Use of AVE0010 for the manufacture of a medicament for the treatment of diabetes mellitus type 2

Description

Subject of the present invention is the use of desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ (AVE0010, lixisenatide) or/and a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of diabetes mellitus type 2. Another subject is a pharmaceutical composition comprising desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof, and optionally comprising pharmaceutically acceptable carriers, adjuvants, or/and auxiliary substances. Yet another aspect is a method for the treatment of diabetes mellitus type 2 comprising administering desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof to a subject in need thereof.

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

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

An increased glucose level in the blood over several years without initial symptoms represents a significant health risk. It could clearly be shown by the large-scale

DCCT study in the USA (The Diabetes Control and Complications Trial Research Group (1993) N. Engl. J. Med. 329, 977-986) that chronically increased levels of blood glucose are a main reason for the development of diabetes complications. Examples for diabetes complications are micro and macrovascular damages that possibly manifest themselves in retinopathies, nephropathies or neuropathies and lead to blindness, renal failure and the loss of extremities and are accompanied by an increased risk of cardiovascular diseases. It can thus be concluded that an improved therapy of diabetes primarily has to aim keeping blood glucose in the physiological range as closely as possible.

A particular risk exists for overweight patients suffering from diabetes type 2, e.g. patients with a body mass index (BMI) ≥ 30. In these patients the risks of diabetes overlap with the risks of overweight, leading e.g. to an increase of cardiovascular diseases compared to diabetes type 2 patients being of a normal weight. Thus, it is particularly necessary to treat diabetes in these patients while reducing the overweight.

The compound desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ (AVE0010, lixisenatide) is a derivative of Exendin-4. AVE0010 is disclosed as SEQ ID NO:93 in WO 01/04156:

SEQ ID NO: 1: AVE0010 (44 AS)
H-G-E-G-T-F-T-S-D-L-S-K-Q-M-E-E-E-A-V-R-L-F-I-E-W-L-K-N-G-G-P-S-S-G-A-P-P-S-K-K-K-K-K-K-NH$_2$
SEQ ID NO: 2: Exendin-4 (39 AS)
H-G-E-G-T-F-T-S-D-L-S-K-Q-M-E-E-E-A-V-R-L-F-I-E-W-L-K-N-G-G-P-S-S-G-A-P-P-P-S-NH$_2$

Exendins are a group of peptides which can lower blood glucose concentration. The Exendin analogue AVE0010 is characterised by C-terminal truncation of the native Exendin-4 sequence. AVE0010 comprises six C-terminal lysine residues not present in Exendin-4.

In the context of the present invention, AVE0010 includes pharmaceutically acceptable salts thereof. The person skilled in the art knows pharmaceutically acceptable salts of AVE0010. A preferred pharmaceutically acceptable salt of AVE0010 employed in the present invention is acetate.

A first aspect of the present invention is the use of desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of diabetes mellitus type 2.

The subject to be treated by the medicament of the present invention suffering from diabetes type 2 may be an obese subject. In the present invention, an obese subject may have a body mass index of at least 30 kg/m^2.

The subject to be treated by the medicament of the present invention may be an adult subject. The subject may have an age of at least 18 years of may have an age in the range of 18 to 80 years, or 40 to 80 years, or 50 to 60 years.
The subject to be treated by the medicament of the present invention preferably does not receive an antidiabetic treatment, for instance by insulin or/and related compounds.

The subject to be treated by the medicament of the present invention may suffer from diabetes mellitus type 2 for at least 1 year or at least 2 years. In particular, in the subject to be treated, diabetes mellitus type 2 has been diagnosed at least 1 year or at least 2 years before onset of therapy by the medicament of the present invention.

The subject to be treated may have a HbA_{1c} value of at least about 8 % or at least about 7,5%. The subject may also have a HbA_{1c} value of about 7 to about 10 %. The example of the present invention demonstrates that treatment by AVE0010 results in a reduction of the HbA_{1c} value in diabetes type 2 patients (see Tables 9, 10).

The active agent of the present invention is preferably used for improving glucose tolerance in the treatment of a patient suffering from diabetes type 2. Improving glucose tolerance means that the postprandial plasma glucose concentration is reduced by the active agent of the present invention. Reduction means in particular that the plasma glucose concentration reaches normoglycemic values or at least approaches these values.

In the present invention, normoglycemic values are blood glucose concentrations of in particular 60 – 140 mg/dl (corresponding to 3,3 bis 7,8 mM/L). This range refers in particular to blood glucose concentrations under fasting conditions and postprandial conditions.

The subject to be treated may have a 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. The example of the present invention demonstrates that treatment by AVE0010 results in a reduction of the blood glucose concentration in diabetes type 2 patients (see Table 15).

The subject to be treated may have a 2 hours postprandial plasma glucose concentration of at least 10 mmol/L, at least 12 mmol/L, or at least 14 mmol/L. These plasma glucose concentrations exceed normoglycemic concentrations. The example of the present invention demonstrates that treatment by AVE0010 results in a reduction of the 2 hours postprandial plasma glucose concentration in diabetes type 2 patients (see Table 11).

The subject to be treated may have a glucose excursion of at least 2 mmol/L, at least 3 mmol/L, at least 4 mmol/L or at least 5 mmol/L. In the present invention, the glucose excursion is in particular the difference of the 2 hours postprandial plasma glucose concentration and the plasma glucose concentration 30 minutes prior to a meal test. In the context of the present invention, a meal test is… The example of the present invention demonstrates that treatment by AVE0010 results in a reduction of the glucose excursion in diabetes type 2 patients (see Table 12).

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

A second aspect of the present invention is the use of desPro^{36}Exendin-4(1-39)-Lys_6-NH_2 or/and a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inducing weight loss in diabetes type 2 patients or/and for preventing weight gain in diabetes type 2 patients. The example of the present invention demonstrates that treatment by AVE0010 results in a weight reduction in diabetes type 2 patients (see Tables 13 and 14).

The active agent, the medicament or/and the pharmaceutical composition of the present invention can be used in the treatment of one or more of the medical indications described herein, for example in treatment of diabetes type 2 patients, or for conditions associated with diabetes type 2, such as reduction of the fasting plasma glucose concentration, reduction of the postprandial plasma glucose concentration, improvement of glucose tolerance, weight loss or/and prevention of weight gain.

In the present invention, desPro^{36}Exendin-4(1-39)-Lys_6-NH_2 may be administered to a subject in need thereof, in an amount sufficient to induce a therapeutic effect.

The compound desPro^{36}Exendin-4(1-39)-Lys_6-NH_2 or/and a pharmaceutically acceptable salt thereof may be administered parenterally, e.g. by injection (such as by intramuscular or by subcutaneous injection). Suitable injection devices, for instance the so-called "pens" comprising a cartridge comprising the active ingredient, and an injection needle, are known. The compound desPro^{36}Exendin-4(1-39)-Lys_6-NH_2 or/and a pharmaceutically acceptable salt thereof may be administered in a

suitable amount, for instance in an amount in the range of 10 to 15 µg per dose or 15 to 20 µg per dose.

In the present invention, desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof may be administered in a daily dose in the range of 10 to 20 µg, in the range of 10 to 15 µg, or in the range of 15 to 20 µg. DesPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof may be administered by one injection per day.

Yet another aspect of the present invention is a pharmaceutical composition comprising desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof, and optionally comprising pharmaceutically acceptable carriers, adjuvants, or/and auxiliary substances.

