MMRM approach with the corresponding baseline value-by-visit interaction as a covariate to compare FRC with GLP-1 RA. Differences between treatment groups and CI were estimated within the framework of MMRM.

2-hour PPG and glucose excursion (for each of which only 1 post-baseline assessment was scheduled) were analyzed using analysis of covariance (ANCOVA) with the missing data at Week 26 imputed by LOCF to compare FRC with GLP-1 RA.

All categorical secondary efficacy endpoints defined were analyzed by a Cochran-Mantel-Haenszel method stratified by the randomization strata. The proportion in each treatment group was provided, as well as the differences in proportions between groups with associated 2-sided 95% CIs.

A step-down testing procedure was applied in order to control the type 1 error. Once the primary endpoint was statistically significant at the 5% 2-sided level, testing was performed according to the following order: percentage of patients reaching HbA1c < 7% at Week 26, FPG, average 7-point SMPG, 2-hour PPG and/or glucose excursion. When an endpoint was not statistically significant at the 5% level, subsequent tests were not performed.

Safety analysis:

Safety analysis was descriptively performed, based on the safety population, defined as all randomized patients who received at least one dose of open-label IMP, regardless of the amount of treatment administered. Patients were analyzed according to the treatment actually received (as treated).

2 GRAPHICAL STUDY DESIGN

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The Graphical Study Design is described in Figure 1.

3 SUMMARY OF RESULTS

Summary:

Population characteristics:

A total of 514 patients were randomized (257 in the FRC group and 257 in the GLP-1 RA group). Demographics and baseline characteristics were balanced between the 2 treatment groups. The median age was 60.0 years, the mean diabetes duration was approximately 11 years and the mean BMI was 32.87 kg/m². The study population was primarily White (94.4%), and 52.5% of the population were male patients. At screening, 59.7% of the patients received a daily GLP-1 RA and 40.3% a weekly one. The most common GLP-1 RAs received were liraglutide (54.5%) and dulaglutide (20.4%) (Table 1, Table 2, Table 3, Table 4).

Efficacy results:

Primary efficacy endpoint:

The primary objective of the study was met as the superiority of FRC compared with unchanged GLP-1 RA on HbA1c change from baseline to Week 26 was demonstrated.

From a similar baseline mean value of approximately 7.8%, the LS mean changes from baseline to Week 26 (MMRM) in HbA1c were -1.02% for the FRC group and -0.38% for the GLP-1 RA group, reaching mean HbA1c levels of 6.74% and 7.41% at Week 26 (MMRM), respectively. Statistical superiority of the FRC over GLP-1 RA was demonstrated (LS mean difference versus GLP-1 RA group = -0.64%; 95% CI: -0.770% to -0.508%; p-value <0.0001) (Table 5, Figure 2). Consistent treatment effects as observed in the primary efficacy analysis could be seen across all subgroups except age ≥75 and Black population (Table 6). The number of patients with age ≥75 and race of Black population was small and therefore the CIs were wide. Baseline factors including type of previous GLP-1 RA treatment had no relevant impact on the between-group differences in the HbA1c change from baseline to Week 26.

Secondary efficacy endpoints:

At Week 26, significantly more patients treated with FRC reached an HbA1c <7% and ≤6.5% compared to those receiving GLP-1 RA: 61.9% versus 25.7% and 40.5% versus 9.9%, respectively. The proportion difference versus GLP-1 RA was 36.05% (95% CI: 28.11% to 43.99%; p-value <0.0001) and 30.61% (95% CI: 23.61% to 37.72%; p-value <0.0001), respectively (Table 7).

Patients treated with FRC had a statistically significantly greater decrease in FPG compared to patients treated with GLP-1 RA. The LS mean change in FPG from baseline to Week 26 (MMRM) was -2.28 mmol/L for the FRC group resulting in a Week 26 mean value of 6.86 mmol/L. LS mean change was -0.60 mmol/L for the GLP-1 RA group with a Week 26 mean value of 8.66 mmol/L. LS mean difference (95% CI) versus GLP-1 RA was -1.67 mmol/L (-2.001 mmol/L to -1.341 mmol/L; p<0.0001) (Table 8, Figure 3).

Patients treated with FRC had a statistically significantly greater decrease in average 7-point SMPG compared to patients treated with GLP-1 RA. The LS mean change from baseline to Week 26 (MMRM) was -1.69 mmol/L for the FRC group resulting in a Week 26 mean value of 7.70 mmol/L. LS mean change was -0.67 mmol/L for the GLP-1 RA group with a Week 26 mean value of 8.79 mmol/L. LS mean difference (95% CI) versus GLP-1 RA was -1.02 mmol/L (-1.325 mmol/L to -0.708 mmol/L; p<0.0001) (Table 9). At Week 26 in the FRC group graphical presentation of the 7-point SMPG profiles showed a marked decrease from baseline in mean plasma glucose values at all time-points. The mean values at all time-points were lower in the FRC group compared to the GLP-1 RA group (Figure 4).

Treatment with FRC significantly improved postprandial glycemic control during a standardized meal test in comparison to GLP-1 RA as shown by the results for the mean change in 2-hour postprandial plasma glucose from baseline to Week 26 (LS mean change was -3.96 and -1.11 mmol/L, respectively; LS mean difference [95% CI] versus GLP-1 RA was -2.85 mmol/L [-3.420 mmol/L to -2.279 mmol/L]; p<0.0001) (Table 10) and mean change in 2-hour glucose excursion from baseline to Week 26 (LS mean change was -1.51 and -0.52 mmol/L, respectively; LS mean difference [95% CI] versus GLP-1 RA was -0.99 mmol/L [-1.468 mmol/L to -0.508 mmol/L]; p<0.0001) (Table 11).

Body weight increased in the FRC group and decreased in the GLP-1 RA group with a LS mean change from baseline to Week 26 of +1.89 kg and -1.14 kg, respectively (LS mean difference was 3.03 kg; 95% CI: 2.417 kg to 3.643 kg). (Table 12).

For the FRC group, the mean daily FRC dose at Week 26 was 43.50 U insulin glargine and 16.55 µg lixisenatide (Table 13 and Table 14).

Safety results:

Overall, the FRC was well tolerated during the 26-week treatment period. The safety profile of the FRC group generally reflected those of its components, and no new or unexpected safety signals were identified. More patients in the FRC group reported treatment-emergent adverse events (TEAEs) compared to the GLP-1 RA group: 163 (63.9%) versus 121 (47.3%) (Table 15). The difference was mainly due to TEAEs reported in the Gastro-intestinal disorders and Metabolism and nutrition disorders System Organ Classes. The most frequently reported TEAEs were nasopharyngitis (9.8% and 9.0%) and nausea (8.6% and 2.3 %) in the FRC and the GLP-1 RA groups, respectively (Table 16).

The overall incidence of gastrointestinal (GI) TEAEs was higher in the FRC group than in the GLP-1 RA group (21.6% versus 10.2%, respectively). The most frequent GI TEAEs were nausea (8.6% and 2.3 %); diarrhea (5.5% and 2.3 %) and vomiting (3.1% and 0.8 %) in the FRC group and the GLP-1 RA group, respectively (Table 16). The overall incidence of metabolism and nutrition disorders TEAEs was higher in the FRC group (5.1% versus 0.4%), with the most frequently reported TEAE being increased appetite (2.4% and 0, respectively). The overall incidence of nervous system disorders was slightly higher in FRC group and the most frequently observed events were dizziness (2.4% and 0.8%, respectively) and headache (3.9% and 2.3%, respectively). However, none of them were related to hypoglycemia according to investigators' answers to routine data queries.

Similar number of Serious TEAEs was reported (10 patients (3.9%) in the FRC group and 9 patients (3.5%) in the GLP-1 RA groups) (Table 17). None of them were assessed as related with IMP except one SAE of hypoglycemic unconsciousness (also reported as severe hypoglycemia, see below) in the FRC group. No death was reported during 26-week randomized treatment period.

A total of 9 patients (3.5%) in the FRC group permanently discontinued treatment due to a TEAE versus none in the GLP-1 RA group. Most of these withdrawals were caused by gastrointestinal adverse events (2.0%, N=5) (Table 18).

Five injection site reaction events were reported in 5 patients (2.7%) in the FRC group and none in the GLP-1 RA groups (Table 19).

Two events (urticaria and asthma) reported in 2 FRC treated patients were adjudicated by the Allergic Reaction Assessment Committee (ARAC) as an allergic reaction not related to study medication (Table 20). No allergic reaction was reported in the GLP-1 RA group.

No pancreatic carcinoma was reported in either treatment group. One FRC treated patient reported a pancreatic TEAE adjudicated by the Pancreatic Safety Assessment Committee (PSAC) as a chronic pancreatitis not related to IMP (Table 21).

No TEAE of increased calcitonin (≥ 20 pg/mL) was reported in the 26-week randomized treatment period.

One female subject in the FRC group experienced pregnancy during treatment period with normal delivery of a healthy baby.

A total of 21 (8.2%) patients in the FRC group and 5 patients (2.0%) in the GLP-1 RA group experienced a device-related event. None was associated with a clinical event (Table 22).

The number of patients with documented (≤ 70 mg/dL) symptomatic hypoglycemia was 27.8% in the FRC group and 2.3% in the GLP-1 RA group with a corresponding number of events per patient-year of 1.54 and 0.08 respectively (Table 23). The number of patients with documented (< 54 mg/dL) symptomatic hypoglycemia was 9.4% in the FRC group and 0.4% in the GLP-1 RA group with a corresponding number of events per patient-year of 0.25 and < 0.01 respectively. One severe hypoglycemia was reported as SAE in the FRC group.

Preliminary Conclusions:

In conclusion, the primary objective of the study was met as the superiority of the FRC compared to GLP-1 RA on HbA1c change from baseline to Week 26 was demonstrated (LS mean treatment difference -0.64%). FRC initiated in patients not well controlled with daily/twice daily or weekly GLP-1 RA and metformin with or without pioglitazone and/or SGLT2 inhibitors, significantly improved HbA1c, allowed more patients to reach HbA1c treatment target, reduced FPG, 2-hour glucose excursions and average 7-point SMPG compared with patients continuing GLP-1 RA.

Overall, the FRC was well tolerated with a safety profile that reflected those of its components. Gastrointestinal events were reported more frequently in the FRC group compared to the GLP-1 RA group. Patients treated with FRC gained more weight and experienced more hypoglycemia versus unchanged GLP-1 RA therapy; these results are consistent with previous findings on GLP-1 RA intensification with insulin-containing therapy. Moreover, the number and event rate of hypoglycemia was low in both groups. One severe hypoglycemia was reported during the 26-week treatment period in the FRC group.

4 Results

4.1 STUDY PATIENTS

4.1.1 Patient accountability

Table 1- Analysis populations

	Fixed Ratio Combination	GLP-1 Receptor Agonist	All
Randomized population	257 (100%)	257 (100%)	514 (100%)
Efficacy population			
Modified Intent-to-Treat (mITT)	252 (98.1%)	253 (98.4%)	505 (98.2%)
Safety population	255	256	511
PK population	0	0	0

PK = pharmacokinetics

Note: The safety population patients are tabulated according to treatment actually received (as treated).

The efficacy population patients are tabulated according to their randomized treatment (as randomized).

There is no patient randomized in a group and taking another study treatment

There is no patient having switched their treatment during the study

4.1.2 Study disposition

Table 2 – Patient disposition for the 26-week randomized treatment period – Randomized population

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)
Randomized and not treated	2 (0.8%)	1 (0.4%)
Subject's request for not treated	2 (0.8%)	1 (0.4%)
Reason for not treated		
Adverse event	0	0
Hypoglycemia	0	0
Lack of efficacy	0	0
Poor compliance to protocol	0	0
Other	2 (0.8%)	1 (0.4%)

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)
Randomized and treated	255 (99.2%)	256 (99.6%)
Completed the 26-week randomized study treatment	230 (89.5%)	246 (95.7%)
Did not complete the 26-week randomized study treatment	25 (9.7%)	10 (3.9%)
Subject's request for treatment discontinuation during the 26-week randomized treatment period	14 (5.4%)	8 (3.1%)
Reason for study treatment discontinuation		
Adverse event	10 (3.9%)	0
Hypoglycemia	0	0
Lack of efficacy	1 (0.4%)*	0
Poor compliance to protocol	2 (0.8%)	0
Other	12 (4.7%)	10 (3.9%)
Status at last study contact of patients who permanently discontinued the treatment during the 26-week randomized treatment period		
Alive	27 (10.5%)	11 (4.3%)
Dead	0	0

Note: Percentages are calculated using the number of randomized patients as denominator.

*Patient 376000200001 was a 65 years old female with obesity, hypertension, hyperlipidemia, persistent depressive disorder and diabetic complication (neuropathy and nephropathy) history treated at screening with metformin (1.7g/day) and Victoza (1.8mg/day). Baseline HbA1c was 7.1%. FRC was used for 91 days and dose titrated up to 60U with no improvement of fasting SMPG compared to baseline. No reasonable explanation was found for insufficient glucose control. Investigator decided to prematurely and permanently discontinue the FRC treatment and to restart previous GLP-1RA treatment.

4.1.3 Demographics and baseline characteristics

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

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
Age (years)			
Number	257	257	514
Mean (SD)	59.2 (9.6)	60.0 (10.3)	59.6 (10.0)
Median	59.0	60.0	60.0
Min : Max	30 : 82	25 : 84	25 : 84
Age group (years) [n (%)]			
Number	257	257	514
< 50	37 (14.4%)	40 (15.6%)	77 (15.0%)
≥ 50 - <65	130 (50.6%)	127 (49.4%)	257 (50.0%)
≥ 65 - <75	84 (32.7%)	75 (29.2%)	159 (30.9%)
≥ 75	6 (2.3%)	15 (5.8%)	21 (4.1%)
Gender [n (%)]			
Number	257	257	514
Male	126 (49.0%)	144 (56.0%)	270 (52.5%)
Female	131 (51.0%)	113 (44.0%)	244 (47.5%)
Race [n (%)]			
Number	257	257	514
American Indian or Alaska Native	0	0	0
Asian/Oriental	3 (1.2%)	4 (1.6%)	7 (1.4%)
Black	12 (4.7%)	7 (2.7%)	19 (3.7%)
Native Hawaiian or Other Pacific Islander	1 (0.4%)	0	1 (0.2%)
White	241 (93.8%)	244 (94.9%)	485 (94.4%)
Other ^a	0	2 (0.8%)	2 (0.4%)
Ethnicity [n (%)]			
Number	257	257	514
Hispanic or Latino	27 (10.5%)	26 (10.1%)	53 (10.3%)
Not Hispanic or Latino	230 (89.5%)	231 (89.9%)	461 (89.7%)
Unknown	0	0	0

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
HbA1c (%) at Visit 1 (Week -2)			
Number	257	257	514
Mean (SD)	7.86 (0.56)	7.88 (0.53)	7.87 (0.54)
Median	7.80	7.90	7.80
Min : Max	7.0 : 9.0	7.0 : 9.0	7.0 : 9.0
Randomization strata of HbA1c (%) at Visit 1 (Week -2) [n (%)]			
Number	257	257	514
<8	149 (58.0%)	147 (57.2%)	296 (57.6%)
≥8	108 (42.0%)	110 (42.8%)	218 (42.4%)
Randomization strata of GLP-1 receptor agonist subtype at screening [n (%)]			
Number	257	257	514
Once/twice daily formulation	153 (59.5%)	154 (59.9%)	307 (59.7%)
Once weekly formulation	104 (40.5%)	103 (40.1%)	207 (40.3%)
Baseline BMI (kg/m²)			
Number	257	257	514
Mean (SD)	32.79 (4.40)	32.95 (4.38)	32.87 (4.38)
Median	32.90	33.00	32.90
Min : Max	21.2 : 40.0	21.5 : 40.0	21.2 : 40.0
Baseline BMI categories (kg/m²) [n (%)]			
Number	257	257	514
< 30	71 (27.6%)	69 (26.8%)	140 (27.2%)
≥ 30	186 (72.4%)	188 (73.2%)	374 (72.8%)

BMI = Body Mass Index.

^a Includes patients with more than one race, unknown or not reported

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

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
Duration of diabetes (years)			
Number	257	257	514
Mean (SD)	11.23 (7.42)	10.95 (6.08)	11.09 (6.78)
Median	10.05	9.83	9.99
Min : Max	1.0 : 57.9	1.4 : 40.1	1.0 : 57.9
Age at onset of Type 2 diabetes (years)			
Number	257	257	514
Mean (SD)	47.9 (10.0)	49.0 (9.2)	48.5 (9.6)
Median	50.0	50.0	50.0
Min : Max	11 : 68	19 : 69	11 : 69
Duration of GLP-1 receptor agonist treatment (years)			
Number	257	257	514
Mean (SD)	1.89 (1.76)	1.92 (1.85)	1.90 (1.81)
Median	1.17	1.13	1.17
Min : Max	0.3 : 13.0	0.3 : 12.1	0.3 : 13.0
GLP-1 receptor agonist use by type at screening in eCRF [n (%)]			
Number	257	257	514
Once/twice daily formulation	153 (59.5%)	154 (59.9%)	307 (59.7%)
Once weekly formulation	104 (40.5%)	103 (40.1%)	207 (40.3%)
Daily dose of liraglutide (mg) at baseline			
Number	135	145	280
Mean (SD)	1.66 (0.25)	1.66 (0.28)	1.66 (0.27)
Median	1.80	1.80	1.80
Min : Max	1.2 : 1.8	1.2 : 3.0	1.2 : 3.0
Daily dose of exenatide (µg) at baseline			
Number	18	9	27
Mean (SD)	18.33 (3.83)	17.78 (4.41)	18.15 (3.96)
Median	20.00	20.00	20.00
Min : Max	10.0 : 20.0	10.0 : 20.0	10.0 : 20.0

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
Weekly dose of exenatide extended-release (mg) at baseline			
Number	45	48	93
Mean (SD)	2.00 (0.00)	2.00 (0.00)	2.00 (0.00)
Median	2.00	2.00	2.00
Min : Max	2.0 : 2.0	2.0 : 2.0	2.0 : 2.0
Weekly dose of albiglutide (mg) at baseline			
Number	5	4	9
Mean (SD)	50.00 (0.00)	45.00 (10.00)	47.78 (6.67)
Median	50.00	50.00	50.00
Min : Max	50.0 : 50.0	30.0 : 50.0	30.0 : 50.0
Weekly dose of dulaglutide (mg) at baseline			
Number	54	51	105
Mean (SD)	1.43 (0.22)	1.40 (0.26)	1.41 (0.24)
Median	1.50	1.50	1.50
Min : Max	0.8 : 1.5	0.8 : 1.5	0.8 : 1.5
Pioglitazone use at screening recorded in eCRF [n (%)]			
Number	257	257	514
Yes	12 (4.7%)	22 (8.6%)	34 (6.6%)
No	245 (95.3%)	235 (91.4%)	480 (93.4%)
Daily dose of pioglitazone at baseline (mg)			
Number	12	22	34
Mean (SD)	31.25 (10.03)	32.73 (8.83)	32.21 (9.14)
Median	30.00	30.00	30.00
Min : Max	15.0 : 45.0	15.0 : 45.0	15.0 : 45.0
SGLT2 inhibitor use at screening [n (%)]			
Number	257	257	514
Yes	26 (10.1%)	26 (10.1%)	52 (10.1%)
No	231 (89.9%)	231 (89.9%)	462 (89.9%)