The pharmaceutical composition of the present invention may be prepared for use in the treatment of diabetes mellitus type 2.

The pharmaceutical composition of the present invention may also be prepared for use in inducing weight loss in diabetes type 2 patients or/and for use in preventing weight gain in diabetes type 2 patients.

The pharmaceutical composition of the present invention may also be prepared for use in the treatment of a subject as described herein.

In the present invention, the pharmaceutical composition or/and the medicament described herein may be a liquid composition comprising desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof. The skilled person knows liquid compositions of AVE0010 suitable for parenteral administration. A liquid composition of the present invention may have an acidic or a physiologic pH. An acidic pH preferably is in the range of pH 1 – 6.8, pH 3.5 - 6.8, or pH 3.5 – 5. A physiologic pH preferably is in the range of pH 2.5 - 8.5, pH 4.0 - 8.5, or pH 6.0 - 8.5. Preferably the range is of pH 4,5 – 5,0.

The pH may be adjusted by a pharmaceutically acceptable diluted acid (typically HCl) or pharmaceutically acceptable diluted base (typically NaOH).

The liquid composition of the present invention may comprise a suitable preservative. A suitable preservative may be selected from phenol, m-cresol, benzyl alcohol and p-hydroxybenzoic acid ester. A preferred preservative is m-cresol.

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

The liquid composition of the present invention may comprise methionine.
Yet another aspect of the present invention is a method for the treatment of diabetes mellitus type 2 comprising administering desPro^{36}Exendin-4(1-39)-Lys$_6$-NH_2 or/and a pharmaceutically acceptable salt thereof to a subject in need thereof.

A further aspect of the present invention is a method for inducing weight loss in diabetes type 2 patients or/and for preventing weight gain in diabetes type 2 patients, said method comprising administering desPro^{36}Exendin-4(1-39)-Lys$_6$-NH_2 or/and a pharmaceutically acceptable salt thereof to a subject in need thereof.

In the method of the present invention, the subject may be the subject defined herein.

In the method of the present invention, the pharmaceutical composition or/and medicament as described herein may be administered.

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

Figure legends

Fig. 1: Study design

Fig. 2: The overall step-down testing procedure

Fig. 3: Kaplan-Meier plot of time to treatment discontinuation due to any reason – Randomized population

Fig. 4: Plot of mean change in HbA_{1c} (%) ± SE from baseline by visit and at endpoint – mITT population. The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 3 days.

Fig. 5: Plot of mean change in body weight (kg) ± SE from baseline by visit and at endpoint – mITT population. The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 3 days.

Fig. 6: Plot of mean change in fasting plasma glucose (mmol/L) ± SE from baseline by visit and at endpoint – mITT population. The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 1 day.

EXAMPLE: A randomized, double-blind, placebo-controlled, parallel-group, multicenter 12-week study assessing the efficacy and safety of Lixisenatide in patients with type 2 diabetes not treated with antidiabetic agents

SUMMARY

Subject of the example is a randomized, double-blind, placebo-controlled, parallel-group, multicenter 12-week study assessing the efficacy and safety of lixisenatide in patients with type 2 diabetes not treated with antidiabetic agents, conducted in 61 centers of 12 countries. The primary objective of the study was to assess the effects of lixisenatide on glycemic control used in a two-step dose titration regimen in comparison to placebo in terms of HbA_{1c} reduction (absolute change) over a period of 12 weeks.

A total of 361 patients were randomized to one of the four treatment groups (61 in the placebo two-step titration group, 61 in the placebo one-step titration group, 120 in the lixisenatide two-step titration group, and 119 in the lixisenatide one-step titration group). The placebo one-step and two-step titration groups were combined in analyses. Two patients were excluded from mITT population for efficacy analyses due to a lack of post-baseline efficacy data. Of 361 randomized patients, 331 (91.7%) completed the 12-week double-blind treatment. Thirty patients discontinued the treatment prematurely and 9 of these patients discontinued due to an adverse event. Demographics and baseline characteristics were generally similar across treatment groups.

The least square (LS) mean changes from baseline to endpoint in HbA_{1c} were -0.19% for the placebo group, -0.73% for the lixisenatide 2-step titration group (LS mean difference vs. placebo = -0.54%; p-value = < .0001), and -0.85% for the lixisenatide 1-step titration group (LS mean difference vs. placebo = -0.66%; p-value = < .0001). The HbA_{1c} responder analysis ($HbA_{1c} \leq 6.5$ or < 7% at endpoint) using CMH method also showed a significant treatment difference versus placebo for both lixisenatide-treated groups.

For 2-hour post-prandial plasma glucose levels, each of the lixisenatide-treated groups demonstrated a significant improvement over the placebo group. The between-group difference in body weight compared to placebo was not statistically significant for either of the lixisenatide-treated groups due to a similar decrease in placebo group. Both lixisenatide-treated groups demonstrated meaningful improvements over the placebo group in fasting plasma glucose using ANCOVA analysis without multiplicity adjustment. A total of 3 lixisenatide-treated patients (2 [1.7%] in 2-step titration and 1 [0.8%] in 1-step titration) received a rescue therapy, and 3 patients [2.5%] in the placebo group.

Lixisenatide (AVE0010) was well tolerated during the 12 weeks of treatment. Incidences of TEAEs (treatment-emergent adverse events) were generally comparable across treatment groups. Only one serious TEAE was reported in a lixisenatide-treated patient (2-step titration), whereas 5 placebo-treated patients reported serious TEAEs. No death was reported in this study. A total of 8 lixisenatide-treated patients (5 [4.2%] in 2-step titration and 3 [2.5%] in 1-step titration) discontinued the treatment, mainly due to gastrointestinal (GI) disorders, while one placebo-treated patient (0.8%) discontinued. There was no obvious difference for GI tolerance in 1-step and 2-step titration lixisenatide-treated patients. The most commonly reported TEAE was nausea (24.2% for lixisenatide 2-step titration, 20.2% for lixisenatide 1-step titration and 4.1% for placebo).

A total of 6 cases (3 [2.5%] in lixisenatide 2-step titration; 1 [0.8%] in lixisenatide 1-step titration; 2 [1.6%] in placebo) of symptomatic hypoglycemia per protocol definition were observed and none of them was severe. No case of elevated lipase or amylase (≥ 3 ULN) was observed in any of the treatment groups.

1 OBJECTIVES

1.1 PRIMARY OBJECTIVE

The primary objective of this example was to assess the effects of lixisenatide on glycemic control used in a two-step dose titration regimen in comparison to placebo

in terms of HbA_{1c} reduction (absolute change) over a period of 12 weeks in patients with type 2 diabetes not treated with antidiabetic agents.

1.2 SECONDARY OBJECTIVE(S)

The secondary objectives of this study were:

- To assess the effects of lixisenatide on:
  - Glycemic control in comparison to placebo in terms of HbA_{1c} reduction when used in a one-step dose titration regimen over a period of 12 weeks,
  - Body weight at week 12,
  - Fasting plasma glucose (FPG) at week 12,
  - 2-hour post-prandial plasma glucose after standardized meal challenge test at week 12 in a subgroup of all the patients in selected sites (approximately 50% of the randomized patients),
- To assess lixisenatide safety and tolerability over a period of 12 weeks,
- To assess lixisenatide PK using population PK approach,
- To assess anti-lixisenatide antibody development.