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
Daily dose of SGLT2 inhibitor at baseline (mg)			
Canagliflozin			
Number	7	12	19
Mean (SD)	214.29 (106.90)	283.33 (57.74)	257.89 (83.77)
Median	300.00	300.00	300.00
Min : Max	100.0 : 300.0	100.0 : 300.0	100.0 : 300.0
Empagliflozin			
Number	6	9	15
Mean (SD)	15.42 (7.49)	16.67 (8.20)	16.17 (7.67)
Median	11.25	12.50	12.50
Min : Max	10.0 : 25.0	5.0 : 25.0	5.0 : 25.0
Dapagliflozin			
Number	13	5	18
Mean (SD)	9.62 (3.80)	9.00 (2.24)	9.44 (3.38)
Median	10.00	10.00	10.00
Min : Max	5.0 : 20.0	5.0 : 10.0	5.0 : 20.0
Duration of metformin treatment (years)			
Number	257	257	514
Mean (SD)	7.20 (5.29)	8.12 (5.21)	7.66 (5.26)
Median	6.53	7.20	6.85
Min : Max	0.3 : 28.8	0.4 : 29.4	0.3 : 29.4
Daily dose of metformin at baseline (mg)			
Number	257	257	514
Mean (SD)	1966.93 (434.56)	2030.74 (497.15)	1998.83 (467.54)
Median	2000.00	2000.00	2000.00
Min : Max	500.0 : 3000.0	500.0 : 3000.0	500.0 : 3000.0
Categorized daily dose of metformin at baseline (mg) [n (%)]			
Number	257	257	514
<1500 mg	18 (7.0%)	18 (7.0%)	36 (7.0%)
≥1500 - <2500 mg	200 (77.8%)	181 (70.4%)	381 (74.1%)
≥2500 - <3000 mg	27 (10.5%)	34 (13.2%)	61 (11.9%)
≥3000 mg	12 (4.7%)	24 (9.3%)	36 (7.0%)
Diabetic retinopathy [n (%)]			
Number	257	257	514
Yes	20 (7.8%)	14 (5.4%)	34 (6.6%)
No	237 (92.2%)	243 (94.6%)	480 (93.4%)

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
Diabetic proliferative retinopathy [n (%)]			
Number	257	257	514
Yes	2 (0.8%)	2 (0.8%)	4 (0.8%)
No	255 (99.2%)	255 (99.2%)	510 (99.2%)
Diabetic neuropathy [n (%)]			
Number	257	257	514
Yes	62 (24.1%)	59 (23.0%)	121 (23.5%)
No	195 (75.9%)	198 (77.0%)	393 (76.5%)
Diabetic nephropathy [n (%)]			
Number	257	257	514
Yes	20 (7.8%)	26 (10.1%)	46 (8.9%)
No	237 (92.2%)	231 (89.9%)	468 (91.1%)
Baseline urinary albumin/creatinine ratio (mg/g) [n (%)]			
Number	253	256	509
< 30 (normal)	197 (77.9%)	203 (79.3%)	400 (78.6%)
≥ 30 to < 300 (microalbuminuria)	48 (19.0%)	45 (17.6%)	93 (18.3%)
≥ 300 (macroalbuminuria)	8 (3.2%)	8 (3.1%)	16 (3.1%)
Estimated eGFR at screening (mL/min/1.73m ²)			
Number	257	257	514
Mean (SD)	88.96 (24.87)	85.71 (22.60)	87.34 (23.79)
Median	86.25	84.06	85.20
Min : Max	40.9 : 296.4	39.5 : 171.8	39.5 : 296.4
Estimated eGFR at screening (mL/min/1.73m ²) [n (%)]			
Number	257	257	514
< 15 (End stage renal disease)	0	0	0
≥ 15 - < 30 (Severe decrease in GFR)	0	0	0
≥ 30 - < 60 (Moderate decrease in GFR)	17 (6.6%)	31 (12.1%)	48 (9.3%)
≥ 60 - < 90 (Mild decrease in GFR)	132 (51.4%)	126 (49.0%)	258 (50.2%)

	Fixed Ratio Combination (N=257)	GLP-1 Receptor Agonist (N=257)	All (N=514)
≥ 90 (Normal)	108 (42.0%)	100 (38.9%)	208 (40.5%)

SGLT2 = Sodium glucose co-transporter 2, eGFR = estimated Glomerular Filtration Rate.

Duration of diabetes (years) = (Date of informed consent - Date of diagnosis of diabetes + 1)/365.25

Age at onset of Type 2 diabetes (years) = (year of diagnosis of diabetes - year of birth)

eGFR is derived using the 4 variable Modification of Diet in Renal Disease formula.

Urine albumin/creatinine ratio is presented in mg/g, and the conversion factor to the standard international unit mg/mmol is 0.1130.

4.2 EFFICACY

4.2.1 Primary efficacy endpoint

Table 5 - Mean change in HbA1c (%) from baseline to Week 26 using MMRM - mITT population

HbA1c(%)	Fixed Ratio Combination (N=252)	GLP-1 Receptor Agonist (N=253)
Baseline		
Number	250	253
Mean (SD)	7.77 (0.63)	7.80 (0.57)
Median	7.70	7.80
Min : Max	6.5 : 10.0	6.2 : 9.3
Week 26		
Number	237	248
Mean (SD)	6.74 (0.77)	7.41 (0.79)
Median	6.70	7.40
Min : Max	5.2 : 9.5	5.0 : 10.9
Change from baseline to Week 26		
Number	250	253
LS Mean (SE) ^a	-1.02 (0.048)	-0.38 (0.048)

HbA1c(%)	Fixed Ratio Combination (N=252)	GLP-1 Receptor Agonist (N=253)
LS Mean difference (SE) vs GLP-1 receptor agonist ^a	-0.64 (0.067)	-
95% CI	(-0.770 to -0.508)	-
p-value	<0.0001	-

^a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination and GLP-1 receptor agonist), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, scheduled visit, treatment-by-visit interaction, and world region as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate.

The analysis included all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue medication.

Included are patients who have measurements at baseline and post-baseline.

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

	Fixed Ratio Combination (N=252)				GLP-1 Receptor Agonist (N=253)	
	N	LSMean (SE) ^a	Compared to GLP-1 Receptor Agonist		N	LSMean (SE) ^a
			Difference in LSMean (SE) ^a	95% CI ^a		
Race						
Black	11	-0.57 (0.232)	-0.33 (0.381)	(-1.077, 0.421)	6	-0.24 (0.305)
White	235	-1.04 (0.050)	-0.67 (0.068)	(-0.803, -0.534)	241	-0.38 (0.049)
Other	4				6	-0.78 (0.310)
Ethnicity						
Hispanic or Latino	26	-0.83 (0.155)	-0.58 (0.216)	(-1.006, -0.158)	25	-0.25 (0.154)
Non Hispanic or Latino	224	-1.05 (0.051)	-0.65 (0.070)	(-0.785, -0.509)	228	-0.40 (0.050)
Age						
<50	36	-1.02 (0.129)	-0.63 (0.177)	(-0.982, -0.287)	38	-0.39 (0.122)
≥50 to <65	125	-1.02 (0.068)	-0.66 (0.094)	(-0.842, -0.471)	126	-0.37 (0.067)
≥65 to <75	83	-1.06 (0.083)	-0.64 (0.120)	(-0.872, -0.400)	74	-0.42 (0.087)
≥75	6	-0.49 (0.318)	-0.17 (0.373)	(-0.904, 0.560)	15	-0.32 (0.197)
Gender						
Male	121	-1.08 (0.069)	-0.73 (0.093)	(-0.914, -0.548)	142	-0.35 (0.063)
Female	129	-0.97 (0.067)	-0.54 (0.097)	(-0.733, -0.350)	111	-0.42 (0.071)
Baseline BMI (kg/m ²)						
<30	68	-1.02 (0.091)	-0.71 (0.128)	(-0.966, -0.462)	68	-0.31 (0.091)
≥30	182	-1.02 (0.057)	-0.61 (0.078)	(-0.766, -0.459)	185	-0.41 (0.056)
GLP-1 receptor agonist subtype at screening						
Once/twice daily formulations	150	-1.02 (0.061)	-0.65 (0.086)	(-0.818, -0.479)	152	-0.37 (0.061)
Once weekly formulations	100	-1.03 (0.076)	-0.63 (0.106)	(-0.834, -0.417)	101	-0.40 (0.074)
Baseline HbA1c (%)						
<8.0	161	-0.96 (0.071)	-0.58 (0.084)	(-0.742, -0.414)	161	-0.38 (0.067)

	Fixed Ratio Combination (N=252)				GLP-1 Receptor Agonist (N=253)	
	Compared to GLP-1 Receptor Agonist					
	N	LSMean (SE) ^a	Difference in LSMean (SE) ^a	95% CI ^a	N	LSMean (SE) ^a
≥8.0	89	-1.16 (0.104)	-0.75 (0.111)	(-0.965, -0.528)	92	-0.41 (0.098)
Pioglitazone use at screening						
Yes	10	-1.16 (0.235)	-0.85 (0.286)	(-1.416, -0.293)	22	-0.30 (0.162)
No	240	-1.02 (0.049)	-0.63 (0.069)	(-0.762, -0.491)	231	-0.39 (0.050)
SGLT2 inhibitor use at screening						
Yes	22	-1.15 (0.161)	-0.88 (0.217)	(-1.306, -0.455)	26	-0.27 (0.148)
No	228	-1.01 (0.051)	-0.61 (0.070)	(-0.751, -0.475)	227	-0.40 (0.051)

BMI = body mass index. SGLT2 = Sodium glucose co-transporter 2.

^a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination and GLP-1 receptor agonist), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, scheduled visit, subgroup factor, treatment-by-visit, treatment-by-subgroup factor, visit-by-subgroup factor, treatment-by-visit-by-subgroup factor, and world region as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate.

^b Difference in LSMean between fixed ratio combination and GLP-1 receptor agonist.

The analysis includes all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy.

Included are patients who have measurements at baseline and post-baseline.

LS Mean and difference in LS Mean were provided for categories with ≥5 patients in each treatment group.

4.2.2 Secondary efficacy endpoints

Table 7 - Number (%) of patients with HbA1c value ≤6.5% or <7% at Week 26 - mITT population

HbA1c (%)	Fixed Ratio Combination (N=252)	GLP-1 Receptor Agonist (N=253)
Number	252	253
≤6.5 %	102 (40.5%)	25 (9.9%)
Proportion difference (95% CI) vs. GLP-1 RA ^a	30.61% (23.61% to 37.62%)	-
p-value	<.0001	-
<7 %	156 (61.9%)	65 (25.7%)
Proportion difference (95% CI) vs. GLP-1 RA ^a	36.05% (28.11% to 43.99%)	-
p-value	<.0001	-

GLP-1 RA = GLP-1 receptor agonist

^a Weighted average of proportion difference between treatment groups (fixed ratio combination vs. GLP-1 receptor agonist) from each stratum (randomization strata of HbA1c [<8.0 or ≥ 8.0 %] at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype [once/twice daily formulations, once weekly formulations] at screening) using Cochran-Mantel-Haenszel weights.

Proportion difference = difference of the proportions of patients achieving HbA1c value ≤6.5% or <7%.

All measurements at week 26 were used, including those obtained after IMP discontinuation or introduction of rescue therapy. If no assessment was available at week 26 at all, patients were treated as non-responders.

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

Fasting plasma glucose (mmol/L)	Fixed Ratio Combination (N=252)	GLP-1 Receptor Agonist (N=253)
Baseline		
Number	251	253
Mean (SD)	9.06 (2.10)	9.45 (1.93)
Median	8.70	9.10
Min : Max	5.1 : 18.6	4.4 : 16.3
Week 26		
Number	228	227
Mean (SD)	6.86 (1.66)	8.66 (2.01)
Median	6.58	8.40
Min : Max	4.0 : 13.4	4.4 : 16.0
Change from baseline to Week 26		
Number	251	253
LS Mean (SE) ^a	-2.28 (0.120)	-0.60 (0.119)

Fasting plasma glucose (mmol/L)	Fixed Ratio Combination (N=252)	GLP-1 Receptor Agonist (N=253)
LS Mean difference (SE) vs GLP-1 receptor agonist ^a	-1.67 (0.168)	-
95% CI	(-2.001 to -1.341)	-
p-value	<0.0001	-

^a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination and GLP-1 receptor agonist), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, scheduled visit, treatment-by-visit interaction, world region as fixed effects, and baseline fasting plasma glucose value-by-visit interaction as a covariate.

The analysis included all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue medication.

Included are patients who have measurements at baseline and post-baseline.

Table 9-Mean change in average 7-point SMPG (mmol/L) from baseline to Week 26 using MMRM - mITT population

Average 7-point SMPG (mmol/L)	Fixed Ratio Combination (N=252)	GLP-1 Receptor Agonist (N=253)
Baseline		
Number	216	220
Mean (SD)	9.41 (1.90)	9.53 (1.80)
Median	9.11	9.19
Min : Max	5.9 : 15.6	6.1 : 15.4
Week 26		
Number	190	198
Mean (SD)	7.70 (1.53)	8.79 (1.79)
Median	7.40	8.50
Min : Max	5.0 : 14.5	5.7 : 19.5
Change from baseline to Week 26		
Number	216	220
LS Mean (SE) ^a	-1.69 (0.114)	-0.67 (0.112)
LS Mean difference (SE) vs GLP-1 receptor agonist ^a	-1.02 (0.157)	-
95% CI	(-1.325 to -0.708)	-
p-value	<0.0001	-

SMPG = Self-monitored plasma glucose.

^a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination and GLP-1 receptor agonist), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, scheduled visit, treatment-by-visit interaction, and world region as fixed effects, and baseline average SMPG value-by-visit interaction as a covariate.

The analysis included all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue medication.

Included are patients who have measurements at baseline and post-baseline.

Table 10- Mean change in 2-hour postprandial plasma glucose (mmol/L) during a standardized meal test from baseline to Week 26 using ANCOVA-mITT population

2-hour postprandial plasma glucose (mmol/L)	Fixed Ratio Combination (N=252)	GLP-1 Receptor Agonist (N=253)
Baseline		
Number	215	222
Mean (SD)	13.60 (3.33)	13.78 (3.25)
Median	13.30	13.66
Min : Max	5.1 : 22.6	5.9 : 26.1
Week 26 (LOCF)		
Number	215	222
Mean (SD)	9.68 (3.09)	12.59 (3.30)
Median	9.44	12.07
Min : Max	4.0 : 23.2	4.8 : 22.8
Change from baseline to Week 26 (LOCF)		
Number	215	222
Mean (SD)	-3.92 (3.81)	-1.19 (3.69)
Median	-4.00	-1.11
Min : Max	-12.6 : 8.7	-15.0 : 11.8
LS Mean (SE) ^a	-3.96 (0.211)	-1.11 (0.205)
LS mean difference (SE) vs GLP-1 RA ^a	-2.85 (0.290)	-
95% CI	(-3.420 to -2.279)	-
p-value	<0.0001	-

LOCF = Last observation carried forward, GLP-1 RA= GLP-1 receptor agonist.

^a Analysis of covariance (ANCOVA) model with treatment groups (fixed ratio combination and GLP-1 receptor agonist), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, and world region as fixed effects and baseline 2-hour postprandial plasma glucose value as a covariate.

The analysis included measurements collected during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy.

Patients with both baseline and Week 26 (LOCF) measurements were included.

Table 11 - Mean change in 2-hour plasma glucose excursion (mmol/L) during a standardized meal test from baseline to Week 26 using ANCOVA - mITT population

2-hour plasma glucose excursion (mmol/L)	Fixed Ratio Combination (N=252)	GLP-1 Receptor Agonist (N=253)
Baseline		
Number	215	220
Mean (SD)	4.32 (2.74)	4.24 (2.60)
Median	4.20	4.18
Min : Max	-6.3 : 13.9	-4.3 : 13.8
Week 26 (LOCF)		
Number	215	220
Mean (SD)	2.77 (2.74)	3.73 (2.73)
Median	2.50	3.70
Min : Max	-2.3 : 15.9	-6.0 : 12.8
Change from baseline to Week 26 (LOCF)		
Number	215	220
Mean (SD)	-1.55 (3.22)	-0.51 (2.81)
Median	-1.70	-0.40
Min : Max	-10.7 : 12.7	-10.2 : 7.2
LS Mean (SE) ^a	-1.51 (0.177)	-0.52 (0.173)
LS mean difference (SE) vs GLP-1 RA ^a	-0.99 (0.244)	-
95% CI	(-1.468 to -0.508)	-
p-value	<0.0001	-

LOCF = Last observation carried forward, GLP-1 RA= GLP-1 receptor agonist.

^a Analysis of covariance (ANCOVA) model with treatment groups (fixed ratio combination and GLP-1 receptor agonist), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, and world region as fixed effects and baseline 2-hour plasma glucose excursion value as a covariate.

The analysis included measurements collected during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy.

Patients with both baseline and Week 26 (LOCF) measurements are included.

Table 12 - Mean change in body weight (kg) from baseline to Week 26 using MMRM - mITT population

Body weight (kg)	Fixed Ratio Combination (N=252)	GLP-1 Receptor Agonist (N=253)
Baseline		
Number	251	253
Mean (SD)	93.01 (16.48)	95.49 (16.92)
Median	93.20	94.50
Min : Max	53.0 : 135.8	50.0 : 139.8
Week 26		
Number	237	247
Mean (SD)	94.91 (16.39)	94.49 (16.87)
Median	93.25	93.10
Min : Max	58.2 : 140.4	51.3 : 139.9
Change from baseline to Week 26		
Number	251	253
LS Mean (SE) ^a	1.89 (0.222)	-1.14 (0.220)
LS Mean difference (SE) vs GLP-1 receptor agonist ^a	3.03 (0.312)	-
95% CI	(2.417 to 3.643)	-

GLP-1 RA = GLP-1 Receptor Agonist.

^a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination and GLP-1 receptor agonist), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, scheduled visit, treatment-by-visit interaction, and world region as fixed effects, and baseline body weight-by-visit interaction as a covariate.

The analysis included measurements collected during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy.

Included are patients who have measurements at baseline and post-baseline.

Table 13 – Daily insulin glargine dose (U) by visit during the 26-week randomized treatment period for fixed ratio combination group – mITT population

Treatment Time point	Daily insulin glargine dose (U)					
	N	Mean	SD	Median	Min	Max
Fixed Ratio Combination(N=255)						
Week 0	247	10.12	1.10	10.00	10.0	20.0
Week 8	246	37.33	13.44	38.00	5.0	60.0
Week 12	243	39.73	14.49	40.00	0.0	60.0
Week 26	229	43.50	15.05	46.00	5.0	60.0

Patient 840000900005 stayed at FRC 5U until week 26 as higher dose were not tolerated. Patient 724000200005, 724001200003 and 840007800005 erroneously initiated treatment with 20U instead of 10U. Patient 840006500006 missed one injection at the day of visit 21(week 12) and the dose recorded was zero.

Table 14– Daily lixisenatide dose (ug) by visit during the 26-week randomized treatment period for fixed ratio combination group – mITT population

Treatment Time point	Daily lixisenatide dose (ug)					
	N	Mean	SD	Median	Min	Max
Fixed Ratio Combination(N=255)						
Week 0	247	5.06	0.55	5.00	5.0	10.0
Week 8	246	15.25	3.81	16.00	2.5	24.0
Week 12	243	15.72	3.93	16.67	0.0	20.0
Week 26	229	16.55	3.82	17.33	2.5	20.0

*Patient 840006300003 used the peach (2U:1µg) pen to administer a FRC daily dose of 48 U and therefore received 24 µg of lixisenatide at week 8. A DRE has been reported.

4.3 SAFETY

Hypoglycemia events were documented on a specific hypoglycemia event form, and not an AE CRF page, and thus were not included in the TEAE summaries. They are summarized separately from TEAEs. If criteria of SAE were met, the event was to be reported as SAE using the appropriate AE CRF page, and thus the event was included in the TEAE summaries.

4.3.1 Treatment-emergent adverse events

Table 15 - Overview of adverse event profile: treatment emergent adverse events during the 26-week randomized treatment period - Safety population

n (%)	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Patients with any TEAE	163 (63.9%)	121 (47.3%)
Patients with any serious TEAE	10 (3.9%)	9 (3.5%)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	9 (3.5%)	0

TEAE: Treatment-emergent adverse event

n (%) = number and percentage of patients with at least one TEAE

Table 16 - Number (%) of patients experiencing common TEAE(s) (PT ≥2% in any treatment group) by primary SOC and PT during the 26-week randomized treatment period- Safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Any TEAE	163 (63.9%)	121 (47.3%)
INFECTIONS AND INFESTATIONS	78 (30.6%)	68 (26.6%)
Bronchitis	6 (2.4%)	5 (2.0%)
Influenza	11 (4.3%)	6 (2.3%)
Nasopharyngitis	25 (9.8%)	23 (9.0%)
Pneumonia	6 (2.4%)	3 (1.2%)
Sinusitis	6 (2.4%)	7 (2.7%)
Upper respiratory tract infection	9 (3.5%)	12 (4.7%)
Urinary tract infection	7 (2.7%)	3 (1.2%)
METABOLISM AND NUTRITION DISORDERS	13 (5.1%)	1 (0.4%)
Increased appetite	6 (2.4%)	0
NERVOUS SYSTEM DISORDERS	30 (11.8%)	13 (5.1%)
Dizziness	6 (2.4%)	2 (0.8%)
Headache	10 (3.9%)	6 (2.3%)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
GASTROINTESTINAL DISORDERS	55 (21.6%)	26 (10.2%)
Diarrhoea	14 (5.5%)	6 (2.3%)
Nausea	22 (8.6%)	6 (2.3%)
Toothache	6 (2.4%)	3 (1.2%)
Vomiting	8 (3.1%)	2 (0.8%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	23 (9.0%)	18 (7.0%)
Back pain	4 (1.6%)	7 (2.7%)
INVESTIGATIONS	15 (5.9%)	4 (1.6%)
Weight increased	7 (2.7%)	0

TEAE: Treatment-emergent adverse event, SOC: System Organ Class, PT: Preferred Term.

MedDRA version: 21.0.

n (%) = number and percentage of patients with at least one TEAE.

Note: Table sorted by SOC internationally agreed order and PT by alphabetic order.

Only SOC with at least one PT $\geq 2\%$ in at least one group are presented.

4.3.2 Deaths, serious treatment-emergent adverse events

No patient experienced any TEAE during 26-week randomized treatment period leading to death.

Table 17 - Number (%) of patients experiencing serious TEAE(s) presented by primary SOC and PT during the 26-week randomized treatment period- Safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Any TEAE	10 (3.9%)	9 (3.5%)
INFECTIONS AND INFESTATIONS	0	1 (0.4%)
Pneumonia	0	1 (0.4%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (0.8%)	3 (1.2%)
Bladder papilloma	0	1 (0.4%)
Endometrial adenocarcinoma	1 (0.4%)	0
Invasive ductal breast carcinoma	0	1 (0.4%)
Papillary thyroid cancer	1 (0.4%)	0
Renal cell carcinoma	0	1 (0.4%)
METABOLISM AND NUTRITION DISORDERS	0	1 (0.4%)
Electrolyte imbalance	0	1 (0.4%)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
NERVOUS SYSTEM DISORDERS	2 (0.8%)	2 (0.8%)
Cerebral infarction	0	1 (0.4%)
Diabetic neuropathy	0	1 (0.4%)
Hypoglycaemic unconsciousness	1 (0.4%)	0
Intraventricular haemorrhage	1 (0.4%)	0
CARDIAC DISORDERS	2 (0.8%)	0
Atrial fibrillation	1 (0.4%)	0
Ischaemic cardiomyopathy	1 (0.4%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.4%)	0
Acute pulmonary oedema	1 (0.4%)	0
GASTROINTESTINAL DISORDERS	1 (0.4%)	1 (0.4%)
Large intestine polyp	0	1 (0.4%)
Rectal haemorrhage	1 (0.4%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.4%)
Dermal cyst	0	1 (0.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.8%)	0
Musculoskeletal chest pain	1 (0.4%)	0
Osteoarthritis	1 (0.4%)	0
RENAL AND URINARY DISORDERS	2 (0.8%)	1 (0.4%)
Acute kidney injury	1 (0.4%)	1 (0.4%)
Urinary retention	1 (0.4%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (0.4%)
Non-cardiac chest pain	0	1 (0.4%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (1.2%)	0
Ankle fracture	1 (0.4%)	0
Fall	2 (0.8%)	0
Foot fracture	1 (0.4%)	0
Laceration	1 (0.4%)	0
Subarachnoid haemorrhage	1 (0.4%)	0

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Subcutaneous haematoma	1 (0.4%)	0

TEAE: Treatment-emergent adverse event, SOC: System Organ Class, PT: Preferred Term.

MedDRA version: 21.0.

n (%) = number and percentage of patients with at least one serious TEAE.

Note: Table sorted by SOC internationally agreed order and PT by alphabetic order.

4.3.3 Adverse events leading to withdrawal

Table 18 - Number (%) of patients experiencing TEAE(s) leading to permanent treatment discontinuation by primary SOC and PT during the 26-week randomized treatment period - Safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Any TEAE	9 (3.5%)	0
NERVOUS SYSTEM DISORDERS	1 (0.4%)	0
Headache	1 (0.4%)	0
CARDIAC DISORDERS	1 (0.4%)	0
Palpitations	1 (0.4%)	0
GASTROINTESTINAL DISORDERS	5 (2.0%)	0
Abdominal distension	1 (0.4%)	0
Flatulence	1 (0.4%)	0
Nausea	3 (1.2%)	0
Vomiting	1 (0.4%)	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (0.4%)	0
Pregnancy	1 (0.4%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.4%)	0
Fatigue	1 (0.4%)	0
INVESTIGATIONS	4 (1.6%)	0
Amylase increased	1 (0.4%)	0
Blood glucose fluctuation	1 (0.4%)	0
Lipase increased	1 (0.4%)	0
Platelet count decreased	1 (0.4%)	0

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Weight increased	2 (0.8%)	0

TEAE: Treatment-emergent adverse event, SOC: System Organ Class, PT: Preferred Term.

MedDRA version: 21.0.

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 PT by alphabetic order.

4.3.4 Other significant adverse events (including AESI, labs)

A pregnancy was confirmed in a 41 year-old female FRC patient on Day 125 day of treatment. No complication of pregnancy, labor or delivery was reported and the patient gave birth to a healthy baby. No congenital anomalies were noted.

None of TEAE of increased calcitonin (≥ 20 pg/mL) was reported in the 26-week randomized treatment period.

Table 19 - Number (%) of patients experiencing injection site reactions during the 26-week on-treatment period - Safety population

Event source Preferred Term	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Any injection site reactions	5 (2.0%)	0
PTs coded from the investigator reported terms		
Injection site pain	3 (1.2%)	0
Injection site erythema	1 (0.4%)	0
Injection site reaction	1 (0.4%)	0
PTs coded from the ARAC diagnosis terms		
Injection site reaction	1 (0.4%)	0

ARAC = Allergic Reaction Assessment Committee, PT = Preferred term.

The 26-week on-treatment period is defined as the time from the first injection of investigational medicinal product (IMP) up to 3 day after the last injection of IMP for patients not eligible to enter the extension period or Visit 28/Week 26 (or Day 183 if Visit 28/Week 26 is missing) for patients eligible to enter the extension period, regardless of the introduction of rescue therapy.

Table 20 - Number (%) of patients with events adjudicated as allergic reaction by ARAC during the 26-week on-treatment period - Safety population

Relationship to Study Treatment (by ARAC)	ARAC Diagnosis Categories	MedDRA Coded Term (PT) for ARAC Diagnosis	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
All	Any category	Any event	2 (0.8%)	0
	Urticaria (hives)		1 (0.4%)	0
		Urticaria	1 (0.4%)	0
	Asthma		1 (0.4%)	0
		Asthma	1 (0.4%)	0
Not related to IMP	Any category	Any event	2 (0.8%)	0
	Urticaria (hives)		1 (0.4%)	0
		Urticaria	1 (0.4%)	0
	Asthma		1 (0.4%)	0
		Asthma	1 (0.4%)	0

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

The 26-week on-treatment period is defined as the time from the first injection of investigational medicinal product (IMP) up to 3 days after the last injection of IMP for patients not eligible to enter the extension period or Visit 28/Week 26 (or Day 183 if Visit 28/Week 26 is missing) for patients eligible to enter the extension period, regardless of the introduction of rescue therapy.

Table 21 - Number (%) of patients with pancreatic events positively adjudicated by PSAC during the 26-week on-treatment period - Safety population

	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Any with "Yes" for pancreatitis by PSAC	1 (0.4%)	0
Acute pancreatitis	0	0
Acute on chronic pancreatitis	0	0
Chronic pancreatitis	1 (0.4%)	0
Unknown pancreatitis	0	0
Any with "Yes" for pancreatic neoplasm by PSAC	0	0
Malignant	0	0
Benign	0	0

PSAC = Pancreatic Safety Assessment Committee.

The 26-week on-treatment period is defined as the time from the first injection of investigational medicinal product (IMP) up to 3 days after the last injection of IMP for patients not eligible to enter the extension period or Visit 28/Week 26 (or Day 183 if Visit 28/Week 26 is missing) for patients eligible to enter the extension period, regardless of the introduction of rescue therapy.

Table 22 - Number (%) of patients with events reported in device-related event questionnaire during the 26-week on-treatment period - Safety population

	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Any device-related events	21 (8.2%)	5 (2.0%)
Associated with a clinical event	0	0
Not associated with a clinical event	21 (8.2%)	5 (2.0%)

Clinical event = symptomatic hypoglycemic event, hyperglycemic adverse event or other adverse event collected in device-related questionnaire.

The 26-week on-treatment period is defined as the time from the first injection of investigational medicinal product (IMP) up to 3 days after the last injection of IMP for patients not eligible to enter the extension period or Visit 28/Week 26 (or Day 183 if Visit 28/Week 26 is missing) for patients eligible to enter the extension period, regardless of the introduction of rescue therapy.

4.3.5 Other safety observation - Hypoglycemia

Table 23 - Summary of symptomatic hypoglycemia recorded on the dedicated eCRF page and meeting protocol definition during the 26-week on-treatment period - Safety population

	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Total patient years of exposure	121.4	127.0
Symptomatic hypoglycemia		
Number of patients with events, n (%)	84 (32.9%)	11 (4.3%)
Number of patients with events per patient year ^a	0.69	0.09
Number of events	246	17
Number of events per patient year ^b	2.03	0.13
Documented symptomatic hypoglycemia (plasma glucose ≤3.9 mmol/L [70 mg/dL])		
Number of patients with events, n (%)	71 (27.8%)	6 (2.3%)
Number of patients with events per patient year ^a	0.58	0.05
Number of events	187	10
Number of events per patient year ^b	1.54	0.08
Documented symptomatic hypoglycemia (plasma glucose <3.3 mmol/L [60 mg/dL])		
Number of patients with events, n (%)	41 (16.1%)	1 (0.4%)
Number of patients with events per patient year ^a	0.34	<0.01
Number of events	69	2
Number of events per patient year ^b	0.57	0.02
Documented symptomatic hypoglycemia (plasma glucose <3.0 mmol/L [54 mg/dL])		

	Fixed Ratio Combination (N=255)	GLP-1 Receptor Agonist (N=256)
Number of patients with events, n (%)	24 (9.4%)	1 (0.4%)
Number of patients with events per patient year ^a	0.20	<0.01
Number of events	30	1
Number of events per patient year ^b	0.25	<0.01
Probable symptomatic hypoglycemia		
Number of patients with events, n (%)	16 (6.3%)	1 (0.4%)
Number of patients with events per patient year ^a	0.13	<0.01
Number of events	27	1
Number of events per patient year ^b	0.22	<0.01
Severe symptomatic hypoglycemia		
Number of patients with events, n (%)	1 (0.4%)	0
Number of patients with events per patient year ^a	<0.01	0
Number of events	1	0
Number of events per patient year ^b	<0.01	0

^a: Calculated as number of patients with events divided by total exposure + 1 day in patient years for daily formulation and number of patients with events divided by total exposure + 7 days in patient years for weekly formulation .

^b: Calculated as number of events divided by total exposure + 1 day in patient years for daily formulation and number of events divided by total exposure + 7 day in patient years for weekly formulation .

Symptomatic hypoglycemia = symptomatic hypoglycemia recorded on the dedicated eCRF and meeting protocol definition for severe, or documented, or probable symptomatic hypoglycemia.

The 26-week on-treatment period is defined as the time from the first injection of investigational medicinal product (IMP) up to 1 day after the last injection of daily IMP (7 days after the last injection of weekly IMP) for patients not eligible to enter the extension period or Visit 28/Week 26 (or Day 183 if Visit 28/Week 26 is missing) for patients eligible to enter the extension period, regardless of the introduction of rescue therapy.

One 69 year-old patient in the FRC group experienced a severe hypoglycemia event associated with a loss of consciousness which was reported as SAE (PT: Hypoglycemic unconsciousness). The event occurred in the morning at 8:30am, about 40 minutes after FRC injection and 10 hours after the last meal. Patient presented with dizziness, confusion and a 3 minute loss of consciousness according to a woman who helped him to lie on the bed and gave him sugar. Blood glucose value was 42mg/dl at 08:51 and 70 mg/dL at 09:16. Patient fully recovered at 09:45. The investigator considered the event as related to the treatment and the FRC dose was decreased accordingly.

Example 2

A randomized, 26-week, active-controlled, open-label, 2-treatment arm, parallel-group and multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed-ratio combination (LixiLan) to lixisenatide on top of oral antidiabetic drugs in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs with a 26-week safety extension period (EFC14112)

Study center(s): 61 centers in Japan
Phase of development: Phase 3
Objectives: Primary Objective The primary objective of this study was to demonstrate the superiority of LixiLan to lixisenatide in HbA1c change from baseline to Week 26. Secondary Objectives - To assess the effects of LixiLan in comparison with lixisenatide over 26 weeks on: - Percentage of patients reaching HbA1c targets <7% or ≤6.5%, - Fasting plasma glucose (FPG), 7-point self-monitored plasma glucose (SMPG) profile, - Percentage of patients reaching HbA1c <7% with no body weight gain, - Body weight. - To assess the safety and tolerability over 26 weeks and 52 weeks in each treatment group. - To assess the development of anti-lixisenatide and/or anti-insulin antibodies (depending on treatment group) as well as of neutralizing anti-lixisenatide antibodies (in anti-lixisenatide antibody-positive patients only) at Week 26 and Week 52. - To assess the plasma concentration of lixisenatide before and following injection (LixiLan and lixisenatide groups) at Week 26 and Week 52.
Methodology: This was an open-label, 1:1 randomized, active-controlled, 2-arm, parallel-group, and multicenter Phase 3 study with a 26-week main treatment period and a 26-week extension period. The study recruited Japanese outpatients with type 2 diabetes mellitus (T2DM) inadequately controlled on oral antidiabetic drugs (OADs). The study comprised 3 periods: - An up to 2-week screening period. - A 52-week open-label randomized treatment period, which included: - A 26-week main treatment period for efficacy and safety evaluation, - A 26-week extension treatment period for safety evaluation. - A 3-day post-treatment safety follow-up period (for all patients after permanent discontinuation of the investigational medicinal product [IMP], except for patients who prematurely discontinued the study treatment but continued in the study). At randomization, any dipeptidyl-peptidase-4 (DPP-4) inhibitors being taken were stopped. In patients with an HbA1c <8% at screening, the dose of sodium-glucose cotransporter 2 (SGLT2) inhibitor, sulfonylurea (SU), or rapid-acting insulin secretagogue (glinide) was decreased by at least 50% (or stopped in case of minimum dose) at randomization in order to decrease the risk of hypoglycemia.
Number of patients: Planned: 318 patients (159 patients per group) Randomized: 321 patients (161 in the LixiLan group, 160 in the lixisenatide group) Treated: 321 patients (161 in the LixiLan group, 160 in the lixisenatide group)

Evaluated:**Efficacy:** 321 patients**Safety:** 321 patients**Diagnosis and criteria for inclusion:**

Inclusion criteria: Patients with T2DM diagnosed for at least 1 year before the screening visit (V1); patient receiving 1 or 2 OADs allowed for the purpose of this study (which included biguanide, thiazolidinedione [TZD], alpha-glucosidase-inhibitor [alpha-GI], SGLT2 inhibitor, SU, glinide, and DPP-4 inhibitor) at least the usual maintenance dose according to the approved label and the OAD dose(s) had been stable during the 3 months before the screening visit; signed written informed consent.

Key exclusion criteria at screening: Age <20 years; HbA1c <7.5% or >10%; FPG >250 mg/dL (13.8 mmol/L); body mass index (BMI) <15 or >40 kg/m²; history of hypoglycemia unawareness; use of oral or injectable glucose-lowering agents other than those stated during the inclusion criteria in the 3 months prior to screening; previous treatment with insulin (except for short-term treatment due to intercurrent illness including gestational diabetes at the discretion of the Investigator).

Study treatments**Investigational medicinal product(s):****LixiLan:**

Formulation: LixiLan was supplied as a sterile aqueous solution in a 3-mL glass cartridge containing 300 U insulin glargine (100 U/mL), 300 µg lixisenatide (100 µg/mL), glycerol (85%), methionine, metacresol, zinc chloride, HCl/NaOH, and water for injection.

Route of administration: subcutaneous injection (self-administered with the black-colored reusable iTango® pen-type injector).

Dose regimen: LixiLan was self-administered once daily in the morning in the hour (0 to 60 minutes) before breakfast. The initial daily dose of LixiLan to be administered during the first week of treatment was 5 dose steps, corresponding to an initial associated dose of 5 U of insulin glargine and 5 µg of lixisenatide according to the 1U:1 µg fixed ratio used. After the first week, the dose was titrated once a week based on the patient's need, until the patient reached a target fasting SMPG of ≥80 and ≤100 mg/dL (≥4.4 and ≤5.6 mmol/L) while avoiding hypoglycemia episodes.

Batch number(s): C1051431/IP0006068, C1051431/IP0006329, C1065458/IP0007555

Lixisenatide (Lyxumia®):

Formulation: Lixisenatide was supplied as a sterile aqueous solution in a pre-filled disposable pen including a 3-mL cartridge containing 300 µg of the active ingredient (100 µg/mL), glycerol (85%), sodium acetate trihydrate, methionine, metacresol, HCl/NaOH, and water for injection.

Route of administration: subcutaneous injection (administered with an orange-colored pre-filled disposable pen).

Dose regimen: Lixisenatide was self-administered once daily in the morning in the hour (0 to 60 minutes) before breakfast. The daily dose of lixisenatide to be administered was 10 µg during the first week of treatment, 15 µg during the second week, and 20 µg from Week 2 (V4) up to the end of the treatment period as tolerated (dose adjustment applied if not tolerated).

Batch number(s): C1056040/IP0006072, C1068635/IP0007227

Non-investigational medicinal product(s):

Background therapy (OADs) and rescue therapy were considered as non-investigational medicinal products (NIMPs).

OADs: in both treatment groups, only 1 to 2 of the following OADs (except DPP-4 inhibitors) was allowed to be used as background therapy during the study: biguanide, TZD, alpha-GI, SGLT2 inhibitor, glinide, and SU.

Rescue therapy: routine central laboratory alerts on HbA1c were set up to ensure that glycemic parameter results remained within predefined thresholds. In the event a patient's HbA1c exceeded predefined threshold (HbA1c >8.5% after V11 [Week 12, including values at V11] to V16 [Week 26, including values at V16] and HbA1c >8.0% after V16 [Week 26] to V23 [Week 52]), if no reason could be found for insufficient glucose control, if appropriate actions fail or if a daily dose of >20 dose steps is necessary (in LixiLan group) to decrease HbA1c below the threshold, a rescue therapy was to be added.

Duration of treatment: up to 52 weeks

Duration of observation: approximately 55 weeks maximum: an up to 2 week screening period, a 52-week open-label randomized treatment period, and a 3-day post-treatment safety follow-up period.

Criteria for evaluation:**Efficacy:**

Primary Endpoint: Change in HbA1c from baseline to Week 26.

Secondary Endpoints:

- Percentage of patients reaching HbA1c <7% or ≤6.5% at Week 26.
- Change in FPG from baseline to Week 26.
- Change in 7-point SMPG profiles from baseline to Week 26 (each time point and average daily value).
- Percentage of patients reaching HbA1c <7% with no body weight gain at Week 26.
- Change in body weight from baseline to Week 26.
- Percentage of patients requiring rescue therapy during the 26-week randomized treatment period.
- Change in daily dose of LixiLan from Day 1 to Week 26.
- All efficacy endpoints were also evaluated over 52 weeks of treatment.

Safety:

- Severe hypoglycemia, documented symptomatic hypoglycemia, and asymptomatic hypoglycemia.
- Adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESI), AEs requiring specific monitoring, safety laboratory values, vital signs, and electrocardiogram (ECG).
- Immunogenicity (antibody variables): anti-lixisenatide antibodies and/or anti-insulin antibodies (depending on the treatment group); neutralizing anti-lixisenatide antibodies in anti-lixisenatide positive patients.
- Safety variables were evaluated over 26 weeks and 52 weeks.

Pharmacokinetics:

- Total plasma concentrations of lixisenatide (LixiLan group and lixisenatide group)

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples were taken from patients in both treatment groups on Day 1 (baseline) at 1 to 4 hours after the first IMP injection, and twice on Week 26 and Week 52 (before IMP injection and between 1 and 4 hours after IMP injection). Post-injection results were calculated for the timeframes of ≥0 to ≤2 hours, >2 to ≤4 hours, and >4 hours after the injection.