2 TRIAL DESIGN

This was a double-blind, randomized, placebo-controlled, 4-arm, unbalanced design, parallel-group multinational study: two-step titration (120 lixisenatide-treated and 60 placebo-treated patients) and one-step titration (120 lixisenatide-treated and 60 placebo-treated patients). The study was double-blind with regard to active and placebo treatments. The study drug volume (i.e., dose of active drug or matching placebo) and the titration regimens (i.e., one-step and two-step) were not blinded.

The patients were stratified by screening values of glycosylated hemoglobin A_{1c} (HbA_{1c}) (< 8%, ≥ 8%) and body mass index (BMI < 30 kg/m^2, ≥ 30 kg/m^2). After a screening period, patients were centrally randomized via interactive voice response system (IVRS) in a 2:1:2:1 ratio to one of the four arms (two-step titration of lixisenatide, two-step titration of placebo, one-step titration of lixisenatide, and one-step titration of placebo).

The study consisted of 3 periods: 1) an up to 3-week screening period, which included an up to 2-week screening phase and a 1-week single-blind placebo run-in phase; 2) a main 12-week double-blind, placebo-controlled treatment period; 3) a 3-day, drug-free post-treatment follow-up period.

The study design is described in Figure 1.

The administration is performed as follows…

3 PRIMARY AND SECONDARY ENDPOINTS

3.1 PRIMARY ENDPOINT

The primary efficacy variable was the absolute change in HbA_{1c} from baseline to Week 12, which was defined as: HbA_{1c} value at Week 12 - HbA_{1c} value at baseline.

If a patient permanently discontinued the treatment prematurely or received rescue therapy during the 12-week double-blind treatment period or did not have HbA_{1c}

value at Week 12, the last post-baseline on-treatment HbA_{1c} measurement during the 12-week double-blind treatment period was to be used as HbA_{1c} value at Week 12 (Last Observation Carry Forward [LOCF] procedure).

3.2 SECONDARY ENDPOINTS

For secondary efficacy variables, the same procedure for handling missing assessments/early discontinuation during the 12-week double-blind treatment period was applied as for the primary efficacy variable.

Continuous variables:

- Change in 2-hour post-prandial plasma glucose (mmol/L) after a standardized meal test from baseline to Week 12,
- Change in body weight (kg) from baseline to Week 12,
- Change in fasting plasma glucose (mmol/L) from baseline to Week 12,
- Change in glucose excursion (mmol/L) (2-hour post-prandial plasma glucose – plasma glucose 30 minutes prior to the meal test, before study drug administration) after a standardized meal test from baseline to Week 12.

Categorical variables:

- Percentage of patients with $HbA_{1c} < 7\%$ at Week 12,
- Percentage of patients with $HbA_{1c} \leq 6.5\%$ at Week 12,
- Percentage of patients requiring rescue therapy during the double-blind treatment period,
- Percentage of patients with ≥ 5% weight loss (kg) from baseline at Week 12.

4 SAMPLE SIZE CALCULATION ASSUMPTIONS

The sample size/power calculation was performed based on the primary efficacy variable, change from baseline to Week 12 in HbA_{1c}.

To detect a difference of 0.5% in the change from baseline in HbA_{1c} between one lixisenatide arm and the combined placebo group at Week 12, 120 patients per group (i.e., 120 patients per lixisenatide arm and 2x60 patients for combined placebo group) provided a power of 90%. This calculation assumed a common standard deviation of 1.2% with a 2-sided test at the 5% significance level. The sample size calculations were based upon the two-sample t test and made using nQuery Advisor 5.0.

5 STATISTICAL METHODS

5.1 ANALYSIS POPULATIONS

The modified-ITT population consisted of all patients who were randomized (analyzed “as randomized”), received at least one dose of double-blind investigational product, and had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variable, irrespective of compliance with the study protocol and procedures.

The safety population was the Total Treated population defined as all patients randomized (via the central randomization system according to the protocol) and exposed to at least one dose of the investigational product, regardless of the amount of treatment administered.

5.2 PRIMARY EFFICACY ANALYSIS

The primary efficacy variable (change in HbA_{1c} from baseline to Week 12) was analyzed using an analysis of covariance (ANCOVA) model with treatment groups (two-step titration lixisenatide and placebo arms, one-step titration lixisenatide and placebo arms), randomization strata of screening HbA_{1c} (< 8.0, ≥ 8.0%), randomization strata of screening BMI (< 30, ≥ 30 kg/m²) values, and country as fixed effects and using the baseline HbA_{1c} values as a covariate. In the ANCOVA model, the two titration placebo arms were included as separate treatment levels, but

they were combined as one group when making comparisons using appropriate contrast (eg, to compare two-step titration lixisenatide group with combined placebo [-0.5, -0.5, 0, +1] in the order of one-step titration placebo, two-step titration placebo, one-step titration lixisenatide and two-step titration lixisenatide group).

A stepwise testing procedure was applied in order to ensure type I error control. First, two-step titration lixisenatide arm was compared with the combined placebo group (primary objective). If the test was statistically significant, then one-step titration lixisenatide arm was compared with the combined placebo group (secondary objective).

As mentioned in Section 3.1, the primary endpoint is the absolute change in HbA_{1c} from baseline to Week 12 using LOCF during the on-treatment period. The on-treatment period for efficacy variables except those from meal challenge test is the time from the first dose of investigational product up to 3 days (except for Fasting Plasma Glucose (FPG) by central laboratory, which is up to 1 day) after the last dose of investigational product or up to the introduction of rescue therapy, whichever is the earliest. The on-treatment period for efficacy variables from meal challenge test including Post-prandial Plasma Glucose (PPG) and glucose excursion is the time from the first dose to the date of the last dose of investigational product or up to the introduction of rescue therapy, whichever is the earliest.

5.3 SECONDARY EFFICACY ANALYSIS

Once the primary variable was statistically significant at $\alpha=0.05$ for both comparisons, the testing procedure was performed to test secondary efficacy variables, see Figure 2.

All continuous secondary efficacy variables at Week 12 were analyzed using a similar ANCOVA model as described in Section 5.2 to compare two-step titration lixisenatide arm with combined placebo group and one-step titration lixisenatide arm with combined placebo group.

The following categorical secondary efficacy variables at Week 12 were analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified on randomization strata (screening HbA_{1c} (< 8.0, ≥ 8.0%) and screening BMI (< 30 kg/m^2, ≥ 30 kg/m^2) values):

- Percentage of patients with HbA_{1c} < 7.0% at Week 12,
- Percentage of patients with HbA_{1c} ≤ 6.5% at Week 12,
- Percentage of patients requiring rescue therapy during 12-week treatment period,

Number and percentage of patients with ≥ 5% weight loss from baseline at Week 12 were presented by treatment groups.

5.4 SAFETY ANALYSIS

Treatment-emergent AEs (TEAEs) were defined as AEs that developed or worsened (according to the Investigator opinion) or became serious during the on-treatment period. The on-treatment period was defined as the time from the first dose of double-blind investigational product (IP) up to 3 days after the last injection of IP administration. The 3-day interval was chosen based on the half-life of the IP (approximately 5 times the half-life).

6 RESULTS

6.1 STUDY PATIENTS

6.1.1 Patient accountability

Of the 795 patients screened, 434 (54.6%) patients were not randomized into the double-blind treatment. The main reason was HbA_{1c} value at screening visit out of the defined protocol ranges (318 (40.0%) patients).