For determination of total concentrations of lixisenatide (bound and unbound to anti-lixisenatide antibodies [ADA] in case of ADA-positive samples), plasma samples were analyzed using a validated enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantification (LLOQ) of 100 pg/mL. In ADA-negative samples, concentrations of lixisenatide were quantified by a validated ELISA with an LLOQ of 5.5 pg/mL.

Statistical methods:**Efficacy analysis:**

Efficacy analysis was based on the modified Intent-to-treat (mITT) population, defined as all randomized patients who were exposed to at least one dose of open-label IMP and had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.

Primary efficacy endpoint analysis:

Analyses of the primary efficacy endpoint (change in HbA1c from baseline to Week 26) were performed on the mITT population, using HbA1c values obtained from the scheduled visits during the on-treatment period. The last observation carried forward (LOCF) procedure was used by taking the last available post-baseline HbA1c measurement during the 26-week on-treatment period as the value at Week 26. The on-treatment period for HbA1c was defined as the time from the first injection of open-label IMP to 14 days after the last injection of open-label IMP or up to the introduction of rescue therapy, whichever was the earliest. The statistical test was 2-sided test at a nominal 5% significance level.

The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) model with treatment groups and randomization strata (HbA1c at screening [$<8.0\%$, $\geq 8.0\%$] and DPP-4 inhibitor use at screening [Yes, No]) as fixed effects and using the baseline HbA1c value as a covariate.

The baseline value was defined as the last available value prior to the first injection of open-label IMP. The adjusted mean change in HbA1c from baseline to Week 26 for each treatment group was estimated in the framework of this model, as well as the difference between treatment groups and the 95% confidence interval (CI) for the adjusted mean.

Secondary efficacy endpoint analysis:

All continuous secondary efficacy endpoints were analyzed using a similar ANCOVA model as described for the primary efficacy endpoint analysis. Differences between treatment groups and the 95% CIs were estimated within the framework of this model. All categorical efficacy endpoints were analyzed by Cochran-Mantel-Haenszel method stratified by the randomization strata. If the primary efficacy test was statistically significant at the 5% level, a hierarchical testing procedure was performed according to a pre-specified hierarchy. The testing was stopped if a test was found not to be statistically significant at the 5% level.

Safety analysis:

Safety analysis was performed descriptively based on the safety population (defined as all randomized patients exposed to at least one dose of open-label IMP, regardless of the amount of treatment administered). Patients were analyzed according to the treatment group actually received (as treated). Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that developed or worsened or became serious during the period from the first injection of the open-label IMP up to 3 days after the last injection of the open-label IMP.

Summary:**Population characteristics:**

A total of 321 Japanese patients were randomized to 1 of the 2 treatment groups: 161 in the LixiLan group and 160 in the lixisenatide group. Demographics and patient baseline characteristics were balanced between the two treatment groups. The randomized population consisted of 64.2% (206 of 321) male and 35.8% (115 of 321) female. The overall mean age was 58.0 years, the mean BMI was 26.82 kg/m², and the mean duration of T2DM was 8.67 years. At screening, 62.9% of patients (202 of 321) used two OADs and 37.1% (119 of 321) used one OAD.

Efficacy results:

The results of this study showed that in Japanese insulin-naïve patients with T2DM not well controlled with one or two OADs, the insulin glargine/lixisenatide fixed-ratio combination (LixiLan) provides better glycemic control assessed by the change in HbA1c as compared to lixisenatide.

Primary efficacy endpoint

The primary objective of this study was met as the statistical superiority of LixiLan compared to lixisenatide on HbA1c change from baseline to Week 26 was demonstrated.

From the comparable baseline levels of 8.39% for the LixiLan group and 8.38% for the lixisenatide group, the least-square (LS) mean changes in HbA1c from baseline to Week 26 were -1.58% for the LixiLan group versus -0.51% for the lixisenatide group, reaching the mean HbA1c levels of 6.73% and 7.79% at Week 26 (LOCF), respectively. Statistical superiority of LixiLan over lixisenatide was demonstrated (LS mean difference versus lixisenatide group = -1.07% [95% CI: -1.251% to -0.889%];

$p < 0.0001$)).

These results were robust across various sensitivity analyses and consistent in various subgroup analyses. No relevant differences in HbA1c changes by antibody status were observed.

Secondary efficacy endpoints

The key secondary efficacy endpoints were tested according to a step-down testing procedure to control the type I error.

Significantly more patients in the LixiLan group (65.2% [105 of 161]) achieved HbA1c <7% at Week 26 as compared to the lixisenatide group (19.4% [31 of 160]) during the 26-week on-treatment period. The proportion difference was 45.90% (95% CI: 36.71% to 55.09%, $p < 0.0001$).

Treatment with LixiLan significantly improved FPG in comparison to lixisenatide. Patients treated with LixiLan had significantly larger decrease in mean FPG from baseline to Week 26 (LOCF) than patients treated with lixisenatide. The LS mean change was -2.38 mmol/L (-42.89 mg/dL) in the LixiLan group versus -0.09 mmol/L (-1.65 mg/dL) in the lixisenatide group; the LS mean difference was -2.29 mmol/L (95% CI: -2.263 to -1.915; $p < 0.0001$) or -41.23 mg/dL (95% CI: -47.968 to -34.501; $p < 0.0001$).

Patients treated with LixiLan also had significantly larger decrease in mean average 7-point SMPG from baseline to Week 26 (LOCF) than patients treated with lixisenatide (LS mean difference: -1.94 mmol/L [95% CI: -2.362 to -1.516; $p < 0.0001$] or -34.99 mg/dL [95% CI: -42.604 to -27.372; $p < 0.0001$]). The 7-point SMPG profiles showed marked decrease in mean SMPG value from baseline to Week 26 across all timepoints in the LixiLan group; the mean SMPG values at all timepoints were lower in the LixiLan group compared to the lixisenatide group.

Significantly more patients treated with LixiLan reached the composite endpoint of HbA1c <7% with no body weight gain (29.8% [48 of 161]) as compared to patients treated with lixisenatide (17.5% [28 of 160]) (proportion difference: 12.39% [95% CI: 3.36% to 21.43%; $p = 0.0089$]).

A mild increase in mean body weight was observed in patients treated with LixiLan (mean [SD]: +0.65 [2.15] kg at Week 26 [LOCF]) as compared to a mean body weight decrease in patients treated with lixisenatide (-1.29 [2.06] kg at Week 26 [LOCF]). The LS mean difference at Week 26 was +1.94 kg (95% CI: 1.479 to 2.407 kg).

Very few patients treated with LixiLan required rescue therapy during the 26-week on-treatment period (1 patient [0.6%] in the LixiLan group versus 19 patients [11.9%] in the lixisenatide group; proportion difference: -11.21% [95% CI: -16.46% to -5.96%]).

In the LixiLan group, the mean average daily insulin glargine dose (SD) was 5.00 (0.00) U at Day 1, 16.69 (4.19) U at Week 26 (LOCF), and 17.01 (4.04) U at Week 52 (LOCF).

During the 26-week extension treatment period from the end of Week 26 to Week 52, the larger decrease in HbA1c, FPG, and 7-point SMPG profile in LixiLan compared to Lixisenatide was maintained.

In conclusion, treatment with LixiLan in T2DM patients significantly improved HbA1c and allowed more patients to reach recommended treatment targets compared to Lixisenatide, along with significant improvement in FPG and 7-point profiles compared to Lixisenatide alone.

Safety results:

LixiLan was well tolerated during the 52-week on-treatment period. The safety profile of the LixiLan group generally reflected those of its components. No new or unexpected safety signals were identified. Compared to lixisenatide, LixiLan was associated with markedly lower rates of nausea and gastrointestinal disorders SOC overall, leading to fewer permanent treatment discontinuations. Whereas nausea mainly occurred during the initial dosing period with lixisenatide, as with GLP-1 receptor agonists in general, a blunting of this phenomenon was observed with introduction of LixiLan.

The median duration of study treatment was identical in both treatment groups (365.0 days).

The incidence of documented symptomatic hypoglycemia (≤ 70 mg/dL [3.9 mmol/L]) was 13.0% (21 of 161) in the LixiLan group versus 2.5% (4 of 160) in the lixisenatide group during the 26 week on-treatment period; and 18.0% (29 of 161) versus 4.4% (7 of 160) during the 52-week on-treatment period. The number of events per patient year was 0.80 in the LixiLan group and 0.10 in the lixisenatide group during the 52-week on-treatment period. No severe hypoglycemia was reported in either treatment group, and no hypoglycemia event was reported as SAE.

Majority of patients in either treatment group experienced at least one TEAE during the 26-week and 52-week on-treatment periods (67.7% [109 of 161] in the LixiLan group and 76.3% [122 of 160] in the lixisenatide group during 26-week; 80.1% [129 of 161] and 86.9% [139 of 160] during 52-week).

The most frequently reported TEAE (PT) was nasopharyngitis with similar incidences in both treatment groups during both the 26-week and 52-week on-treatment periods.

Nausea was the second most frequently reported TEAE with markedly lower incidence in the LixiLan group compared to the lixisenatide group (23 patients [14.3%] versus 43 patients [26.9%] during the 26 week on-treatment period; 24 [14.9%] versus

45 [28.1%] during the 52-week on-treatment period).

The overall incidence of gastrointestinal disorders SOC was also markedly lower in the LixiLan group than in the lixisenatide group (29.2% [47 of 161] in the LixiLan group versus 42.5% [68 of 160] in the lixisenatide group during the 26-week on-treatment period; 36.0% [58 of 161] versus 50.0% [80 of 160] during the 52-week on-treatment period).

Overall, 1 patient from the lixisenatide group died during the study treatment period due to TEAEs of cardiac failure congestive (related to IMP per Investigator) and pulmonary alveolar haemorrhage (not related to IMP); no patient died in the LixiLan group. Serious TEAEs were reported in 5 patients (3.1%) in the LixiLan group and 4 patients (2.5%) in the lixisenatide group during the 26-week on-treatment period; 7 (4.3%) versus 13 (8.1%) during the 52-week on-treatment period. The difference seen during the 52-week on-treatment period was driven by a higher incidence of serious TEAE in the Infections and Infestations SOC reported in the lixisenatide group.

The overall incidence of TEAEs leading to permanent treatment discontinuation was markedly lower in the LixiLan group than in the lixisenatide group (4 [2.5%] versus 17 [10.6%] during the 26-week on-treatment period; 4 [2.5%] versus 20 [12.5%] during the 52-week on-treatment period). Most of treatment discontinuations were due to gastrointestinal TEAEs in the lixisenatide group, with nausea being the most frequent PT leading to treatment discontinuation.

No pancreatic or thyroid carcinoma was reported in either treatment group. No TEAE of increased calcitonin (≥ 20 pg/mL) was reported in either treatment group.

One patient in the lixisenatide group reported acute pancreatitis due to bile duct obstruction. TEAE of amylase/lipase increase were reported in 2 patients (1.2%) in the LixiLan group and 5 patients (3.1%) in the lixisenatide group during the 52-week on-treatment period.

One patient (0.6%) in the LixiLan group and 2 patients (1.3%) in the lixisenatide group experienced TEAEs of ALT increase >3 ULN during the 52-week on-treatment period. One event with ALT >3 ULN and total bilirubin >2 ULN was reported in a patient in the lixisenatide group with Jaundice cholestatic due to gallstones.

A total of 5 patients (3.1%) in the LixiLan group and 13 patients (8.1%) in the lixisenatide group experienced injection site reactions during the 52-week on-treatment period. The percentage of patients who reported a suspected allergic event on the specific adverse event form was 7 patients (4.3%) in the LixiLan group and 6 patients (3.8%) in the lixisenatide group during the 52-week on-treatment period.

No particular safety concerns were identified in the review of clinical laboratory parameters, vital signs, physical examination findings, or ECGs.

During the 26-week and 52-week on-treatment periods, the percentage of patients who developed positive ADA status (from negative status at baseline) was 63.5% (101 of 159) in the LixiLan group and 73.8% (110 of 149) in the lixisenatide group at Week 26; 57.1% (89 of 156) and 79.4% (108 of 136) at Week 52. There was no substantial difference in the safety profile between ADA-positive patients and ADA-negative patients in either treatment group, and between AIA-positive patients and AIA-negative patients in the LixiLan group.

Pharmacokinetic results:

In patients treated with LixiLan or lixisenatide who were ADA negative at Week 26, the median postdose total lixisenatide concentrations increased from baseline to Week 26 due to the increase in dose. From Week 26 to Week 52 the postdose total concentrations did not change in neither of the treatment groups.

In patients treated with LixiLan or lixisenatide who were ADA positive at Week 26, the median postdose total lixisenatide concentrations were higher than in ADA-negative patients. From Week 26 to Week 52 the median postdose total concentrations did not change essentially in neither of the treatment groups. The median postdose total lixisenatide concentrations in ADA-positive patients stayed higher than in ADA-negative patients.

In summary, the PK behavior of lixisenatide when administered as LixiLan is in line with the PK behavior of lixisenatide as observed when administered alone.

Conclusions: Treatment with LixiLan significantly improved glycemic control compared to lixisenatide alone, and allowed more patients to reach HbA1c targets without body weight gain. This was achieved with a safety profile in line with its components, so that the benefit-risk ratio is positive.

The concept of this fixed-ratio combination allows both insulin glargine titration to fasting glucose targets and concomitant slow dose increase of lixisenatide. These properties allow individualization of treatment taking into account patient response and tolerance, thereby mitigating the side-effect profile of GLP-1 receptor agonists and favoring adherence to therapy.

The present study provides an evidence base that supports the use of this new dual therapeutic paradigm as an injectable therapy to advance diabetes treatment in patients with T2DM when OADs are not sufficient.

Example 3

A randomized, 26-week, active-controlled, open label, 2-treatment arm, parallel-group and multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed-ratio combination (LixiLan) to insulin glargine on top of oral antidiabetic drugs in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs (EFC14114)

Study center(s): 113 centers in Japan	
Phase of development: Phase 3	
Objectives: Primary Objective To demonstrate the superiority of the insulin glargine/lixisenatide fixed-ratio combination (LixiLan) to insulin glargine in glycated hemoglobin A1c (HbA1c) change from baseline to Week 26. Secondary Objective(s) To assess the effects of LixiLan in comparison with insulin glargine over 26 weeks on: • Percentage of patients reaching HbA1c targets <7% or ≤6.5%. • Glycemic control in relation to a meal as evaluated by 2-hour postprandial plasma glucose (PPG) and glucose excursion during a standardized meal test. • 7-point self-monitored plasma glucose (SMPG) profile. • Percentage of patients reaching HbA1c targets with no body weight gain and/or documented symptomatic hypoglycemia. • Body weight. • Insulin glargine dose (in the LixiLan and insulin glargine groups). • Fasting plasma glucose (FPG). To assess the safety and tolerability in each treatment group. To assess the development of anti-lixisenatide and/or anti-insulin antibodies (depending on treatment group).	
Methodology: This was an open-label, 1:1 randomized, active-controlled, 2-arm, 26-week treatment duration, parallel-group, and multicenter Phase 3 study. The study recruited Japanese outpatients with type 2 diabetes mellitus (T2DM) inadequately controlled on oral antidiabetic drugs (OADs). The study comprised 3 periods: • An up to 2-week screening period • A 26-week open label randomized treatment period: at randomization, Dipeptidyl-peptidase-4 (DPP-4) inhibitor if previously taken was stopped. In patients with a screening HbA1c <8% the dose of sodium-glucose co-transporter 2 (SGLT2) inhibitor, sulfonylurea or rapid-acting insulin secretagogue (glinide) was decreased by at least 50% (or stopped in case of minimum dose) at randomization in order to decrease the risk of hypoglycemia • A 3-day post-treatment safety follow-up period for all the patients after permanent investigational medicinal product (IMP) discontinuation (except for patients who prematurely discontinued the study treatment but continued in the study).	
Number of patients: Planned: 534 patients (267 patients per group) Randomized: 521 patients (260 in the LixiLan group, 261 in the insulin glargine group) Treated: 521 patients (260 in the LixiLan group, 261 in the insulin glargine group)	
Evaluated:	Efficacy: 520 patients

Safety: 521 patients

Diagnosis and criteria for inclusion:

Inclusion criteria: patient with T2DM diagnosed for at least 1 year before the screening visit; patient receiving 1 or 2 OADs allowed for the purpose of this study (which included biguanide, thiazolidinedione [TZD], alpha-glucosidase-inhibitor [alpha-GI], SGLT2 inhibitor, sulfonylurea [SU], glinide, and DPP-4 inhibitor) at least the usual maintenance dose according to the approved label; in case of use of DPP-4 inhibitor, patient could receive up to 3 OADs; the OAD dose(s) had to be stable during the 3 months before the screening visit; signed written informed consent.

Key exclusion criteria at screening: age <20 years; HbA1c <7.5% or >9.5%; FPG >180 mg/dL (10.0 mmol/L) and confirmed FPG >180 mg/dL (10.0 mmol/L) by a repeat test before randomization; body mass index (BMI) <15 or >40 kg/m²; use of oral or injectable glucose-lowering agents other than those stated during the inclusion criteria in the 3 months prior to screening; previous treatment with insulin (except for short-term treatment due to intercurrent illness including gestational diabetes at the discretion of the trial physician).

Study treatments

Investigational medicinal product(s):

LixiLan:

Formulation: LixiLan (1 U:1 µg) was supplied as a sterile aqueous solution for SC injection in a 3 mL glass cartridge containing 300 U insulin glargine (100 U/mL) and 300 µg lixisenatide (100 µg/mL), glycerol (85%), methionine, metacresol, zinc chloride, HCl/NaOH and water for injection.

Route(s) of administration: subcutaneous injection

Dose regimen: LixiLan was self-administered with a reusable iTango® pen-type injector once daily in the morning in the hour (0 to 60 minutes) before breakfast. The initial daily dose of LixiLan to be administered during the first week of treatment was 5 dose steps; this corresponded to an initial associated dose of 5 U of insulin glargine and 5 µg of lixisenatide according to the 1U:1 µg fixed ratio used. Dose was adjusted weekly. After the first week, the dose was titrated once a week based on the patient's need, until the patient reached a target fasting SMPG of ≥80 and ≤100 mg/dL (≥4.4 and ≤5.6 mmol/L) while avoiding hypoglycemia episodes.

Batch number(s): C1051431

Insulin glargine (Lantus®):

Formulation: insulin glargine was supplied as a sterile aqueous solution for SC injection in a 3 mL glass cartridge containing 300 U of the active ingredient (ie, 100 U/mL insulin glargine), glycerol (85%), metacresol, zinc chloride, HCl/NaOH, and water for injection.

Route(s) of administration: subcutaneous injection

Dose regimen: insulin glargine, in a pre-filled disposable Lantus Solostar®, was self-administered once daily according to the approved label (ie, before breakfast or at bedtime) but at about the same time every day. The initial daily dose of insulin glargine to be administered during the first week of treatment was 5 U. The dose was adjusted weekly following the same algorithm as for LixiLan.

Batch number(s): C1054370 and C1057728

Noninvestigational medicinal product(s) (if applicable): background therapy (OADs) and rescue therapy were considered as noninvestigational medicinal products (NIMPs).

OADs: in both treatment groups, only 1 to 2 of the following OADs (except DPP-4 inhibitors) were allowed to be used as background therapy during the study: biguanide, TZD, alpha-GI, SGLT2 inhibitor, glinide, and SU.

Rescue therapy: routine central laboratory alerts on HbA1c were set up to ensure that glycemic parameter results remained within predefined thresholds. The thresholds values were defined as: after Visit 11 (Week 12, including values at Visit 11) to Visit 16 (Week 26, including values at Visit 16): HbA1c >8.5%. In the event that HbA1c exceeded the thresholds, if no reason could be found for insufficient glucose control, if appropriate actions failed or if a dose >20 dose steps in the LixiLan group or >20 U in the insulin glargine group was necessary to decrease HbA1c below the threshold, a rescue treatment was to be added.

Duration of treatment: up to 26 weeks

Duration of observation: the maximum study duration per patient was approximately 29 weeks: an up to 2 week screening period, a 26-week open label randomized treatment period, and a 3-day post-treatment safety follow-up period.

Criteria for evaluation:

Efficacy:

Primary Endpoint: change in HbA1c from baseline to Week 26.

Secondary Endpoint(s):

- Percentage of patients reaching HbA1c <7% or ≤6.5% at Week 26.
- Change in 2-hour PPG and in blood glucose excursion during standardized meal test from baseline to Week 26.
- Change in 7-point SMPG profiles from baseline to Week 26 (each time point and average daily value).
- Percentage of patients reaching HbA1c <7% with no body weight gain at Week 26.
- Change in body weight from baseline to Week 26.
- Percentage of patients reaching HbA1c <7% with no body weight gain at Week 26 and with no documented (plasma glucose ≤70 mg/dL [3.9 mmol/L]) symptomatic hypoglycemia during the 26-week randomized treatment period.
- Change in daily dose of insulin glargine from Day 1 to Week 26.
- Percentage of patients reaching HbA1c <7% at Week 26 with no documented (plasma glucose ≤70 mg/dL [3.9 mmol/L]) symptomatic hypoglycemia during the 26-week randomized treatment period.
- Change in FPG from baseline to Week 26.
- Percentage of patients requiring rescue therapy during the 26-week randomized treatment period.

Safety:

- Severe hypoglycemia, documented symptomatic hypoglycemia and asymptomatic hypoglycemia.
- Adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs), AEs requiring specific monitoring, safety laboratory values, vital signs, and electrocardiogram (ECG).
- Immunogenicity (antibody variables): anti-lixisenatide antibodies and/or anti-insulin antibodies (depending on the treatment group).

Statistical methods:

Efficacy analysis:

Efficacy analysis was based on the modified Intent-to-treat (mITT) population, defined as all randomized patients who were exposed to at least one injection of open-label IMP and had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.

Primary efficacy endpoint analysis:

Analyses of the primary efficacy endpoint (change in HbA1c from baseline to Week 26) were performed on the mITT population, using HbA1c values obtained from the scheduled visits during the on-treatment period. The last observation carried forward (LOCF) procedure was used by taking the last available post-baseline HbA1c measurement during the on-treatment period as the value at Week 26. The on-treatment period for HbA1c was defined as the time from the first injection of open-label IMP to 14 days after the last injection of open-label IMP or up to the introduction of rescue therapy, whichever was the earliest. The statistical test was 2-sided at the significance level of 0.05.

The primary analysis method for the primary efficacy endpoint was an analysis of covariance (ANCOVA) model with treatment groups, randomization strata (HbA1c at screening [≤8.0%, ≥8.0%]) and DPP-4 inhibitor use at screening [Yes, No] as fixed effects and using the baseline HbA1c value as a covariate.

The baseline value was defined as the last available value prior to the first injection of open-label IMP. The adjusted mean change in HbA1c from baseline to Week 26 for each treatment group was estimated in the framework of this model, as well as the difference between treatment groups and the 95% confidence interval (CI) for the adjusted mean.

Secondary efficacy endpoint analysis:

The continuous secondary efficacy endpoints were analyzed using a similar ANCOVA model as described for the primary efficacy endpoint analysis. Differences between treatment groups and the 95% CIs were estimated within the framework of this model. Categorical efficacy endpoints were analyzed by Cochran-Mantel-Haenszel method stratified by the randomization strata (HbA1c

at screening [$<8.0\%$, $\geq 8.0\%$] and DPP-4 inhibitor use at screening [Yes, No]). If the primary efficacy test was statistically significant at the 5% level, a hierarchical testing procedure was performed according to a pre-specified hierarchy. The testing was to be stopped when an endpoint was found not to be statistically significant at the 5% level.

Safety analysis:

Safety analysis was descriptively performed based on the safety population, defined as all randomized patients exposed to at least one injection of open-label IMP, regardless of the amount of treatment administered. Patients were analyzed according to the treatment actually received (as treated). Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during the period from the first injection of the open-label IMP up to 3 days after the last injection of the open-label IMP.

Summary:

Population characteristics:

A total of 521 patients were randomized (260 in the LixiLan group and 261 in the insulin glargine group). Demographics and baseline characteristics were balanced between the 2 treatment groups. The overall mean age was 59.7 years old and the mean BMI was 26.04 kg/m². The mean diabetes duration was 9.25 years. Overall, 34.5% (180 of 521 patients) of the study population was female. At screening, most of the patients (51.6% [269 of 521 patients]) used two OADs, and 34.5% (180 of 521 patients) of the patients used one OAD.

Efficacy results:

Primary efficacy endpoint:

The primary objective of the study was met as the statistical superiority of LixiLan compared to insulin glargine on HbA1c change from baseline to Week 26 was demonstrated.

From comparable baseline levels of 8.08% for the LixiLan group and 8.01% for the insulin glargine group, the adjusted mean changes (hereafter referred to as the least squared [LS] mean changes) in HbA1c were -1.40% for the LixiLan group and -0.76% for the insulin glargine group, reaching mean HbA1c levels of 6.66% and 7.26% at Week 26 (LOCF), respectively.

Statistical superiority of the LixiLan over insulin glargine was demonstrated (LS mean difference versus insulin glargine group = -0.63%; 95% CI: -0.749% to -0.514%; p-value <0.0001).

Secondary efficacy endpoints:

The improvement in HbA1c was reflected in the higher proportion of LixiLan-treated patients reaching pre-specified HbA1c target $<7\%$ versus patients in the insulin glargine group (71.5% [186 of 260 patients] and 38.5% [100 of 260 patients], respectively). The proportion difference versus insulin glargine was 32.94%; p-value <0.0001 .

Treatment with LixiLan significantly improved postprandial glycemic control during a standardized meal test in comparison to insulin glargine as shown by the results for the 2-hour glucose excursion (LS mean change was -4.26 mmol/L [-76.77 mg/dL] and 0.19 mmol/L [3.38 mg/dL], respectively; the LS mean difference versus insulin glargine was -4.45 mmol/L [-80.15 mg/dL];

p <0.0001). A greater decrease in 2-hour PPG from baseline to Week 26 was also observed in the LixiLan group compared to the insulin glargine group (the LS mean difference versus insulin glargine was -4.78 mmol/L [-86.07 mg/dL]).

Patients treated with LixiLan had a statistically significantly greater decrease in average 7-point SMPG profile compared to patients treated with insulin glargine (LS mean difference versus insulin glargine: -1.36 mmol/L [-24.56 mg/dL]; p <0.0001). The 7-point SMPG profiles showed a marked decrease in mean plasma glucose at all time-points at Week 26 compared with the baseline in the LixiLan group; the mean values at all time-points were lower in the LixiLan group compared to the insulin glargine group.

A statistically significantly higher proportion of patients reached the composite endpoint of HbA1c $<7\%$ with no body weight gain at Week 26 in the LixiLan group (35.4% [92 of 260 patients]) compared to the insulin glargine group (11.5% [30 of 260 patients]) (proportion difference versus insulin glargine was 23.86%, p <0.0001).

Body weight increased less in the LixiLan group compared to the insulin glargine group with a LS mean change in body weight from baseline to Week 26 (LOCF) of 0.26 kg and 1.33 kg, respectively. A statistically significant difference in the body weight change from baseline to Week 26 (LOCF) was found in favor of the LixiLan group (LS mean difference was -1.06 kg; p <0.0001).

A statistically significantly higher proportion of patients reached the composite endpoint of HbA1c $<7\%$ with no body weight gain at Week 26 and with no documented (plasma glucose concentration ≤ 70 mg/dL [3.9 mmol/L]) symptomatic hypoglycemia in the LixiLan group (30.8% [80 of 260 patients]) compared to the insulin glargine group (10.0% [26 of 260 patients]); the proportion difference versus insulin glargine was 20.78%; p <0.0001 .

The insulin dose increased in both treatment groups with the steepest increase observed from Week 2 (when up-titration was

allowed) until week 14. The insulin glargine group reached a higher insulin glargine dose at Week 26 (mean average daily dose of 15.10 U in the LixiLan group and 17.30 U in the insulin glargine group at Week 26 [LOCF]). The LS mean change in average daily insulin glargine dose from Day 1 to Week 26 was statistically significantly lower in the LixiLan group (10.11 U) compared to the insulin glargine group (12.31 U) (the LS mean difference = -2.20 U; $p < 0.0001$).

More patients reached the endpoint of HbA1c $< 7\%$ with no documented (plasma glucose concentration ≤ 70 mg/dL [3.9 mmol/L]) symptomatic hypoglycemia during the on-treatment period in the LixiLan group (60.0% [156 of 260 patients]) compared to the insulin glargine group (34.6% [90 of 260 patients]), and the difference between the LixiLan group vs. insulin glargine was statistically significant (proportion difference versus insulin glargine = 25.28%, $p < 0.0001$).

The LS mean change in FPG from baseline to Week 26 (LOCF) was greater in the LixiLan group (-1.77 mmol/L [-31.84 mg/dL]) compared to the insulin glargine group (-1.37 mmol/L [-24.75 mg/dL]); LS mean difference versus insulin glargine was -0.39 mmol/L (-7.09 mg/dL); $p = 0.0030$.

Safety results:

LixiLan was well tolerated during the 26-week on-treatment period; the safety profile of the LixiLan group reflected those of its components. No new or unexpected safety signals were identified.

Median duration of study treatment was identical in both treatment groups (183.0 days).

The incidence of documented (≤ 70 mg/dL) symptomatic hypoglycemia was 14.2% [37 of 260 patients] in the LixiLan group and 12.3% [32 of 261 patients] in the insulin glargine group with corresponding event rates per patient-year of 0.73 and 0.54 respectively. No severe hypoglycemia was reported in either treatment group, and no hypoglycemia event was reported as SAE.

A total of 163 patients (62.7%) in the LixiLan group and 166 patients (63.6%) in the insulin glargine group reported TEAEs.

The most frequently occurring TEAEs (preferred term [PT] $\geq 5\%$) in the LixiLan group and in the insulin glargine group were nasopharyngitis (18.8% [49 of 260 patients] and 23.8% [62 of 261 patients], respectively) and nausea (9.6% [25 of 260 patients] and 1.9% [5 of 261 patients], respectively).

The overall incidence of gastrointestinal adverse events was 26.2% (68 of 260 patients) and 14.9% (39 of 261 patients) in the LixiLan group and in the insulin glargine group, respectively. In the LixiLan group, nausea was the most frequently reported gastrointestinal adverse events (9.6%). All patients who had nausea had events of mild or moderate intensity.

Two patients (0.8%) in the LixiLan group permanently discontinued IMP treatment due to nausea.

One patient in the LixiLan group died during the on-treatment period due to a TEAE of cardiac disorder; the fatal event was considered not related to the IMP by the Investigator. No patient in the insulin glargine group experienced any TEAE leading to death.

Serious TEAEs were reported in 6 patients (2.3%) and 8 patients (3.1%) in the LixiLan group and in the insulin glargine group, respectively.

The overall incidence of TEAEs leading to permanent treatment discontinuation was 1.5% (4 of 260 patients) and 0.8% (2 of 261 patients) in the LixiLan group and in the insulin glargine group, respectively. Most of these withdrawals were caused by gastrointestinal adverse events in the LixiLan group (0.8% [2 of 260 patients]) compared to the insulin glargine group (0%).

No pancreatic or thyroid carcinoma was reported in either treatment group. No TEAE of increased calcitonin (≥ 20 pg/mL) was reported in either treatment group.

No patient in either group experienced any AE of alanine aminotransferase (ALT) increase (> 3 upper limit of normal [ULN]) during the 26-week on-treatment period. None of the events which met the definition for Hy's Law occurred.

Conclusions:

Treatment with LixiLan significantly improved the benefit/risk ratio compared to insulin glargine alone, and allowed more patients to reach HbA1c targets without body weight gain and without increasing the rate of documented symptomatic hypoglycemia compared to insulin glargine alone.

The concept of this fixed-ratio combination allows both insulin glargine titration to fasting glucose targets and concomitant slow dose increase of lixisenatide. These properties allow individualization of treatment taking into account patient response and tolerance, thereby mitigating the side-effect profile of GLP-1 receptor agonists and favoring adherence to therapy.

The present study provides an evidence base that supports the use of this new dual therapeutic paradigm as an injectable therapy to advance diabetes treatment in patients with T2DM when OADs are not sufficient.

Example 4**Concomitant use of a fixed-dose ratio formulation of insulin glargine and lixisenatide with SGLT2i – subgroup analysis of Example 1**

The concomitant use of a fixed-dose ratio combination (FRC) of insulin glargine and lixisenatide with an SGLT2 inhibitor (SGLT2i) is supported by subgroup analyses of the patient group being subject of Example 1 (study EFC13794). In this study, 26 patients (10.1%) received concomitantly the FRC, metformin and a SGLT2i.

The FRC was provided in a single formulation, as described in Example 1.

An improvement was observed in efficacy results (change from baseline to Week 26 in glycated hemoglobin [HbA1c], fasting plasma glucose [FPG] and 2-hour postprandial plasma glucose [PPG]) in both treatment groups (Table 3, Table 4 and Table 5).

In patients receiving an SGLT2 inhibitor, the effect of the fixed-ratio formulation was larger than in the comparative treatment, compared with the patient group not receiving an SGLT2 inhibitor.

In patients receiving an SGLT2 inhibitor, after 26 weeks improvement in HbA1c was 0.88 % in view of the active comparator (GLP-1 RA), compared with 0.61 % in patients not receiving an SGLT2 inhibitor (Table 3).

In patients receiving an SGLT2 inhibitor, after 26 weeks improvement in fasting plasma glucose was 2.06 mmol/L in view of the active comparator (GLP-1 RA), compared with 1.64 mmol/L in patients not receiving an SGLT2 inhibitor (Table 4).

In patients receiving an SGLT2 inhibitor, after 26 weeks improvement in 2 hour postprandial glucose was 3.26 mmol/L in view of the active comparator (GLP-1 RA), compared with 2.81 mmol/L in patients not receiving an SGLT2 inhibitor (Table 5).

Overview of safety did not reveal relevant differences for SGLT2i users compared to

non-users. In the FRC group, none of the SGLT2i users discontinued treatment due to an adverse event and no patients reported adverse events of body weight increase. Among the SGLT2i users no patients reported nausea or diarrhea in either treatment group, and only 1 patient reported vomiting in the FRC group (Table 6, Table7).

Documented symptomatic hypoglycemia (plasma glucose ≤ 3.9 mmol/L [≤ 70 mg/dL]) was reported less frequently in the FRC group using SGLT2i versus non-users (0.72 events per patient year for SGLT2i users versus 1.62 for non-users) (Table 8).

Table 1 - Demographics and patient characteristics at screening or baseline by SGLT2 inhibitor use at screening - Randomized population (EFC13794)

	SGLT2 inhibitor use at screening Yes (N=52)		SGLT2 inhibitor use at screening No (N=462)	
	Fixed Ratio Combination (N=26)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=231)	GLP-1 Receptor Agonist (N=231)
Age (years)				
Number	26	26	231	231
Mean (SD)	59.7 (8.9)	58.8 (10.9)	59.2 (9.7)	60.1 (10.2)
Median	59.5	59.0	59.0	60.0
Min : Max	40 : 82	32 : 74	30 : 78	25 : 84
Age group (years) [n (%)]				
Number	26	26	231	231
< 50	2 (7.7%)	3 (11.5%)	35 (15.2%)	37 (16.0%)
≥ 50 - <65	17 (65.4%)	14 (53.8%)	113 (48.9%)	113 (48.9%)
≥ 65 - <75	6 (23.1%)	9 (34.6%)	78 (33.8%)	66 (28.6%)
≥ 75	1 (3.8%)	0	5 (2.2%)	15 (6.5%)
Gender [n (%)]				
Number	26	26	231	231
Male	11 (42.3%)	18 (69.2%)	115 (49.8%)	126 (54.5%)
Female	15 (57.7%)	8 (30.8%)	116 (50.2%)	105 (45.5%)
Race [n (%)]				
Number	26	26	231	231
American Indian or Alaska Native	0	0	0	0
Asian/Oriental	0	1 (3.8%)	3 (1.3%)	3 (1.3%)
Black	1 (3.8%)	0	11 (4.8%)	7 (3.0%)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.4%)	0
White	25 (96.2%)	24 (92.3%)	216 (93.5%)	220 (95.2%)
Othera	0	1 (3.8%)	0	1 (0.4%)
Ethnicity [n (%)]				
Number	26	26	231	231

	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=52)		No (N=462)	
	Fixed Ratio Combination (N=26)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=231)	GLP-1 Receptor Agonist (N=231)
Hispanic or Latino	4 (15.4%)	4 (15.4%)	23 (10.0%)	22 (9.5%)
Not Hispanic or Latino	22 (84.6%)	22 (84.6%)	208 (90.0%)	209 (90.5%)
Unknown	0	0	0	0
HbA1c (%) at Visit 1 (Week -2)				
Number	26	26	231	231
Mean (SD)	7.83 (0.53)	7.90 (0.51)	7.86 (0.56)	7.88 (0.54)
Median	7.90	7.95	7.80	7.80
Min : Max	7.0 : 9.0	7.0 : 8.7	7.0 : 9.0	7.0 : 9.0
Randomization strata of HbA1c (%) at Visit 1 (Week -2) [n (%)]				
Number	26	26	231	231
<8	15 (57.7%)	13 (50.0%)	134 (58.0%)	134 (58.0%)
≥8	11 (42.3%)	13 (50.0%)	97 (42.0%)	97 (42.0%)
Randomization strata of GLP-1 receptor agonist subtype at screening [n (%)]				
Number	26	26	231	231
Once/twice daily formulation	11 (42.3%)	11 (42.3%)	142 (61.5%)	143 (61.9%)
Once weekly formulation	15 (57.7%)	15 (57.7%)	89 (38.5%)	88 (38.1%)
Baseline BMI (kg/m ²)				
Number	26	26	231	231
Mean (SD)	30.48 (4.03)	32.85 (3.51)	33.05 (4.37)	32.96 (4.47)
Median	30.75	33.00	33.00	33.00
Min : Max	24.5 : 39.0	25.2 : 38.9	21.2 : 40.0	21.5 : 40.0
Baseline BMI categories (kg/m ²) [n (%)]				
Number	26	26	231	231
< 30	12 (46.2%)	5 (19.2%)	59 (25.5%)	64 (27.7%)
≥ 30	14 (53.8%)	21 (80.8%)	172 (74.5%)	167 (72.3%)

BMI = Body Mass Index, SGLT2 = Sodium glucose co-transporter 2

a Includes patients with more than one race, unknown or not reported

Table 2 - Disease characteristics at screening or baseline by SGLT2 inhibitor use at screening - Randomized population (EFC13794)

	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=52)		No (N=462)	
	Fixed Ratio Combination (N=26)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=231)	GLP-1 Receptor Agonist (N=231)
Duration of diabetes (years)				

	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=52)		No (N=462)	
	Fixed Ratio Combination (N=26)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=231)	GLP-1 Receptor Agonist (N=231)
Number	26	26	231	231
Mean (SD)	12.31 (6.86)	10.91 (5.39)	11.11 (7.49)	10.96 (6.16)
Median	11.20	9.87	9.79	9.83
Min : Max	1.4 : 26.5	2.5 : 21.2	1.0 : 57.9	1.4 : 40.1
Age at onset of Type 2 diabetes (years)				
Number	26	26	231	231
Mean (SD)	47.3 (9.3)	47.8 (9.9)	48.0 (10.0)	49.1 (9.1)
Median	49.0	51.0	50.0	50.0
Min : Max	33 : 64	27 : 63	11 : 68	19 : 69
Duration of GLP-1 receptor agonist treatment (years)				
Number	26	26	231	231
Mean (SD)	1.75 (1.24)	2.06 (1.70)	1.91 (1.81)	1.90 (1.87)
Median	1.62	1.41	1.15	1.06
Min : Max	0.4 : 5.2	0.5 : 6.4	0.3 : 13.0	0.3 : 12.1
GLP-1 receptor agonist use by type at screening in eCRF [n (%)]				
Number	26	26	231	231
Once/twice daily formulation	11 (42.3%)	11 (42.3%)	142 (61.5%)	143 (61.9%)
Once weekly formulation	15 (57.7%)	15 (57.7%)	89 (38.5%)	88 (38.1%)
Daily dose of liraglutide (mg) at baseline				
Number	11	11	124	134
Mean (SD)	1.69 (0.24)	1.69 (0.24)	1.66 (0.26)	1.66 (0.29)
Median	1.80	1.80	1.80	1.80
Min : Max	1.2 : 1.8	1.2 : 1.8	1.2 : 1.8	1.2 : 3.0
Daily dose of exenatide (µg) at baseline				
Number	0	0	18	9
Mean (SD)			18.33 (3.83)	17.78 (4.41)
Median			20.00	20.00
Min : Max			10.0 : 20.0	10.0 : 20.0
Weekly dose of exenatide extended- release (mg) at baseline				
Number	4	3	41	45
Mean (SD)	2.00 (0.00)	2.00 (0.00)	2.00 (0.00)	2.00 (0.00)
Median	2.00	2.00	2.00	2.00
Min : Max	2.0 : 2.0	2.0 : 2.0	2.0 : 2.0	2.0 : 2.0
Weekly dose of albiglutide (mg) at baseline				
Number	0	2	5	2