A total of 361 patients were randomized to one of the four treatment groups (61 in the placebo two-step titration group, 61 in the placebo one-step titration group, 120 in the lixisenatide two-step titration group, 119 in the lixisenatide one-step titration group) in 61 centers of 12 countries (Belgium, India, Israel, Japan, Korea, Mexico, Poland, Romania, Russia, Tunisia, Ukraine, and United States). All 361 randomized patients were exposed to double-blind treatment. Two patients were excluded from mITT population for efficacy analyses due to lack of post-baseline efficacy data. Table 1 below provides the number of patients included in each analysis population.

Table 1 - Analysis populations – Randomized population

	Placebo			Lixisenatide			
	Two-step Titration	One-step Titration	Combined	Two-step Titration	One-step Titration	Combined	All
Randomized population	61 (100%)	61 (100%)	122 (100%)	120 (100%)	119 (100%)	239 (100%)	361 (100%)
Efficacy populations							
Modified Intent-to-Treat (mITT)	61 (100%)	60 (98.4%)	121 (99.2%)	120 (100%)	118 (99.2%)	238 (99.6%)	359 (99.4%)
PK Population	6	1	7	114	117	231	238
Safety population	61	61	122	120	119	239	361

PK = pharmacokinetics.
Note: The Safety and PK population patients are tabulated according to treatment actually received (as treated).
For the efficacy population, patients are tabulated according to their randomized treatment (as randomized).

6.1.2 Study disposition

Table 2 below provides the summary of patient disposition for each treatment group. Of the 361 randomized patients, 30 (8.3%) patients prematurely discontinued from study treatment, mainly due to reasons classified as “other” (i.e. subject’s decision, 18 patients) followed by adverse events (9 patients). The time-to-onset of treatment discontinuation is depicted in Figure 3 and no particular pattern was observed.

Table 2 - Patient disposition – Randomized population

	Placebo			Lixisenatide		
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Randomized and treated	61 (100%)	61 (100%)	122 (100%)	120 (100%)	119 (100%)	239 (100%)
Did not complete the study treatment period	4 (6.6%)	5 (8.2%)	9 (7.4%)	10 (8.3%)	11 (9.2%)	21 (8.8%)
Subject's request for treatment discontinuation	4 (6.6%)	5 (8.2%)	9 (7.4%)	10 (8.3%)	10 (8.4%)	20 (8.4%)
Reason for study treatment discontinuation						
Adverse event	1 (1.6%)	0	1 (0.8%)	5 (4.2%)	3 (2.5%)	8 (3.3%)
Lack of efficacy	0	1 (1.6%)	1 (0.8%)	0	0	0
Poor compliance to protocol	0	1 (1.6%)	1 (0.8%)	1 (0.8%)	0	1 (0.4%)
Lost to follow-up	0	0	0	0	0	0
Other reasons	3 (4.9%)	3 (4.9%)	6 (4.9%)	4 (3.3%)	8 (6.7%)	12 (5.0%)
Status at last study contact						
Alive	61 (100%)	61 (100%)	122 (100%)	120 (100%)	119 (100%)	239 (100%)
Dead	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0

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

6.1.3 Demographics and baseline characteristics

Table 3 below provides the summary of baseline and demographic characteristics for each treatment group and overall. The demographic and baseline information were generally similar across treatment groups for the safety population. The study population was balanced between genders, and the median age was 54 years. The majority of the patients were Caucasian (72.9%).

Table 3 - Demographics and patient characteristics at screening - Safety population

	Placebo			Lixisenatide			
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)	All (N=361)
Age (years)							
Number	61	61	122	120	119	239	361
Mean (SD)	54.5 (11.2)	53.6 (10.9)	54.1 (11.0)	53.3 (9.7)	53.8 (10.9)	53.5 (10.3)	53.7 (10.5)
Median	55.0	53.0	54.5	54.0	53.0	54.0	54.0
Min : Max	31 : 75	33 : 85	31 : 85	21 : 78	20 : 82	20 : 82	20 : 85
Age Group (years) [n (%)]							
Number	61	61	122	120	119	239	361
< 50	20 (32.8%)	20 (32.8%)	40 (32.8%)	44 (36.7%)	34 (28.6%)	78 (32.6%)	118 (32.7%)
≥ 50 to < 65	30 (49.2%)	34 (55.7%)	64 (52.5%)	64 (53.3%)	69 (58.0%)	133 (55.6%)	197 (54.6%)
≥ 65 to < 75	8 (13.1%)	5 (8.2%)	13 (10.7%)	11 (9.2%)	11 (9.2%)	22 (9.2%)	35 (9.7%)
≥ 75	3 (4.9%)	2 (3.3%)	5 (4.1%)	1 (0.8%)	5 (4.2%)	6 (2.5%)	11 (3.0%)
Sex [n (%)]							
Number	61	61	122	120	119	239	361
Male	36 (59.0%)	24 (39.3%)	60 (49.2%)	63 (52.5%)	63 (52.9%)	126 (52.7%)	186 (51.5%)
Female	25 (41.0%)	37 (60.7%)	62 (50.8%)	57 (47.5%)	56 (47.1%)	113 (47.3%)	175 (48.5%)

	Placebo			Lixisenatide			
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)	All (N=361)
Race [n (%)]							
Number	61	61	122	120	119	239	361
Caucasian/White	43 (70.5%)	47 (77.0%)	90 (73.8%)	88 (73.3%)	85 (71.4%)	173 (72.4%)	263 (72.9%)
Black	2 (3.3%)	1 (1.6%)	3 (2.5%)	0	3 (2.5%)	3 (1.3%)	6 (1.7%)
Asian/Oriental	14 (23.0%)	10 (16.4%)	24 (19.7%)	27 (22.5%)	29 (24.4%)	56 (23.4%)	80 (22.2%)
Other	2 (3.3%)	3 (4.9%)	5 (4.1%)	5 (4.2%)	2 (1.7%)	7 (2.9%)	12 (3.3%)
Ethnicity [n (%)]							
Number	61	61	122	120	119	239	361
Hispanic	15 (24.6%)	16 (26.2%)	31 (25.4%)	25 (20.8%)	22 (18.5%)	47 (19.7%)	78 (21.6%)
Non Hispanic	46 (75.4%)	45 (73.8%)	91 (74.6%)	95 (79.2%)	97 (81.5%)	192 (80.3%)	283 (78.4%)
Screening HbA_{1c} (%)							
Number	61	61	122	120	119	239	361
Mean (SD)	8.15 (0.87)	8.20 (0.91)	8.18 (0.89)	8.11 (0.91)	8.20 (0.84)	8.16 (0.87)	8.16 (0.88)
Median	8.00	8.00	8.00	7.95	8.00	8.00	8.00
Min : Max	7.0 : 10.0	7.0 : 10.0	7.0 : 10.0	7.0 : 10.0	7.0 : 9.9	7.0 : 10.0	7.0 : 10.0
Randomized strata of screening HbA_{1c} (%) [n (%)]							
Number	61	61	122	120	119	239	361
< 8	30 (49.2%)	30 (49.2%)	60 (49.2%)	60 (50.0%)	58 (48.7%)	118 (49.4%)	178 (49.3%)
≥ 8	31 (50.8%)	31 (50.8%)	62 (50.8%)	60 (50.0%)	61 (51.3%)	121 (50.6%)	183 (50.7%)
Screening BMI (kg/m^2)							
Number	61	61	122	120	119	239	361
Mean (SD)	31.70 (6.64)	31.81 (6.79)	31.76 (6.69)	32.34 (6.72)	31.65 (6.62)	31.99 (6.66)	31.91 (6.66)
Median	30.80	31.18	30.96	31.13	30.89	31.05	31.05
Min : Max	20.1 : 56.0	20.6 : 58.7	20.1 : 58.7	20.6 : 50.3	20.8 : 53.7	20.6 : 53.7	20.1 : 58.7

	Placebo			Lixisenatide			
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)	All (N=361)
Randomized strata of screening BMI (kg/m^2) [n (%)]							
Number	61	61	122	120	119	239	361
< 30	25 (41.0%)	26 (42.6%)	51 (41.8%)	50 (41.7%)	49 (41.2%)	99 (41.4%)	150 (41.6%)
≥ 30	36 (59.0%)	35 (57.4%)	71 (58.2%)	70 (58.3%)	70 (58.8%)	140 (58.6%)	211 (58.4%)

BMI = Body Mass Index.

Table 4 below describes the diabetic history for each treatment group and overall for the safety population. Diabetic histories were generally comparable across treatment groups.

Table 4 - Disease characteristics at screening– Safety population

	Placebo			Lixisenatide			
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)	All (N=361)
Duration of diabetes (years)							
Number	61	61	122	120	119	239	361
Mean (SD)	2.49 (2.44)	2.47 (2.87)	2.48 (2.66)	2.59 (3.51)	2.48 (3.82)	2.53 (3.66)	2.52 (3.35)
Median	1.46	1.03	1.37	1.42	1.11	1.30	1.33
Min : Max	0.2 : 9.6	0.2 : 12.5	0.2 : 12.5	0.2 : 21.5	0.2 : 23.9	0.2 : 23.9	0.2 : 23.9
Age at onset of T2D (years)							
Number	61	61	122	120	119	239	361
Mean (SD)	51.97 (11.27)	51.18 (11.17)	51.57 (11.18)	50.69 (9.53)	51.30 (11.27)	51.00 (10.41)	51.19 (10.67)
Median	53.00	51.00	52.00	51.00	51.00	51.00	51.00
Min : Max	30.0 : 75.0	28.0 : 83.0	28.0 : 83.0	21.0 : 76.0	17.0 : 82.0	17.0 : 82.0	17.0 : 83.0

	Placebo			Lixisenatide			
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)	All (N=361)
Prior use of GLP-1 receptor agonist [n (%)]							
Number	61	61	122	120	119	239	361
Yes	1 (1.6%)	1 (1.6%)	2 (1.6%)	0	1 (0.8%)	1 (0.4%)	3 (0.8%)
No	60 (98.4%)	60 (98.4%)	120 (98.4%)	120 (100%)	118 (99.2%)	238 (99.6%)	358 (99.2%)
Diabetic retinopathy [n (%)]							
Number	59	59	118	118	119	237	355
Yes	1 (1.7%)	1 (1.7%)	2 (1.7%)	3 (2.5%)	3 (2.5%)	6 (2.5%)	8 (2.3%)
No	53 (89.8%)	53 (89.8%)	106 (89.8%)	110 (93.2%)	106 (89.1%)	216 (91.1%)	322 (90.7%)
Diabetic sensory or motor neuropathy [n (%)]							
Number	59	59	118	117	119	236	354
Yes	2 (3.4%)	4 (6.8%)	6 (5.1%)	6 (5.1%)	2 (1.7%)	8 (3.4%)	14 (4.0%)
No	55 (93.2%)	52 (88.1%)	107 (90.7%)	107 (91.5%)	112 (94.1%)	219 (92.8%)	326 (92.1%)
Diabetic autonomic neuropathy [n (%)]							
Number	59	59	118	118	119	237	355
Yes	0	0	0	0	0	0	0
No	57 (96.6%)	55 (93.2%)	112 (94.9%)	114 (96.6%)	114 (95.8%)	228 (96.2%)	340 (95.8%)
Diabetic nephropathy [n (%)]							
Number	59	59	118	118	119	237	355
Yes	0	0	0	1 (0.8%)	0	1 (0.4%)	1 (0.3%)
No	57 (96.6%)	55 (93.2%)	112 (94.9%)	111 (94.1%)	113 (95.0%)	224 (94.5%)	336 (94.6%)

	Placebo			Lixisenatide			
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)	All (N=361)
Albuminuria [n (%)]							
Number	5	7	12	9	11	20	32
< 3 mg/L (Not reportable)	0	1 (14.3%)	1 (8.3%)	2 (22.2%)	3 (27.3%)	5 (25.0%)	6 (18.8%)
≥ 3 mg/L (Reportable)	5 (100%)	6 (85.7%)	11 (91.7%)	7 (77.8%)	8 (72.7%)	15 (75.0%)	26 (81.3%)
< 20 mg/L	3 (60.0%)	3 (50.0%)	6 (54.5%)	5 (71.4%)	6 (75.0%)	11 (73.3%)	17 (65.4%)
≥ 20 - < 200 mg/L	2 (40.0%)	2 (33.3%)	4 (36.4%)	2 (28.6%)	2 (25.0%)	4 (26.7%)	8 (30.8%)
≥ 200 mg/L	0	1 (16.7%)	1 (9.1%)	0	0	0	1 (3.8%)
Creatinine clearance (ml/min)							
Number	61	61	122	120	119	239	361
Mean (SD)	129.65 (48.86)	124.41 (46.24)	127.03 (47.44)	129.22 (47.70)	123.67 (44.63)	126.46 (46.18)	126.65 (46.55)
Median	129.82	120.41	122.84	122.79	118.51	120.94	121.73
Min : Max	56.9 : 265.9	27.6 : 324.1	27.6 : 324.1	49.9 : 304.7	46.2 : 283.6	46.2 : 304.7	27.6 : 324.1
Creatinine clearance [n (%)]							
Number	61	61	122	120	119	239	361
< 30 ml/min (severe renal impairment)	0	1 (1.6%)	1 (0.8%)	0	0	0	1 (0.3%)
≥ 30 - < 50 ml/min (moderate renal impairment)	0	0	0	1 (0.8%)	2 (1.7%)	3 (1.3%)	3 (0.8%)
≥ 50 - ≤ 80 ml/min (mild renal impairment)	9 (14.8%)	6 (9.8%)	15 (12.3%)	13 (10.8%)	17 (14.3%)	30 (12.6%)	45 (12.5%)
> 80 ml/min (no renal impairment	52 (85.2%)	54 (88.5%)	106 (86.9%)	106 (88.3%)	100 (84.0%)	206 (86.2%)	312 (86.4%)

GLP-1= Glucagon like peptide-1.

Table 5 below presents the descriptive summaries of efficacy variables at baseline for each treatment group and overall for the safety population. Efficacy variables at baseline were generally comparable across treatment groups.