	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=52)		No (N=462)	
	Fixed Ratio Combination (N=26)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=231)	GLP-1 Receptor Agonist (N=231)
Mean (SD)		40.00 (14.14)	50.00 (0.00)	50.00 (0.00)
Median		40.00	50.00	50.00
Min : Max		30.0 : 50.0	50.0 : 50.0	50.0 : 50.0
Weekly dose of dulaglutide (mg) at baseline				
Number	11	10	43	41
Mean (SD)	1.36 (0.30)	1.43 (0.24)	1.45 (0.19)	1.39 (0.27)
Median	1.50	1.50	1.50	1.50
Min : Max	0.8 : 1.5	0.8 : 1.5	0.8 : 1.5	0.8 : 1.5
Pioglitazone use at screening recorded in eCRF [n (%)]				
Number	26	26	231	231
Yes	1 (3.8%)	1 (3.8%)	11 (4.8%)	21 (9.1%)
No	25 (96.2%)	25 (96.2%)	220 (95.2%)	210 (90.9%)
Daily dose of pioglitazone at baseline (mg)				
Number	1	1	11	21
Mean (SD)	30.00 (NC)	30.00 (NC)	31.36 (10.51)	32.86 (9.02)
Median	30.00	30.00	30.00	30.00
Min : Max	30.0 : 30.0	30.0 : 30.0	15.0 : 45.0	15.0 : 45.0
SGLT2 inhibitor use at screening (%)				
Number	26	26	231	231
Yes	26 (100%)	26 (100%)	0	0
No	0	0	231 (100%)	231 (100%)
Daily dose of SGLT2 inhibitor at baseline (mg)				
Canagliflozin				
Number	7	12	0	0
Mean (SD)	214.29 (106.90)	283.33 (57.74)		
Median	300.00	300.00		
Min : Max	100.0 : 300.0	100.0 : 300.0		
Empagliflozin				
Number	6	9	0	0
Mean (SD)	15.42 (7.49)	16.67 (8.20)		
Median	11.25	12.50		
Min : Max	10.0 : 25.0	5.0 : 25.0		
Dapagliflozin				
Number	13	5	0	0
Mean (SD)	9.62 (3.80)	9.00 (2.24)		
Median	10.00	10.00		
Min : Max	5.0 : 20.0	5.0 : 10.0		

	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=52)		No (N=462)	
	Fixed Ratio Combination (N=26)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=231)	GLP-1 Receptor Agonist (N=231)
Duration of metformin treatment (years)				
Number	26	26	231	231
Mean (SD)	7.35 (6.34)	8.59 (5.35)	7.18 (5.17)	8.06 (5.20)
Median	4.21	7.16	6.56	7.20
Min : Max	0.5 : 18.6	0.7 : 21.2	0.3 : 28.8	0.4 : 29.4
Daily dose of metformin at baseline (mg)				
Number	26	26	231	231
Mean (SD)	1730.77 (496.00)	1805.77 (529.21)	1993.51 (420.04)	2056.06 (488.15)
Median	2000.00	2000.00	2000.00	2000.00
Min : Max	1000.0 : 2550.0	500.0 : 3000.0	500.0 : 3000.0	500.0 : 3000.0
Categorized daily dose of metformin at baseline (mg) [n (%)]				
Number	26	26	231	231
<1500 mg	7 (26.9%)	5 (19.2%)	11 (4.8%)	13 (5.6%)
≥1500 - <2500 mg	17 (65.4%)	19 (73.1%)	183 (79.2%)	162 (70.1%)
≥2500 - <3000 mg	2 (7.7%)	1 (3.8%)	25 (10.8%)	33 (14.3%)
≥3000 mg	0	1 (3.8%)	12 (5.2%)	23 (10.0%)
Diabetic retinopathy [n (%)]				
Number	26	26	231	231
Yes	4 (15.4%)	1 (3.8%)	16 (6.9%)	13 (5.6%)
No	22 (84.6%)	25 (96.2%)	215 (93.1%)	218 (94.4%)
Diabetic proliferative retinopathy [n (%)]				
Number	26	26	231	231
Yes	0	0	2 (0.9%)	2 (0.9%)
No	26 (100%)	26 (100%)	229 (99.1%)	229 (99.1%)
Diabetic neuropathy [n (%)]				
Number	26	26	231	231
Yes	8 (30.8%)	7 (26.9%)	54 (23.4%)	52 (22.5%)
No	18 (69.2%)	19 (73.1%)	177 (76.6%)	179 (77.5%)
Diabetic nephropathy [n (%)]				
Number	26	26	231	231
Yes	1 (3.8%)	4 (15.4%)	19 (8.2%)	22 (9.5%)
No	25 (96.2%)	22 (84.6%)	212 (91.8%)	209 (90.5%)
Baseline urinary albumin/creatinine ratio (mg/g) [n (%)]				
Number	26	26	227	230
< 30 (normal)	21 (80.8%)	23 (88.5%)	176 (77.5%)	180 (78.3%)
≥ 30 to < 300 (microalbuminuria)	5 (19.2%)	3 (11.5%)	43 (18.9%)	42 (18.3%)
≥ 300 (macroalbuminuria)	0	0	8 (3.5%)	8 (3.5%)

	SGLT2 inhibitor use at screening Yes (N=52)		SGLT2 inhibitor use at screening No (N=462)	
	Fixed Ratio Combination (N=26)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=231)	GLP-1 Receptor Agonist (N=231)
Estimated eGFR at screening (mL/min/1.73m ²)				
Number	26	26	231	231
Mean (SD)	93.51 (27.52)	82.70 (18.57)	88.45 (24.57)	86.05 (23.02)
Median	92.19	84.43	85.36	84.06
Min : Max	46.5 : 169.0	42.5 : 112.5	40.9 : 296.4	39.5 : 171.8
Estimated eGFR at screening (mL/min/1.73m ²) [n (%)]				
Number	26	26	231	231
< 15 (End stage renal disease)	0	0	0	0
≥ 15 - < 30 (Severe decrease in GFR)	0	0	0	0
≥ 30 - < 60 (Moderate decrease in GFR)	3 (11.5%)	4 (15.4%)	14 (6.1%)	27 (11.7%)
≥ 60 - < 90 (Mild decrease in GFR)	10 (38.5%)	13 (50.0%)	122 (52.8%)	113 (48.9%)
≥ 90 (Normal)	13 (50.0%)	9 (34.6%)	95 (41.1%)	91 (39.4%)

SGLT2 = Sodium glucose co-transporter 2, eGFR = estimated Glomerular Filtration Rate.

Duration of diabetes (years) = (Date of informed consent - Date of diagnosis of diabetes + 1)/365.25

Age at onset of Type 2 diabetes (years) = (year of diagnosis of diabetes - year of birth)

eGFR is derived using the 4 variable Modification of Diet in Renal Disease formula.

Urine albumin/creatinine ratio is presented in mg/g, and the conversion factor to the standard international unit mg/mmol is 0.1130.

Table 3 - Mean change in HbA1c (%) from baseline to Week 26 by SGLT2 inhibitor use at screening - mITT population (EFC13794)

	Fixed Ratio Combination (N=252)				GLP-1 Receptor Agonist (N=253)	
	Compared to GLP-1 Receptor Agonist				N	LSMean (SE) _a
	Difference in					
	N	LSMean (SE) _a	LSMean (SE) _a	95% CI _a		
SGLT2 inhibitor use at screening						
Yes	22	-1.15 (0.161)	-0.88 (0.217)	(-1.306, -0.455)	26	-0.27 (0.148)
No	228	-1.01 (0.051)	-0.61 (0.070)	(-0.751, -0.475)	227	-0.40 (0.051)

SGLT2 = Sodium glucose co-transporter 2.

- a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination and GLP-1 receptor agonist), randomization strata of HbA1c (<8.0%, ≥8.0%) at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, scheduled visit, subgroup factor, treatment-by-visit, treatment-by-subgroup factor, visit-by-subgroup factor, treatment-by-visit-by-subgroup factor, and world region as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate.

Difference in LS Mean between fixed ratio combination and GLP-1 receptor agonist.

The analysis includes all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy.

Included are patients who have measurements at baseline and post-baseline.

LS Mean and difference in LS Mean were provided for categories with ≥5 patients in each treatment group.

Table 4 - Mean change in fasting plasma glucose (mmol/L) from baseline to Week 26 by SGLT2 inhibitor use at screening - mITT population (EFC13794)

SGLT2 inhibitor use at screening	Fixed Ratio Combination (N=252)				GLP-1 Receptor Agonist (N=253)	
	Compared to GLP-1 Receptor Agonist					
	N	LSMean (SE) _a	Difference in		N	LSMean (SE) _a
			LSMean (SE) _a	95% CI _a		
Yes	23	-2.83 (0.394)	-2.06 (0.536)	(-3.114, -1.009)	26	-0.77 (0.369)
No	228	-2.22 (0.126)	-1.64 (0.177)	(-1.984, -1.288)	227	-0.58 (0.127)

SGLT2 = Sodium glucose co-transporter 2.

- a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination and GLP-1 receptor agonist), randomization strata of HbA1c (<8.0%, ≥8.0%) at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, scheduled visit, subgroup factor, treatment-by-visit, treatment-by-subgroup factor, visit-by-subgroup factor, treatment-by-visit-by-subgroup factor, and world region as fixed effects, and baseline fasting plasma glucose value-by-visit interaction as a covariate.

Difference in LS Mean between fixed ratio combination and GLP-1 receptor agonist.

The analysis includes all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy.

Included are patients who have measurements at baseline and post-baseline.

LS Mean and difference in LS Mean were provided for categories with ≥ 5 patients in each treatment group.

Table 5 - Mean change in 2-hour postprandial plasma glucose (mmol/L) during a standardized meal test from baseline to Week 26 by SGLT2 inhibitor use at screening - mITT population (EFC13794)

SGLT2 inhibitor use at screening	Fixed Ratio Combination (N=252)				GLP-1 Receptor Agonist (N=253)	
	Compared to GLP-1 Receptor Agonist					
	N	LSMean (SE) _a	Difference in		N	LSMean (SE) _a
			LSMean (SE) _a	95% CI _a		
Yes	21	-5.04 (0.665)	-3.26 (0.896)	(-5.021, -1.498)	25	-1.78 (0.619)
No	194	-3.83 (0.223)	-2.81 (0.306)	(-3.411, -2.209)	197	-1.02 (0.219)

SGLT2 = Sodium glucose co-transporter 2.

a Analysis of covariance (ANCOVA) model with treatment groups (fixed ratio combination and GLP-1 receptor agonist), randomization strata of HbA1c (<8.0%, ≥8.0%) at Visit 1 (Week -2), randomization strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, subgroup factor, treatment-by-subgroup factor and world region as fixed effects and baseline 2-hour postprandial plasma glucose value as a covariate.

Difference in LS Mean between fixed ratio combination and GLP-1 receptor agonist.

The analysis includes all scheduled measurements obtained during the 26-week randomized treatment period, including those obtained after IMP discontinuation or introduction of rescue therapy.

Patients with both baseline and Week 26 (LOCF) measurements were included.

LS Mean and difference in LS Mean were provided for categories with ≥5 patients in each treatment group.

Table 6 - Overview of adverse event profile: treatment-emergent adverse events by SGLT-2 inhibitor use at screening during the 26-week randomized treatment period - Safety population (EFC13794)

n (%)	SGLT2 inhibitor use at screening Yes (N=51)		SGLT2 inhibitor use at screening No (N=460)	
	Fixed Ratio Combination (N=25)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=230)	GLP-1 Receptor Agonist (N=230)
Patients with any TEAE	14 (56.0%)	15 (57.7%)	149 (64.8%)	106 (46.1%)
Patients with any serious TEAE	2 (8.0%)	1 (3.8%)	8 (3.5%)	8 (3.5%)
Patients with any TEAE leading to death	0	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	0	9 (3.9%)	0

SGLT2 = Sodium glucose co-transporter 2

TEAE: Treatment-emergent adverse event

n (%) = number and percentage of patients with at least one TEAE

Table 7 - Number (%) of patients experiencing common TEAE(s) (PT ≥ 2 % in any treatment group) by primary SOC and PT and by SGLT-2 inhibitor use at screening during the 26-week on-treatment period - Safety population (EFC13794)

Primary System Organ Class Preferred Term [n (%)]	SGLT2 inhibitor use at screening Yes (N=51)		SGLT2 inhibitor use at screening No (N=460)	
	Fixed Ratio Combination (N=25)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=230)	GLP-1 Receptor Agonist (N=230)
Any TEAE	14 (56.0%)	15 (57.7%)	149 (64.8%)	106 (46.1%)
Infections and infestations	5 (20.0%)	10 (38.5%)	73 (31.7%)	58 (25.2%)
Nasopharyngitis	3 (12.0%)	5 (19.2%)	22 (9.6%)	18 (7.8%)
Influenza	1 (4.0%)	2 (7.7%)	10 (4.3%)	4 (1.7%)
Upper respiratory tract infection	0	2 (7.7%)	9 (3.9%)	10 (4.3%)
Urinary tract infection	0	0	7 (3.0%)	3 (1.3%)
Bronchitis	0	0	6 (2.6%)	5 (2.2%)
Pneumonia	0	0	6 (2.6%)	3 (1.3%)

Primary System Organ Class Preferred Term [n (%)]	SGLT2 inhibitor use at screening Yes (N=51)		SGLT2 inhibitor use at screening No (N=460)	
	Fixed Ratio Combination (N=25)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=230)	GLP-1 Receptor Agonist (N=230)
Sinusitis	2 (8.0%)	0	4 (1.7%)	7 (3.0%)
Metabolism and nutrition disorders	0	0	13 (5.7%)	1 (0.4%)
Increased appetite	0	0	6 (2.6%)	0
Nervous system disorders	3 (12.0%)	0	27 (11.7%)	13 (5.7%)
Headache	0	0	10 (4.3%)	6 (2.6%)
Dizziness	0	0	6 (2.6%)	2 (0.9%)
Gastrointestinal disorders	1 (4.0%)	3 (11.5%)	54 (23.5%)	23 (10.0%)
Nausea	0	0	22 (9.6%)	6 (2.6%)
Diarrhoea	0	0	14 (6.1%)	6 (2.6%)
Vomiting	1 (4.0%)	0	7 (3.0%)	2 (0.9%)
Toothache	0	0	6 (2.6%)	3 (1.3%)
Musculoskeletal and connective tissue disorders	2 (8.0%)	3 (11.5%)	21 (9.1%)	15 (6.5%)
Back pain	0	1 (3.8%)	4 (1.7%)	6 (2.6%)
Investigations	0	1 (3.8%)	15 (6.5%)	3 (1.3%)
Weight increased	0	0	7 (3.0%)	0

TEAE: Treatment-emergent adverse event, SOC: System Organ Class, PT: Preferred Term, SGLT2 = Sodium glucose co-transporter 2.

MedDRA version: 21.0

n (%) = number and percentage of patients with at least one TEAE.

Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing frequency within a SOC according to all TEAE summary.

Only SOC with at least one PT $\geq 2\%$ in at least one treatment group are presented.

Table 8 - Summary of documented symptomatic hypoglycemia recorded on the dedicated eCRF page and meeting protocol definition by SGLT2 inhibitor use at screening during the 26-week on-treatment period - Safety population (EFC13794)

Type	SGLT2 inhibitor use at screening Yes (N=51)		SGLT2 inhibitor use at screening No (N=460)	
	Fixed Ratio Combination (N=25)	GLP-1 Receptor Agonist (N=26)	Fixed Ratio Combination (N=230)	GLP-1 Receptor Agonist (N=230)
Total patient years of exposure	11.0	13.2	110.3	113.8
Documented symptomatic hypoglycemia (plasma glucose ≤ 70 mg/dL [3.9 mmol/L])				
Number of patients with events, n (%)	6 (24.0%)	0	65 (28.3%)	6 (2.6%)
Number of patients with events per patient year ^a	0.54	0	0.59	0.05
Number of events	8	0	179	10
Number of events per patient year ^b	0.72	0	1.62	0.09

SGLT2 = Sodium glucose co-transporter 2

- a* Calculated as number of patients with events divided by total exposure + 1 day in patient years for daily formulation and number of patients with events divided by total exposure + 7 days in patient years for weekly formulation.
- b* Calculated as number of events divided by total exposure + 1 day in patient years for daily formulation and number of events divided by total exposure + 7 day in patient years for weekly formulation.

Documented symptomatic hypoglycemia = symptomatic hypoglycemia recorded on the dedicated eCRF and meeting protocol definition for documented symptomatic hypoglycemia.

The 26-week on-treatment period is defined as the time from the first injection of investigational medicinal product (IMP) up to 1 day after the last injection of daily IMP (7 days after the last injection of weekly IMP) for patients not eligible to enter the extension period or Visit 28/Week 26 (or Day 183 if Visit 28/Week 26 is missing) for patients eligible to enter the extension period, regardless of the introduction of rescue therapy.

Example 5**Concomitant use of a fixed-dose ratio formulation of insulin glargine and lixisenatide with SGLT2i – subgroup analysis of Example 2**

The concomitant use of a fixed-dose ratio combination (FRC) of insulin glargine and lixisenatide with an SGLT2 inhibitor (SGLT2i) is supported by subgroup analyses of the patient group being subject of Example 2 (study EFC14112). In this study, 34 patients (21.1%) received concomitantly the FRC and a SGLT2i.

The FRC was provided in a single formulation, as described in Example 2.

Efficacy results (change from baseline to Week 26 in HbA1c and FPG) in both treatment groups were generally similar in SGLT2i users and non-users (Table 3, Table 4).

Overview of safety did not reveal differences between SGLT2i users and non-users (Table 5). With regard to common treatment-emergent adverse events (TEAEs) (Table 6), TEAEs in the gastrointestinal disorder System Organ Class (SOC) were reported less frequently in the FRC treatment group in SGLT2i users when compared to the SGLT2i non-users (17.6% versus 32.3%, respectively). Similarly, documented symptomatic hypoglycemia (plasma glucose ≤ 3.9 mmol/L [≤ 70 mg/dL]) in the FRC group was reported less frequently in SGLT2i users compared to non-users (number of events per patient year: 0.18 and 1.14, respectively) (Table 7). No new safety signal was identified when patients in the FRC treatment group were using SGLT2i as background therapy compared to SGLT2i non-users.