Table 5 - Baseline efficacy variables – Safety population

	Placebo			Lixisenatide			
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)	All (N=361)
HbA_{1c} (%)							
Number	61	61	122	120	119	239	361
Mean (SD)	8.10 (0.95)	8.05 (0.87)	8.07 (0.91)	7.98 (0.92)	8.07 (0.87)	8.03 (0.89)	8.04 (0.90)
Median	7.90	7.80	7.80	7.70	7.90	7.80	7.80
Min : Max	6.5 : 10.7	6.5 : 10.1	6.5 : 10.7	6.6 : 10.1	6.7 : 10.5	6.6 : 10.5	6.5 : 10.7
Weight (kg)							
Number	61	61	122	120	119	239	361
Mean (SD)	86.53 (19.91)	85.64 (24.45)	86.08 (22.21)	89.04 (22.16)	86.50 (21.00)	87.77 (21.58)	87.20 (21.78)
Median	82.00	82.00	82.00	87.00	84.50	85.20	84.20
Min : Max	48.0 : 133.0	46.2 : 186.0	46.2 : 186.0	47.0 : 160.0	44.5 : 159.2	44.5 : 160.0	44.5 : 186.0
FPG (mmol/L)							
Number	61	61	122	120	119	239	361
Mean (SD)	8.88 (2.26)	8.93 (2.07)	8.90 (2.16)	9.15 (1.99)	9.04 (1.97)	9.09 (1.97)	9.03 (2.04)
Median	8.50	8.50	8.50	8.80	8.70	8.80	8.60
Min : Max	4.7 : 15.4	5.8 : 17.5	4.7 : 17.5	4.8 : 16.7	5.6 : 16.3	4.8 : 16.7	4.7 : 17.5
2-hour post-prandial plasma glucose* (mmol/L)							
Number	26	34	60	59	65	124	184
Mean (SD)	14.02 (5.06)	14.45 (4.74)	14.27 (4.84)	14.81 (3.87)	14.62 (3.41)	14.71 (3.62)	14.57 (4.05)
Median	14.05	14.15	14.15	14.80	14.50	14.65	14.45
Min : Max	5.5 : 23.7	6.5 : 30.2	5.5 : 30.2	6.1 : 23.5	6.5 : 22.6	6.1 : 23.5	5.5 : 30.2
Glucose excursion* (mmol/L)							
Number	26	34	60	59	65	124	184
Mean (SD)	4.77 (4.23)	4.86 (3.30)	4.82 (3.69)	5.67 (3.05)	5.34 (2.96)	5.49 (3.00)	5.27 (3.25)
Median	5.85	4.80	5.10	5.60	5.50	5.50	5.50
Min : Max	-5.9 : 13.1	-1.1 : 11.8	-5.9 : 13.1	-2.9 : 11.5	-1.9 : 11.9	-2.9 : 11.9	-5.9 : 13.1

* For patients in selected sites where the meal challenge test was performed.

FPG = Fasting Plasma Glucose.

Glucose excursion = 2-hour postprandial plasma glucose - plasma glucose 30 minutes prior to the meal test, before study drug administration.

6.1.4 Dosage and duration

Treatment exposure and dosage are summarized in Table 6, Table 7 and

Table 8 below. The average treatment exposure was similar across treatment groups. Of the 361 safety patients, 335 (92.8%) were exposed to 57 days or more, 349 (96.7%) reached the target dose 20 µg at the end of titration, and 335 (92.8%) had the final dose with the target dose 20 µg at the end of double-blind treatment.

Table 6 - Exposure to investigational product – Safety population

	Placebo			Lixisenatide		
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Cumulative exposure to treatment (patient years)	13.8	13.4	27.2	26.7	26.6	53.3
Duration of study treatment (days)						
Number	61	61	122	120	119	239
Mean (SD)	82.6 (12.8)	80.0 (18.5)	81.3 (15.9)	81.2 (16.5)	81.8 (15.3)	81.5 (15.9)
Median	85.0	85.0	85.0	85.0	85.0	85.0
Min : Max	19 : 95	7 : 92	7 : 95	1 : 103	12 : 98	1 : 103
Duration of study treatment by category [n (%)]						
1-14 days	0	2 (3.3%)	2 (1.6%)	2 (1.7%)	1 (0.8%)	3 (1.3%)
15-28 days	1 (1.6%)	2 (3.3%)	3 (2.5%)	4 (3.3%)	5 (4.2%)	9 (3.8%)
29-56 days	2 (3.3%)	1 (1.6%)	3 (2.5%)	3 (2.5%)	3 (2.5%)	6 (2.5%)
57-84 days	15 (24.6%)	10 (16.4%)	25 (20.5%)	14 (11.7%)	18 (15.1%)	32 (13.4%)
> 84 days	43 (70.5%)	46 (75.4%)	89 (73.0%)	97 (80.8%)	92 (77.3%)	189 (79.1%)

	Placebo			Lixisenatide		
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Number of patients with duration of study treatment by category [n (%)]						
≥ 1 day	61 (100%)	61 (100%)	122 (100%)	120 (100%)	119 (100%)	239 (100%)
≥ 15 days	61 (100%)	59 (96.7%)	120 (98.4%)	118 (98.3%)	118 (99.2%)	236 (98.7%)
≥ 29 days	60 (98.4%)	57 (93.4%)	117 (95.9%)	114 (95.0%)	113 (95.0%)	227 (95.0%)
≥ 57 days	58 (95.1%)	56 (91.8%)	114 (93.4%)	111 (92.5%)	110 (92.4%)	221 (92.5%)
≥ 85 days	43 (70.5%)	46 (75.4%)	89 (73.0%)	97 (80.8%)	92 (77.3%)	189 (79.1%)

Duration of exposure = (date of the last double-blind IP injection - date of the first double-blind IP injection) + 1.

Table 7 - Number (%) of patients by final dose at the end of the double-blind treatment – Safety population

	Placebo			Lixisenatide		
Final Dose	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
10 µg	0	1 (1.6%)	1 (0.8%)	5 (4.2%)	13 (10.9%)	18 (7.5%)
15 µg	0	0	0	6 (5.0%)	1 (0.8%)	7 (2.9%)
20 µg	61 (100%)	60 (98.4%)	121 (99.2%)	109 (90.8%)	105 (88.2%)	214 (89.5%)

Dose = Dose of active drug or volume-matched placebo.

Note: Percents are calculated using the number of safety patients as the denominator.

Table 8 - Number (%) of patients by dose at the end of titration – Safety population

Dose at the end of titration	Placebo			Lixisenatide		
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
< 10 µg	0	0	0	0	1 (0.8%)	1 (0.4%)
10 µg	0	2 (3.3%)	2 (1.6%)	3 (2.5%)	3 (2.5%)	6 (2.5%)
15 µg	0	0	0	3 (2.5%)	0	3 (1.3%)
20 µg	61 (100%)	59 (96.7%)	120 (98.4%)	114 (95.0%)	115 (96.6%)	229 (95.8%)

Dose = Dose of active drug or volume-matched placebo.
The scheduled visit for end of titration per protocol would be Visit 5/Week 2.
Note: Percents are calculated using the number of safety patients as the denominator.

6.2 EFFICACY

6.2.1 Primary efficacy parameter

Main analysis

Table 1 summarizes the results of the primary efficacy parameter, the change from baseline to endpoint in HbA_{1c} using LOCF ANCOVA analysis. Figure 4 illustrates the Mean (±SE) change from baseline in HbA_{1c} over time during the 12-week double-blind treatment.

Based on the pre-specified primary analysis, both lixisenatide-treated groups demonstrated statistically significant reduction of HbA_{1c} from baseline to endpoint, compared to the placebo group (for the lixisenatide two-step titration group, LS mean difference = -0.54%; p-value = < .0001; for the lixisenatide one-step titration group, LS mean difference = -0.66%; p-value = < .0001). Moreover HbA_{1c} seems to reach a plateau after week 8 in the placebo group, while HbA_{1c} is continuously decreasing in both lixisenatide-treated groups.

Table 9 - Mean change in HbA_{1c} (%) from baseline to endpoint – mITT population

HbA_{1c} (%)	Placebo Combined (N=121)	Lixisenatide Two-step Titration (N=120)	Lixisenatide One-step Titration (N=118)
Baseline			
Number	112	113	114
Mean (SD)	8.07 (0.92)	7.97 (0.91)	8.06 (0.85)
Median	7.80	7.70	7.90
Min : Max	6.5 : 10.7	6.6 : 9.9	6.7 : 10.5
Endpoint			
Number	112	113	114
Mean (SD)	7.80 (1.35)	7.20 (1.19)	7.11 (0.89)
Median	7.50	6.90	7.00
Min : Max	5.4 : 13.6	5.2 : 13.0	5.4 : 9.8
Change from baseline to endpoint			
Number	112	113	114
Mean (SD)	-0.27 (1.09)	-0.77 (0.94)	-0.94 (0.72)
Median	-0.30	-0.80	-0.90
Min : Max	-2.7 : 3.3	-3.0 : 3.1	-3.0 : 0.8
LS Mean (SE) [(a)]	-0.19 (0.121)	-0.73 (0.116)	-0.85 (0.119)
LS Mean difference (SE) vs. placebo combined [(a)]		-0.54 (0.123)	-0.66 (0.122)
95% CI		(-0.785 to -0.300)	(-0.903 to -0.423)
p-value		< 0.0001	< 0.0001

(a) Analysis of covariance (ANCOVA) model with treatment groups (two-step titration lixisenatide and placebo arms, one-step titration lixisenatide and placebo arms), randomization strata of screening HbA_{1c} (< 8.0, ≥ 8.0%), randomization strata of screening body mass index (< 30, ≥ 30 kg/m^2), and country as fixed effects and baseline HbA_{1c} value as a covariate. The comparison between each lixisenatide group and the placebo combined group was achieved through appropriate contrasts.
The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 3 days.

Secondary analyses

Table 10 summarizes the proportion of patients with treatment response (HbA_{1c} ≤ 6.5 or < 7% at endpoint, respectively). Treatment responses were similar between lixisenatide-treated groups and the treatment difference between each of lixisenatide-treated groups versus placebo was statistically significant.

Table 10 - Number (%) of patients with HbA_{1c} value ≤ 6.5% or < 7% at endpoint – mITT population

HbA_{1c} (%)	Placebo Combined (N=121)	Lixisenatide Two-step Titration (N=120)	Lixisenatide One-step Titration (N=118)
Number	112	113	114
≤ 6.5%	14 (12.5%)	36 (31.9%)	29 (25.4%)
> 6.5%	98 (87.5%)	77 (68.1%)	85 (74.6%)
p-value vs. Placebo Combined[(a)]	-	0.0005	0.0095
Number	112	113	114
< 7.0%	30 (26.8%)	59 (52.2%)	53 (46.5%)
≥ 7.0%	82 (73.2%)	54 (47.8%)	61 (53.5%)
p-value vs. Placebo Combined[(a)]	-	< 0.0001	0.0013

(a) Cochran-Mantel-Haenszel (CMH) method stratified by randomization strata of screening HbA_{1c} (< 8.0 or ≥ 8.0 %) and randomization strata of screening body mass index (< 30 or ≥ 30 kg/m^2). The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 3 day.

6.2.2 Secondary efficacy parameters

Table 11, Table 12, Table 13 and Table 15 summarize the ANCOVA analyses of 2-hour post-prandial plasma glucose, glucose excursion, body weight and FPG, respectively.

Table 14 and Table 16 present the proportion of patients with weight loss ≥ 5% from baseline to endpoint and the percentage of patients requiring rescue therapy, respectively. Figure 5 and Figure 6 demonstrate the Mean (±SE) change from baseline in body weight and FPG over time during the 12-week double-blind treatment period.

Both lixisenatide-treated groups showed statistically significant improvement over the placebo group in 2-hour post-prandial plasma glucose, supported by the same ANCOVA analysis in glucose excursion.

Table 11 - Mean change in 2-hour post-prandial plasma glucose (mmol/L) from baseline to endpoint in selected sites – mITT population

2-hr Post-prandial Plasma Glucose (mmol/L)	Placebo Combined (N=62)	Lixisenatide	
		Two-step Titration (N=60)	One-step Titration (N=65)
Baseline			
Number	54	53	62
Mean (SD)	13.99 (4.78)	14.67 (3.78)	14.55 (3.36)
Median	14.15	14.80	14.15
Min : Max	5.5 : 30.2	6.1 : 22.0	6.5 : 22.6
Endpoint			
Number	54	53	62
Mean (SD)	13.42 (4.54)	9.90 (5.05)	8.77 (4.11)
Median	12.80	8.40	8.20
Min : Max	4.7 : 26.3	3.5 : 25.1	4.3 : 26.3
Change from baseline to endpoint			
Number	54	53	62
Mean (SD)	-0.57 (4.44)	-4.77 (4.53)	-5.77 (3.90)
Median	-0.90	-4.90	-5.80
Min : Max	-14.7 : 17.8	-16.6 : 5.3	-12.7 : 10.4
LS Mean (SE) [(a)]	-0.65 (0.563)	-4.51 (0.572)	-5.47 (0.549)
LS Mean difference (SE) vs. placebo combined [(a)]		-3.86 (0.765)	-4.82 (0.741)
95% CI		(-5.375 to -2.353)	(-6.287 to -3.361)
p-value		< 0.0001	< 0.0001

(a) Analysis of covariance (ANCOVA) model with treatment groups (two-step titration lixisenatide and placebo arms, one-step titration lixisenatide and placebo arms), randomization strata of screening HbA_{1c} (< 8.0, ≥ 8.0%), randomization strata of screening body mass index (< 30, ≥ 30 kg/m²), and country as fixed effects and baseline 2-hour post-prandial plasma glucose value as a covariate. The comparison between each lixisenatide group and the placebo combined group was achieved through appropriate contrasts.
The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation.