Table 1 - Demographics and patient characteristics at screening or baseline by SGLT2 inhibitor use at screening - Randomized population (EFC14112)

	SGLT2 inhibitor use at screening Yes (N=64)		SGLT2 inhibitor use at screening No (N=257)	
	Fixed Ratio Combination (N=34)	Lixisenatide (N=30)	Fixed Ratio Combination (N=127)	Lixisenatide (N=130)
Age (years)				
Number	34	30	127	130
Mean (SD)	52.4 (10.7)	50.2 (10.6)	59.9 (9.1)	59.5 (11.0)
Median	52.0	51.0	61.0	60.0
Min : Max	26 : 72	27 : 72	37 : 81	33 : 82
Age group (years) [n (%)]				
Number	34	30	127	130
< 65	28 (82.4%)	27 (90.0%)	87 (68.5%)	83 (63.8%)
≥ 65 to < 75	6 (17.6%)	3 (10.0%)	35 (27.6%)	36 (27.7%)
≥ 75	0	0	5 (3.9%)	11 (8.5%)
Gender [n (%)]				
Number	34	30	127	130
Male	20 (58.8%)	19 (63.3%)	84 (66.1%)	83 (63.8%)
Female	14 (41.2%)	11 (36.7%)	43 (33.9%)	47 (36.2%)
Race [n (%)]				
Number	34	30	127	130
Asian	34 (100%)	30 (100%)	127 (100%)	130 (100%)
HbA1c (%) at screening				
Number	34	30	127	130
Mean (SD)	8.47 (0.65)	8.35 (0.64)	8.42 (0.62)	8.44 (0.64)
Median	8.50	8.10	8.30	8.30
Min : Max	7.6 : 9.8	7.5 : 9.7	7.5 : 10.0	7.5 : 10.0
HbA1c (%) categories at screening [n (%)]				
Number	34	30	127	130
< 8	9 (26.5%)	12 (40.0%)	34 (26.8%)	31 (23.8%)
≥ 8	25 (73.5%)	18 (60.0%)	93 (73.2%)	99 (76.2%)
Randomization strata of HbA1c (%) from IVRS/IWRS				
Number	34	30	127	130
< 8	9 (26.5%)	12 (40.0%)	34 (26.8%)	31 (23.8%)
≥ 8	25 (73.5%)	18 (60.0%)	93 (73.2%)	99 (76.2%)
Randomization strata of DPP-4 inhibitor use at screening from IVRS/IWRS				
Number	34	30	127	130
Yes	6 (17.6%)	3 (10.0%)	66 (52.0%)	68 (52.3%)
No	28 (82.4%)	27 (90.0%)	61 (48.0%)	62 (47.7%)
Baseline BMI (kg/m ²)				

	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=64)		No (N=257)	
	Fixed Ratio Combination (N=34)	Lixisenatide (N=30)	Fixed Ratio Combination (N=127)	Lixisenatide (N=130)
Number	34	30	127	130
Mean (SD)	28.34 (5.15)	27.36 (4.59)	26.38 (4.16)	26.73 (4.08)
Median	27.36	27.56	26.40	26.32
Min : Max	20.5 : 39.6	19.4 : 38.7	18.8 : 40.2	18.9 : 39.4
Baseline BMI categories (kg/m ²) [n (%)]				
Number	34	30	127	130
< 25	10 (29.4%)	8 (26.7%)	52 (40.9%)	44 (33.8%)
≥ 25 to < 30	14 (41.2%)	14 (46.7%)	53 (41.7%)	62 (47.7%)
≥ 30	10 (29.4%)	8 (26.7%)	22 (17.3%)	24 (18.5%)
FPG (mmol/L) at screening				
Number	34	30	127	130
Mean (SD)	9.47 (1.54)	9.01 (1.57)	10.00 (1.51)	10.03 (1.70)
Median	9.52	8.77	9.77	9.94
Min : Max	6.5 : 12.1	6.7 : 11.9	6.1 : 13.4	6.5 : 13.5
FPG (mg/dL) at screening				
Number	34	30	127	130
Mean (SD)	170.7 (27.8)	162.3 (28.3)	180.2 (27.2)	180.7 (30.6)
Median	171.5	158.0	176.0	179.0
Min : Max	117 : 218	121 : 215	109 : 241	117 : 244

SGLT2 = Sodium glucose co-transporter 2, BMI = Body Mass Index, FPG = Fasting plasma glucose, DPP-4 = Dipeptidyl-peptidase-4, IVRS/IWRS = Interactive Voice/Web Response System.

Table 2 - Disease characteristics at screening or baseline by SGLT2 inhibitor use at screening - Randomized population (EFC14112)

	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=64)		No (N=257)	
	Fixed Ratio Combination (N=34)	Lixisenatide (N=30)	Fixed Ratio Combination (N=127)	Lixisenatide (N=130)
Duration of diabetes (years)				
Number	34	30	127	130
Mean (SD)	5.21 (3.83)	5.73 (5.52)	8.90 (6.30)	10.03 (6.32)
Median	3.88	4.56	7.90	9.35
Min : Max	1.1 : 16.8	1.1 : 29.4	1.0 : 38.5	1.0 : 30.4
Age at onset of Type 2 diabetes (years)				
Number	34	30	127	130
Mean (SD)	47.1 (10.1)	44.5 (9.8)	51.0 (9.9)	49.4 (10.2)
Median	47.0	44.0	52.0	50.0
Min : Max	25 : 69	26 : 61	24 : 77	24 : 79
Prior use of insulin [n (%)]				
Number	34	30	127	130

	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=64)		No (N=257)	
	Fixed Ratio Combination (N=34)	Lixisenatide (N=30)	Fixed Ratio Combination (N=127)	Lixisenatide (N=130)
Yes	3 (8.8%)	1 (3.3%)	8 (6.3%)	10 (7.7%)
No	31 (91.2%)	29 (96.7%)	119 (93.7%)	120 (92.3%)
Prior use of GLP-1 receptor agonist [n (%)]				
Number	34	30	127	130
Yes	10 (29.4%)	7 (23.3%)	24 (18.9%)	26 (20.0%)
No	24 (70.6%)	23 (76.7%)	103 (81.1%)	104 (80.0%)
History of gestational diabetes [n (%)]				
Number (Female)	14	11	43	47
Yes (Female)	0	0	1 (2.3%)	4 (8.5%)
No (Female)	14 (100%)	11 (100%)	42 (97.7%)	43 (91.5%)
Diabetic retinopathy [n (%)]				
Number	34	30	127	130
Yes	5 (14.7%)	4 (13.3%)	23 (18.1%)	28 (21.5%)
Photocoagulation performed:				
Yes	1 (2.9%)	2 (6.7%)	6 (4.7%)	5 (3.8%)
Photocoagulation performed:				
No	4 (11.8%)	2 (6.7%)	17 (13.4%)	23 (17.7%)
Vitrectomy performed because of diabetic retinopathy: Yes	1 (2.9%)	1 (3.3%)	2 (1.6%)	1 (0.8%)
Vitrectomy performed because of diabetic retinopathy: No	4 (11.8%)	3 (10.0%)	21 (16.5%)	27 (20.8%)
No	29 (85.3%)	26 (86.7%)	102 (80.3%)	100 (76.9%)
Unknown	0	0	2 (1.6%)	2 (1.5%)
Diabetic sensory or motor neuropathy [n (%)]				
Number	34	30	127	130
Yes	5 (14.7%)	4 (13.3%)	16 (12.6%)	17 (13.1%)
No	25 (73.5%)	25 (83.3%)	106 (83.5%)	109 (83.8%)
Unknown	4 (11.8%)	1 (3.3%)	5 (3.9%)	4 (3.1%)
Diabetic autonomic neuropathy [n (%)]				
Number	34	30	127	130
Yes	1 (2.9%)	1 (3.3%)	3 (2.4%)	2 (1.5%)
No	29 (85.3%)	28 (93.3%)	117 (92.1%)	123 (94.6%)
Unknown	4 (11.8%)	1 (3.3%)	7 (5.5%)	5 (3.8%)
Diabetic nephropathy [n (%)]				
Number	34	30	127	130
Yes	10 (29.4%)	6 (20.0%)	34 (26.8%)	36 (27.7%)
Impaired renal function (estimated GFR by MDRD below 60 ml/min)	0	0	3 (2.4%)	2 (1.5%)
Microalbuminuria (30 to 299 mcg per mg creatinine)	7 (20.6%)	6 (20.0%)	27 (21.3%)	30 (23.1%)

	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes		No	
	(N=64)		(N=257)	
	Fixed Ratio Combination (N=34)	Lixisenatide (N=30)	Fixed Ratio Combination (N=127)	Lixisenatide (N=130)
Overt proteinuria (equal to or above 300 mcg per mg creatinine)	3 (8.8%)	0	4 (3.1%)	4 (3.1%)
No	24 (70.6%)	24 (80.0%)	92 (72.4%)	92 (70.8%)
Unknown	0	0	1 (0.8%)	2 (1.5%)
eGFR at screening (ml/min/1.73m ²)				
Number	34	30	127	130
Mean (SD)	115.35 (27.23)	128.84 (28.36)	106.86 (26.98)	108.92 (30.24)
Median	112.20	125.75	104.60	107.25
Min : Max	64.3 : 210.7	77.0 : 184.8	57.9 : 180.2	47.0 : 229.6
eGFR categories at screening (ml/min/1.73m ²) [n (%)]				
Number	34	30	127	130
<15 (end stage renal disease)	0	0	0	0
≥15 to <30 (severe decrease in GFR)	0	0	0	0
≥30 to <60 (moderate decrease in GFR)	0	0	1 (0.8%)	4 (3.1%)
≥60 to <90 (mild decrease in GFR)	4 (11.8%)	4 (13.3%)	33 (26.0%)	30 (23.1%)
≥90 (normal)	30 (88.2%)	26 (86.7%)	93 (73.2%)	96 (73.8%)

GLP-1 = Glucagon like peptide-1, GFR = Glomerular filtration rate, eGFR = Estimated glomerular filtration rate, SGLT2 = Sodium glucose co-transporter 2.

eGFR value is derived using the equation of IDMS-MDRD formula.

Table 3 - Mean change in HbA1c (%) from baseline to Week 26 during the 26-week on-treatment period by SGLT2 inhibitor use at screening - mITT population (EFC14112)

	Fixed Ratio Combination (N=161)				Lixisenatide (N=160)			
	Compared to Lixisenatide							
	N	LSMean (SE) ^a	Difference in LSMean (SE) ^a	95% CI ^a	N	LSMean (SE) ^a		
SGLT2 inhibitor use at screening								
Yes	34	-1.39 (0.148)	-1.00 (0.217)	(-1.429 to -0.573)	30	-0.39 (0.161)		
No	127	-1.66 (0.077)	-1.11 (0.110)	(-1.325 to -0.890)	127	-0.55 (0.081)		

SGLT2 = Sodium glucose co-transporter 2.

^a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination, lixisenatide), randomization strata of DPP-4 inhibitor use at screening (Yes, No), visit (Week 4, 8, 12, 16, 20, and 26), subgroup factor, treatment-by-visit, treatment-by-subgroup factor, visit-by-subgroup factor, treatment-by-visit-by-subgroup factor as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate.

The analysis included measurements obtained before the introduction of rescue medication and up to 14 days after the last injection of open-label investigational medicinal product on or before Visit 16 (Week 26), or Day 183 if Visit 16 (Week 26) is not available.

Included are patients who have measurements at baseline and post-baseline.

LS Mean and difference in LS Mean were provided for categories with ≥5 patients in each treatment group.

Table 4 - Mean change in fasting plasma glucose (mmol/L) from baseline to Week 26 during the 26-week on-treatment period by SGLT2 inhibitor use at screening - mITT population (EFC14112)

	Fixed Ratio Combination (N=161)				Lixisenatide (N=160)			
	Compared to Lixisenatide							
	N	LSMean (SE) ^a	Difference in LSMean (SE) ^a	95% CI ^a	N	LSMean (SE) ^a		
SGLT2 inhibitor use at screening								
Yes	34	-1.75 (0.287)	-2.16 (0.415)	(-2.977 to -1.343)	30	0.41 (0.318)		
No	127	-2.48 (0.150)	-2.23 (0.212)	(-2.647 to -1.813)	125	-0.25 (0.160)		

SGLT2 = Sodium glucose co-transporter 2.

a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination, lixisenatide), randomization strata of DPP-4 inhibitor use at screening (Yes, No), visit (Week 4, 8, 12, 16, 20, and 26), subgroup factor, treatment-by-visit, treatment-by-subgroup factor as fixed effects, and baseline fasting plasma glucose value-by-visit interaction as a covariate.

The analysis included measurements obtained before the introduction of rescue medication and up to 1 day after the last injection of open-label investigational medicinal product on or before Visit 16 (Week 26), or Day 183 if Visit 16 (Week 26) is not available.

Included are patients who have measurements at baseline and post-baseline.

LS Mean and difference in LS Mean were provided for categories with ≥ 5 patients in each treatment group.

Table 5 - Overview of adverse event profile: treatment emergent adverse events by SGLT-2 Inhibitor use at screening during the 26-week on-treatment period - Safety population (EFC14112)

n (%)	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=64)		No (N=257)	
	Fixed Ratio Combination (N=34)	Lixisenatide (N=30)	Fixed Ratio Combination (N=127)	Lixisenatide (N=130)
Patients with any TEAE	24 (70.6%)	24 (80.0%)	85 (66.9%)	98 (75.4%)
Patients with any serious TEAE	1 (2.9%)	0	4 (3.1%)	4 (3.1%)
Patients with any TEAE leading to death	0	0	0	1 (0.8%)
Patients with any TEAE leading to permanent treatment discontinuation	0	1 (3.3%)	4 (3.1%)	16 (12.3%)

SGLT2 = Sodium glucose co-transporter 2, TEAE: Treatment emergent adverse event.

n (%) = number and percentage of patients with at least one TEAE.

The 26-week on-treatment period is defined as the time from the first injection of open-label investigational medicinal product (IMP) up to 3 days after the last injection of open-label IMP on or before Week 26 visit (or Day 183 if Week 26 visit is missing), regardless of the introduction of rescue therapy.

Table 6 - Number (%) of patients experiencing common TEAE(s) (PT ≥2 % in any treatment group) presented by primary SOC and PT and by SGLT-2 inhibitor use at screening during the 26-week on-treatment period - Safety population (EFC14112)

Primary System Organ Class Preferred Term n (%)	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=64)		No (N=257)	
	Fixed Ratio Combination (N=34)	Lixisenatide (N=30)	Fixed Ratio Combination (N=127)	Lixisenatide (N=130)
Any class	24 (70.6%)	24 (80.0%)	85 (66.9%)	98 (75.4%)
Infections and infestations	14 (41.2%)	15 (50.0%)	48 (37.8%)	48 (36.9%)
Nasopharyngitis	6 (17.6%)	6 (20.0%)	32 (25.2%)	29 (22.3%)
Conjunctivitis	1 (2.9%)	0	4 (3.1%)	0
Gastroenteritis	2 (5.9%)	1 (3.3%)	3 (2.4%)	5 (3.8%)
Bronchitis	0	3 (10.0%)	4 (3.1%)	3 (2.3%)
Cystitis	1 (2.9%)	2 (6.7%)	1 (0.8%)	2 (1.5%)
Influenza	0	1 (3.3%)	0	6 (4.6%)
Metabolism and nutrition disorders	0	1 (3.3%)	8 (6.3%)	6 (4.6%)
Decreased appetite	0	1 (3.3%)	5 (3.9%)	4 (3.1%)
Nervous system disorders	2 (5.9%)	3 (10.0%)	17 (13.4%)	8 (6.2%)
Somnolence	1 (2.9%)	1 (3.3%)	5 (3.9%)	0
Dizziness	0	0	4 (3.1%)	2 (1.5%)
Gastrointestinal disorders	6 (17.6%)	11 (36.7%)	41 (32.3%)	57 (43.8%)
Nausea	0	5 (16.7%)	23 (18.1%)	38 (29.2%)
Vomiting	1 (2.9%)	1 (3.3%)	8 (6.3%)	7 (5.4%)
Diarrhoea	0	2 (6.7%)	8 (6.3%)	8 (6.2%)
Abdominal discomfort	1 (2.9%)	0	6 (4.7%)	2 (1.5%)
Dyspepsia	2 (5.9%)	5 (16.7%)	2 (1.6%)	4 (3.1%)

Primary System Organ Class Preferred Term n (%)	SGLT2 inhibitor use at screening Yes (N=64)		SGLT2 inhibitor use at screening No (N=257)	
	Fixed Ratio Combination (N=34)		Fixed Ratio Combination (N=127)	
	Lixisenatide (N=30)		Lixisenatide (N=130)	
Constipation	1 (2.9%)	2 (6.7%)	1 (0.8%)	7 (5.4%)
Skin and subcutaneous tissue disorders	4 (11.8%)	3 (10.0%)	12 (9.4%)	8 (6.2%)
Eczema	1 (2.9%)	2 (6.7%)	3 (2.4%)	1 (0.8%)
Musculoskeletal and connective tissue disorders	5 (14.7%)	5 (16.7%)	11 (8.7%)	10 (7.7%)
Back pain	2 (5.9%)	0	3 (2.4%)	5 (3.8%)
General disorders and administration site conditions	1 (2.9%)	2 (6.7%)	12 (9.4%)	17 (13.1%)
Injection site reaction	1 (2.9%)	1 (3.3%)	0	3 (2.3%)
Injury, poisoning and procedural complications	4 (11.8%)	1 (3.3%)	10 (7.9%)	10 (7.7%)
Ligament sprain	2 (5.9%)	0	5 (3.9%)	3 (2.3%)
Contusion	0	1 (3.3%)	2 (1.6%)	4 (3.1%)

SGLT2 = Sodium glucose co-transporter 2, TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term.

MedDRA 20.1.

n (%) = number and percentage of patients with at least one TEAE.

Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT sorted by decreasing frequency within a SOC according to all TEAE summary.

Only SOC with at least one PT ≥2% in at least one treatment group are presented.

The 26-week on-treatment period is defined as the time from the first injection of open-label investigational medicinal product (IMP) up to 3 days after the last injection of open-label IMP on or before Week 26 visit (or Day 183 if Week 26 visit is missing), regardless of the introduction of rescue therapy.

Table 7 - Summary of documented symptomatic hypoglycemia recorded on the dedicated eCRF page and meeting protocol definition by SGLT2 inhibitor use at screening during the 26-week on-treatment period - Safety population (EFC14112)

	SGLT2 inhibitor use at screening Yes (N=64)		SGLT2 inhibitor use at screening No (N=257)	
	Fixed Ratio Combination (N=34)		Fixed Ratio Combination (N=127)	
	Lixisenatide (N=30)		Lixisenatide (N=130)	
Total patient years of exposure	17.1	14.9	63.1	59.5
Documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L])				
Number of patients with events, n (%)	2 (5.9%)	1 (3.3%)	19 (15.0%)	3 (2.3%)
Number of patients with events per patient year ^a	0.12	0.07	0.30	0.05
Number of events	3	1	72	5
Number of events per patient year ^b	0.18	0.07	1.14	0.08

SGLT2 = Sodium glucose co-transporter 2, IMP = Investigational medicinal product, eCRF = Electronic case report form.

Total patient years of exposure: calculated as the time from the first injection of open-label IMP up to 1 day after the last injection of open-label IMP during the 26-week treatment period.

a Calculated as number of patients with events divided by total patient years of exposure.

b Calculated as number of events divided by total patient years of exposure.

The 26-week on-treatment period is defined as the time from the first injection of open-label investigational medicinal product (IMP) up to 1 day after the last injection of open-label IMP on or before Week 26 visit (or Day 183 if Week 26 visit is missing), regardless of the introduction of rescue therapy.

Example 6**Concomitant use of a fixed-dose ratio formulation of insulin glargine and lixisenatide with SGLT2i – subgroup analysis of Example 3**

The concomitant use of a fixed-dose ratio combination (FRC) of insulin glargine and lixisenatide with an SGLT2 inhibitor (SGLT2i) is supported by subgroup analyses of the patient group being subject of Example 3 (study EFC14114). In this study, 59 patients (22.7%) received concomitantly the FRC and a SGLT2i.

The FRC was provided in a single formulation, as described in Example 3.

Efficacy results (change from baseline to Week 26 in HbA1c, FPG and 2-hour PPG) in both treatment groups were generally similar in SGLT2i users and non-users (Table 3, Table 4, Table 5). In particular, there was no indication of a decreased efficacy of the FRC in the SGLT2i user subgroup.

Overview of safety did not reveal differences between SGLT2i users and non-users (Table 6). With regard to common TEAEs (Table 7), TEAEs in the gastrointestinal SOC were also reported numerically less frequently in the FRC group in SGLT2i users when compared to SGLT2i non-users (22.0% versus 27.4%, respectively). No new safety signal was identified when patients in the FRC treatment group were using SGLT2i as background therapy compared to SGLT2i non-users.

Table 1 - Demographics and patient characteristics at screening or baseline by SGLT2 inhibitor use at screening - Randomized population (EFC14114)

	SGLT2 inhibitor use at screening		SGLT2 inhibitor use at screening	
	Yes (N=115)		No (N=406)	
	Fixed Ratio Combination (N=59)	Insulin glargine (N=56)	Fixed Ratio Combination (N=201)	Insulin glargine (N=205)
Age (years)				
Number	59	56	201	205
Mean (SD)	53.8 (10.8)	56.4 (11.2)	60.8 (10.6)	61.2 (9.8)
Median	53.0	57.0	62.0	62.0

	SGLT2 inhibitor use at screening Yes (N=115)		SGLT2 inhibitor use at screening No (N=406)	
	Fixed Ratio Combination (N=59)	Insulin glargine (N=56)	Fixed Ratio Combination (N=201)	Insulin glargine (N=205)
Min : Max	27 : 79	34 : 80	30 : 81	40 : 82
Age group (years) [n (%)]				
Number	59	56	201	205
< 65	48 (81.4%)	40 (71.4%)	120 (59.7%)	121 (59.0%)
≥ 65 to < 75	9 (15.3%)	14 (25.0%)	66 (32.8%)	68 (33.2%)
≥ 75	2 (3.4%)	2 (3.6%)	15 (7.5%)	16 (7.8%)
Gender [n (%)]				
Number	59	56	201	205
Male	40 (67.8%)	34 (60.7%)	134 (66.7%)	133 (64.9%)
Female	19 (32.2%)	22 (39.3%)	67 (33.3%)	72 (35.1%)
Race [n (%)]				
Number	59	56	201	205
Asian	59 (100%)	56 (100%)	201 (100%)	205 (100%)
HbA1c (%) at screening				
Number	59	56	201	205
Mean (SD)	8.25 (0.55)	8.18 (0.47)	8.15 (0.51)	8.10 (0.46)
Median	8.20	8.10	8.10	8.00
Min : Max	7.5 : 9.4	7.5 : 9.4	7.5 : 9.5	7.5 : 9.5
HbA1c (%) categories at screening[n (%)]				
Number	59	56	201	205
< 8	21 (35.6%)	19 (33.9%)	89 (44.3%)	90 (43.9%)
≥ 8	38 (64.4%)	37 (66.1%)	112 (55.7%)	115 (56.1%)
Randomization strata of HbA1c (%) from IVRS/IWRS				
Number	59	56	201	205
< 8	21 (35.6%)	20 (35.7%)	89 (44.3%)	90 (43.9%)
≥ 8	38 (64.4%)	36 (64.3%)	112 (55.7%)	115 (56.1%)
Randomization strata of DPP-4 inhibitor use at screening from IVRS/IWRS				
Number	59	56	201	205
Yes	16 (27.1%)	18 (32.1%)	114 (56.7%)	115 (56.1%)
No	43 (72.9%)	38 (67.9%)	87 (43.3%)	90 (43.9%)
Baseline BMI (kg/m ²)				
Number	59	56	201	205
Mean (SD)	27.68 (4.18)	26.84 (4.36)	25.76 (4.25)	25.61 (4.29)
Median	27.04	26.00	25.38	25.39
Min : Max	20.2 : 37.8	20.1 : 38.6	17.6 : 39.7	17.0 : 39.3
Baseline BMI categories (kg/m ²) [n(%)]				
Number	59	56	201	205
< 25	17 (28.8%)	21 (37.5%)	94 (46.8%)	96 (46.8%)
≥ 25 to < 30	26 (44.1%)	23 (41.1%)	73 (36.3%)	80 (39.0%)
≥ 30	16 (27.1%)	12 (21.4%)	34 (16.9%)	29 (14.1%)

	SGLT2 inhibitor use at screening Yes (N=115)		SGLT2 inhibitor use at screening No (N=406)	
	Fixed Ratio Combination (N=59)	Insulin glargine (N=56)	Fixed Ratio Combination (N=201)	Insulin glargine (N=205)
FPG(mmol/L) at screening				
Number	59	56	201	205
Mean (SD)	8.25 (0.89)	8.60 (0.99)	8.65 (0.87)	8.74 (0.93)
Median	8.22	8.85	8.77	8.83
Min : Max	5.8 : 10.0	6.3 : 10.0	5.4 : 10.0	4.7 : 10.5
FPG(mg/dL) at screening				
Number	59	56	201	205
Mean (SD)	148.7 (16.1)	155.0 (17.9)	155.9 (15.6)	157.5 (16.7)
Median	148.0	159.5	158.0	159.0
Min : Max	105 : 180	114 : 180	97 : 180	85 : 189

SGLT2 = Sodium glucose co-transporter 2, BMI = Body Mass Index, FPG = Fasting plasma glucose, IVRS/IWRS = Interactive Voice/Web Response System.

Table 2 - Disease characteristics at screening or baseline by SGLT2 inhibitor use at screening - Randomized population (EFC14114)

	SGLT2 inhibitor use at screening Yes (N=115)		SGLT2 inhibitor use at screening No (N=406)	
	Fixed Ratio Combination (N=59)	Insulin glargine (N=56)	Fixed Ratio Combination (N=201)	Insulin glargine (N=205)
Duration of diabetes (years)				
Number	59	56	201	205
Mean (SD)	6.46 (4.99)	7.76 (5.45)	9.59 (6.72)	10.12 (6.98)
Median	5.25	6.60	8.01	8.45
Min : Max	1.0 : 25.2	1.1 : 26.4	1.0 : 32.5	1.0 : 41.4
Age at onset of Type 2 diabetes (years)				
Number	59	56	201	205
Mean (SD)	47.3 (10.5)	48.6 (11.4)	51.2 (10.1)	51.1 (10.3)
Median	45.0	48.5	52.0	52.0
Min : Max	26 : 78	20 : 69	14 : 74	25 : 76
Prior use of insulin [n (%)]				
Number	59	56	201	205
Yes	2 (3.4%)	3 (5.4%)	17 (8.5%)	15 (7.3%)
No	57 (96.6%)	53 (94.6%)	184 (91.5%)	190 (92.7%)
Prior use of GLP-1 receptor agonist [n (%)]				
Number	59	56	201	205
Yes	10 (16.9%)	12 (21.4%)	35 (17.4%)	36 (17.6%)
No	49 (83.1%)	44 (78.6%)	166 (82.6%)	169 (82.4%)
History of gestational diabetes [n (%)]				

	SGLT2 inhibitor use at screening Yes (N=115)		SGLT2 inhibitor use at screening No (N=406)	
	Fixed Ratio Combination (N=59)	Insulin glargine (N=56)	Fixed Ratio Combination (N=201)	Insulin glargine (N=205)
Number (Female)	19	22	67	72
Yes (Female)	1 (5.3%)	0	3 (4.5%)	1 (1.4%)
No (Female)	18 (94.7%)	22 (100%)	64 (95.5%)	71 (98.6%)
Diabetic retinopathy [n (%)]				
Number	59	56	201	205
Yes	6 (10.2%)	11 (19.6%)	35 (17.4%)	46 (22.4%)
Photocoagulation performed: Yes	1 (1.7%)	3 (5.4%)	5 (2.5%)	7 (3.4%)
Photocoagulation performed: No	5 (8.5%)	8 (14.3%)	29 (14.4%)	39 (19.0%)
Vitreotomy performed because of diabetic retinopathy: Yes	0	0	1 (0.5%)	3 (1.5%)
Vitreotomy performed because of diabetic retinopathy: No	6 (10.2%)	11 (19.6%)	34 (16.9%)	43 (21.0%)
No	50 (84.7%)	43 (76.8%)	160 (79.6%)	154 (75.1%)
Unknown	3 (5.1%)	2 (3.6%)	6 (3.0%)	5 (2.4%)
Diabetic sensory or motor neuropathy [n (%)]				
Number	59	56	201	205
Yes	7 (11.9%)	6 (10.7%)	35 (17.4%)	31 (15.1%)
No	49 (83.1%)	49 (87.5%)	159 (79.1%)	168 (82.0%)
Unknown	3 (5.1%)	1 (1.8%)	7 (3.5%)	6 (2.9%)
Diabetic autonomic neuropathy [n (%)]				
Number	59	56	201	205
Yes	3 (5.1%)	1 (1.8%)	7 (3.5%)	12 (5.9%)
No	52 (88.1%)	54 (96.4%)	184 (91.5%)	186 (90.7%)
Unknown	4 (6.8%)	1 (1.8%)	10 (5.0%)	7 (3.4%)
Diabetic nephropathy [n (%)]				
Number	59	56	201	205
Yes	7 (11.9%)	6 (10.7%)	52 (25.9%)	43 (21.0%)
Impaired renal function (estimated GFR by MDRD below 60 ml/min)	1 (1.7%)	1 (1.8%)	6 (3.0%)	4 (2.0%)
Microalbuminuria (30 to 299 mcg per mg creatinine)	5 (8.5%)	4 (7.1%)	43 (21.4%)	30 (14.6%)
Overt proteinuria (equal to or above 300 mcg per mg creatinine)	1 (1.7%)	1 (1.8%)	4 (2.0%)	9 (4.4%)
No	49 (83.1%)	48 (85.7%)	144 (71.6%)	160 (78.0%)
Unknown	3 (5.1%)	2 (3.6%)	5 (2.5%)	2 (1.0%)
eGFR at screening (ml/min/1.73m ²)				
Number	59	56	201	205
Mean (SD)	116.76 (30.95)	113.19 (32.47)	104.58 (26.50)	106.93 (29.36)
Median	112.30	107.65	103.90	104.90
Min : Max	46.3 : 196.7	53.9 : 209.3	55.9 : 229.5	50.3 : 335.7
eGFR categories at screening (ml/min/1.73m ²) [n (%)]				
Number	59	56	201	205
<15 (end stage renal disease)	0	0	0	0

	SGLT2 inhibitor use at screening Yes (N=115)		SGLT2 inhibitor use at screening No (N=406)	
	Fixed Ratio Combination (N=59)	Insulin glargine (N=56)	Fixed Ratio Combination (N=201)	Insulin glargine (N=205)
≥15 to <30 (severe decrease in GFR)	0	0	0	0
≥30 to <60 (moderate decrease in GFR)	1 (1.7%)	2 (3.6%)	3 (1.5%)	3 (1.5%)
≥60 to <90 (mild decrease in GFR)	7 (11.9%)	11 (19.6%)	59 (29.4%)	51 (24.9%)
≥90 (normal)	51 (86.4%)	43 (76.8%)	139 (69.2%)	151 (73.7%)

SGLT2 = Sodium glucose co-transporter 2, GLP-1 = Glucagon like peptide-1. GFR = Glomerular filtration rate, eGFR = Estimated glomerular filtration rate.

eGFR value is derived using the equation of IDMS-MDRD formula.

Table 3 - Mean change in HbA1c (%) from baseline to Week 26 during the on-treatment period by SGLT2 inhibitor use at screening - mITT population (EFC14114)

	Fixed Ratio Combination (N=260)				Insulin Glargine (N=260)			
	Compared to Insulin Glargine							
	N	LSMean (SE) ^a	Difference in LSMean (SE) ^a	95% CI ^a	N	LSMean (SE) ^a		
SGLT2 inhibitor use at screening								
Yes	58	-1.19 (0.088)	-0.70 (0.126)	(-0.952 to -0.455)	55	-0.49 (0.091)		
No	199	-1.48 (0.047)	-0.65 (0.067)	(-0.780 to -0.518)	205	-0.83 (0.047)		

SGLT2 = Sodium glucose co-transporter 2.

^a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination, insulin glargine), randomization strata of HbA1c (<8.0%, ≥8.0%) at Visit 1 (Week -2), randomization strata of DPP-4 inhibitor use at screening (Yes, No), visit (Week 4, 8, 12, 16, 20, and 26), subgroup factor, treatment-by-visit, treatment-by-subgroup factor, visit-by-subgroup factor, treatment-by-visit-by-subgroup factor as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate.

The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 14 days.

Included are patients who have measurements at baseline and post-baseline.

LS Mean and difference in LS Mean were provided for categories with ≥5 patients in each treatment group.

Table 4 - Mean change in fasting plasma glucose (mmol/L) from baseline to Week 26 during the on-treatment period by SGLT2 inhibitor use at screening - mITT population (EFC14114)

	Fixed Ratio Combination (N=260)				Insulin Glargine (N=260)			
	Compared to Insulin Glargine							
	N	LSMean (SE) ^a	Difference in LSMean (SE) ^a	95% CI ^a	N	LSMean (SE) ^a		
SGLT2 inhibitor use at screening								
Yes	58	-1.24 (0.198)	-0.23 (0.283)	(-0.785 to 0.327)	55	-1.01 (0.205)		

	Fixed Ratio Combination (N=260)				Insulin Glargine (N=260)			
	Compared to Insulin Glargine						N	LSMean (SE) ^a
	N	LSMean (SE) ^a	Difference in LSMean (SE) ^a	95% CI ^a				
No	198	-1.93 (0.106)	-0.47 (0.149)	(-0.759 to -0.175)	205	-1.46 (0.104)		

SGLT2 = Sodium glucose co-transporter 2.
a Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination, insulin glargine), randomization strata of HbA1c (<8.0%, ≥8.0%) at Visit 1 (Week -2), randomization strata of DPP-4 inhibitor use at screening (Yes, No), visit (Week 4, 8, 12, 16, 20, and 26), subgroup factor, treatment-by-visit, treatment-by-subgroup factor, visit-by-subgroup factor, treatment-by-visit-by-subgroup factor as fixed effects, and baseline fasting plasma glucose value-by-visit interaction as a covariate.
The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 1 day.
Included are patients who have measurements at baseline and post-baseline.
LS Mean and difference in LS Mean were provided for categories with ≥5 patients in each treatment group.

Table 5 - Mean change in 2-hour postprandial plasma glucose (mmol/L) during a standardized meal test from baseline to Week 26 during the on-treatment period by SGLT2 inhibitor use at screening - mITT population (EFC14114)

	Fixed Ratio Combination (N=260)		Insulin Glargine (N=260)			
	Compared to Insulin Glargine					
	N	LSMean (SE) ^a	Difference in LSMean (SE) ^a	95% CI ^a	N	LSMean (SE) ^a
SGLT2 inhibitor use at screening						
Yes	57	-5.56 (0.350)	-4.18 (0.495)	(-5.149 to -3.202)	53	-1.38 (0.363)
No	191	-6.24 (0.189)	-4.95 (0.263)	(-5.470 to -4.439)	199	-1.29 (0.185)

SGLT2 = Sodium glucose co-transporter 2.

a Analysis of covariance (ANCOVA) model with treatment groups (fixed ratio combination, insulin glargine), randomization strata of DPP-4 inhibitor use at screening (Yes, No), subgroup factor and treatment-by-subgroup factor as fixed effects, and baseline 2-hour postprandial plasma glucose value-by-visit interaction as a covariate.

For fixed ratio combination group, the analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation.

For insulin glargine group, the analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 1 day.

Patients with both baseline and Week 26 (LOCF) measurements were included.

LS Mean and difference in LS Mean were provided for categories with ≥ 5 patients in each treatment group.

Table 6 - Overview of adverse event profile: treatment emergent adverse events by SGLT-2 inhibitor use at screening - Safety population (EFC14114)

n (%)	SGLT2 inhibitor use at screening Yes (N=115)		SGLT2 inhibitor use at screening No (N=406)	
	Fixed Ratio Combination (N=59)	Insulin glargine (N=56)	Fixed Ratio Combination (N=201)	Insulin glargine (N=205)
Patients with any TEAE	41 (69.5%)	36 (64.3%)	122 (60.7%)	130 (63.4%)
Patients with any serious TEAE	1 (1.7%)	1 (1.8%)	5 (2.5%)	7 (3.4%)
Patients with any TEAE leading to death	0	0	1 (0.5%)	0
Patients with any TEAE leading to permanent treatment discontinuation	1 (1.7%)	1 (1.8%)	3 (1.5%)	1 (0.5%)

SGLT2 = Sodium glucose co-transporter 2, TEAE: Treatment emergent adverse event.

n (%) = number and percentage of patients with at least one TEAE.

Table 7 - Number (%) of patients experiencing common TEAE(s) (PT ≥2% in any treatment group) by primary SOC and PT and by SGLT-2 inhibitor use at screening - Safety population (EFC14114)

Primary System Organ Class Preferred Term n (%)	SGLT2 inhibitor use at screening Yes (N=115)		SGLT2 inhibitor use at screening No (N=406)	
	Fixed Ratio Combination (N=59)	Insulin glargine (N=56)	Fixed Ratio Combination (N=201)	Insulin glargine (N=205)
Any class	41 (69.5%)	36 (64.3%)	122 (60.7%)	130 (63.4%)
Infections and infestations	19 (32.2%)	19 (33.9%)	61 (30.3%)	73 (35.6%)
Nasopharyngitis	12 (20.3%)	10 (17.9%)	37 (18.4%)	52 (25.4%)
Pharyngitis	1 (1.7%)	3 (5.4%)	7 (3.5%)	2 (1.0%)
Influenza	0	1 (1.8%)	7 (3.5%)	3 (1.5%)
Metabolism and nutrition disorders	2 (3.4%)	1 (1.8%)	8 (4.0%)	6 (2.9%)
Decreased appetite	0	0	7 (3.5%)	0
Nervous system disorders	7 (11.9%)	6 (10.7%)	19 (9.5%)	19 (9.3%)
Dizziness	4 (6.8%)	0	4 (2.0%)	7 (3.4%)
Headache	1 (1.7%)	3 (5.4%)	5 (2.5%)	4 (2.0%)
Gastrointestinal disorders	13 (22.0%)	7 (12.5%)	55 (27.4%)	32 (15.6%)
Nausea	3 (5.1%)	2 (3.6%)	22 (10.9%)	3 (1.5%)
Diarrhoea	1 (1.7%)	0	11 (5.5%)	6 (2.9%)
Abdominal discomfort	3 (5.1%)	0	8 (4.0%)	0
Constipation	3 (5.1%)	0	6 (3.0%)	3 (1.5%)
Dyspepsia	3 (5.1%)	0	3 (1.5%)	1 (0.5%)
Dental caries	0	1 (1.8%)	4 (2.0%)	5 (2.4%)
Skin and subcutaneous tissue disorders	6 (10.2%)	5 (8.9%)	9 (4.5%)	20 (9.8%)
Hyperhidrosis	2 (3.4%)	1 (1.8%)	1 (0.5%)	6 (2.9%)
Musculoskeletal and connective tissue disorders	7 (11.9%)	7 (12.5%)	28 (13.9%)	25 (12.2%)
Back pain	3 (5.1%)	3 (5.4%)	8 (4.0%)	6 (2.9%)

Primary System Organ Class Preferred Term n (%)	SGLT2 inhibitor use at screening Yes (N=115)		SGLT2 inhibitor use at screening No (N=406)	
	Fixed Ratio Combination (N=59)	Insulin glargine (N=56)	Fixed Ratio Combination (N=201)	Insulin glargine (N=205)
General disorders and administration site conditions	10 (16.9%)	3 (5.4%)	21 (10.4%)	15 (7.3%)
Fatigue	0	0	6 (3.0%)	4 (2.0%)

SGLT2 = Sodium glucose co-transporter 2, TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term, MedDRA 20.1.

n (%) = number and percentage of patients with at least one TEAE.

Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT sorted by decreasing frequency within a SOC according to all TEAE summary.

Only SOC with at least one PT $\geq 2\%$ in at least one treatment group are presented.

Table 8 - Summary of documented symptomatic hypoglycemia recorded on the dedicated eCRF page and meeting protocol definition by SGLT2 inhibitor use at screening during the on-treatment period - Safety population (EFC14114)

	SGLT2 inhibitor use at screening Yes (N=115)		SGLT2 inhibitor use at screening No (N=406)	
	Fixed Ratio Combination (N=59)	Insulin glargine (N=56)	Fixed Ratio Combination (N=201)	Insulin glargine (N=205)
Total patient years of exposure	29.4	27.3	97.9	102.4
Documented symptomatic hypoglycemia (plasma glucose ≤ 70 mg/dL [3.9 mmol/L])				
Number of patients with events, n (%)	8 (13.6%)	3 (5.4%)	29 (14.4%)	29 (14.1%)
Number of patients with events per patient year ^a	0.27	0.11	0.30	0.28
Number of events	15	8	78	62
Number of events per patient year ^b	0.51	0.29	0.80	0.61

SGLT2 = Sodium glucose co-transporter 2, IMP = Investigational medicinal product, eCRF = Electronic case report form.

Total patient years of exposure: calculated as the time from the first injection of open-label IMP up to 1 day after the last injection of open-label IMP.

^a Calculated as number of patients with events divided by total patient years of exposure.

^b Calculated as number of events divided by total patient years of exposure.

Any hypoglycemia = Hypoglycemia recorded on the dedicated eCRF and meeting protocol definition for severe hypoglycemia, documented symptomatic hypoglycemia or asymptomatic hypoglycemia.

The on-treatment period is defined as the time from the first injection of open-label IMP up to 1 day after the last injection of open-label IMP, regardless of the introduction of rescue therapy.