Table 12 - Mean change in glucose excursion (mmol/L) from baseline to endpoint in selected sites mITT population

		Lixisenatide	
Glucose Excursion (mmol/L)	Placebo Combined (N=62)	Two-step Titration (N=60)	One-step Titration (N=65)
Baseline			
Number	54	53	62
Mean (SD)	4.72 (3.65)	5.45 (3.02)	5.25 (2.89)
Median	5.10	5.40	5.40
Min : Max	-5.9 : 13.1	-2.9 : 11.5	-1.9 : 10.8
Endpoint			
Number	54	53	62
Mean (SD)	4.20 (3.42)	1.39 (3.90)	0.60 (3.09)
Median	4.25	0.50	-0.10
Min : Max	-5.9 : 12.4	-4.4 : 11.8	-3.2 : 13.8
Change from baseline to endpoint			
Number	54	53	62
Mean (SD)	-0.52 (3.76)	-4.06 (3.60)	-4.66 (3.27)
Median	-0.82	-4.20	-4.53
Min : Max	-12.8 : 10.3	-12.0 : 3.8	-11.2 : 3.5
LS Mean (SE) [(a)]	-0.67 (0.447)	-3.77 (0.454)	-4.36 (0.436)
LS Mean difference (SE) vs. placebo combined [(a)]		-3.10 (0.608)	-3.69 (0.589)
95% CI		(-4.300 to -1.898)	(-4.853 to -2.527)

(a) Analysis of covariance (ANCOVA) model with treatment groups (two-step titration lixisenatide and placebo arms, one-step titration lixisenatide and placebo arms), randomization strata of screening HbA_{1c} (< 8.0, ≥ 8.0%), randomization strata of screening body mass index (< 30, ≥ 30 kg/m²), and country as fixed effects and baseline glucose excursion value as a covariate.
The comparison between each lixisenatide group and the placebo combined group was achieved through appropriate contrasts.
The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation.
Glucose excursion = 2-hour postprandial plasma glucose – plasma glucose 30 minutes prior to the meal test before study drug administration.

No difference in the changes in body weight were observed between the lixisenatide groups and placebo (Table 13), likewise a comparable percentage of patients across the treatment groups who had lost weight 5% or more in body weight (Table 14).

Table 13 - Mean change in body weight (kg) from baseline to endpoint – mITT population

Body Weight (kg)	Placebo Combined (N=121)	Lixisenatide Two-step Titration (N=120)	Lixisenatide One-step Titration (N=118)
Baseline			
Number	116	117	115
Mean (SD)	85.75 (22.06)	89.13 (22.21)	87.14 (20.93)
Median	82.00	87.00	84.70
Min : Max	46.2 : 186.0	47.0 : 160.0	44.5 : 159.2
Endpoint			
Number	116	117	115
Mean (SD)	83.77 (21.57)	87.12 (21.78)	85.21 (20.94)
Median	80.60	84.00	82.90
Min : Max	44.8 : 186.0	47.5 : 156.0	45.1 : 156.3
Change from baseline to endpoint			
Number	116	117	115
Mean (SD)	-1.98 (2.77)	-2.01 (2.68)	-1.92 (2.78)
Median	-1.35	-1.50	-2.00
Min : Max	-12.9 : 2.7	-11.9 : 4.4	-11.8 : 6.1
LS Mean (SE) [(a)]	-1.98 (0.341)	-1.96 (0.326)	-1.92 (0.338)
LS Mean difference (SE) vs. placebo combined [(a)]		0.02 (0.344)	0.06 (0.343)
95% CI		(-0.654 to 0.701)	(-0.612 to 0.737)
p-value		0.9462	0.8549

(a) Analysis of covariance (ANCOVA) model with treatment groups (two-step titration lixisenatide and placebo arms, one-step titration lixisenatide and placebo arms), randomization strata of screening HbA_{1c} (< 8.0, ≥ 8.0%), randomization strata of screening body mass index (< 30, ≥ 30 kg/m²), and country as fixed effects and baseline body weight value as a covariate.

The comparison between each lixisenatide group and the placebo combined group was achieved through appropriate contrasts.

The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 3 days.

Table 14 - Number (%) of patients with > =5 % weight loss from baseline to endpoint – mITT population

		Lixisenatide	
Weight loss	Placebo Combined (N=121)	Two-step Titration (N=120)	One-step Titration (N=118)
Number	116	117	115
≥ 5%	20 (17.2%)	19 (16.2%)	21 (18.3%)
< 5%	96 (82.8%)	98 (83.8%)	94 (81.7%)

The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 3 days.

Per the testing strategy adjusting for multiplicity (step-down procedure), inferential testing for FPG was made in an exploratory manner because the preceding test (body weight) failed to show statistically significant between-group difference. Both lixisenatide-treated groups demonstrated meaningful improvement over the placebo group in FPG using ANCOVA analysis without multiplicity adjustment.

Table 15 - Mean change in fasting plasma glucose (mmol/L) from baseline to endpoint – mITT population

		Lixisenatide	
Fasting Plasma Glucose (mmol/L)	Placebo Combined (N=121)	Two-step Titration (N=120)	One-step Titration (N=118)
Baseline			
Number	121	119	118
Mean (SD)	8.91 (2.17)	9.17 (1.98)	9.02 (1.97)
Median	8.50	8.80	8.65
Min : Max	4.7 : 17.5	4.8 : 16.7	5.6 : 16.3
Endpoint			
Number	121	119	118
Mean (SD)	9.16 (2.96)	8.51 (2.38)	8.16 (1.73)
Median	8.40	8.20	7.88
Min : Max	4.7 : 22.9	4.6 : 19.7	5.0 : 14.5

Fasting Plasma Glucose (mmol/L)	Placebo Combined (N=121)	Lixisenatide Two-step Titration (N=120)	Lixisenatide One-step Titration (N=118)
Change from baseline to endpoint			
Number	121	119	118
Mean (SD)	0.25 (2.52)	-0.66 (1.95)	-0.87 (1.62)
Median	-0.05	-0.50	-0.70
Min : Max	-5.1 : 17.6	-7.5 : 6.3	-6.4 : 4.6
LS Mean (SE) [(a)]	0.19 (0.255)	-0.68 (0.247)	-0.89 (0.254)
LS Mean difference (SE) vs. placebo combined [(a)]		-0.87 (0.257)	-1.08 (0.257)
95% CI		(-1.374 to -0.361)	(-1.586 to -0.577)
p-value		0.0008	< 0.0001

(a) Analysis of covariance (ANCOVA) model with treatment groups (two-step titration lixisenatide and placebo arms, one-step titration lixisenatide and placebo arms), randomization strata of screening HbA_{1c} (< 8.0, ≥ 8.0%), randomization strata of screening body mass index (< 30, ≥ 30 kg/m²), and country as fixed effects and baseline fasting plasma glucose value as a covariate.
The comparison between each lixisenatide group and the placebo combined group was achieved through appropriate contrasts.
The analysis excluded measurements obtained after the introduction of rescue medication and/or after the treatment cessation plus 1 day.

There was no evidence for difference difference between the lixisenatide-treated groups and the placebo group in percentage of patients who required rescue therapy due to the low incidence of rescued patients during the double-blind treatment period.

Table 16 - Number (%) of patients requiring rescue therapy during the double-blind treatment period – mITT population

Requiring rescue therapy	Placebo Combined (N=121)	Lixisenatide Two-step Titration (N=120)	Lixisenatide One-step Titration (N=118)
Number	121	120	118
Yes	3 (2.5%)	2 (1.7%)	1 (0.8%)
No	118 (97.5%)	118 (98.3%)	117 (99.2%)
p-value vs. Placebo Combined[(a)]	-	0.6518	0.3260

(a) Cochran-Mantel-Haenszel (CMH) method stratified by randomization strata of screening HbA_{1c} (< 8.0 or ≥ 8.0 %) and randomization strata of screening BMI (< 30 or ≥ 30 kg/m^2).

6.3 SAFETY

Table 17 below presents the overall summary of patients who had adverse events during the double-blind treatment and

Table 18, and Table 19 show serious TEAEs, and TEAEs leading to treatment discontinuation, respectively. The proportion of patients who had TEAEs was generally comparable between the placebo group and the lixisenatide-treated groups. The incidence of serious TEAE was low, with 5 occurrences (4.1%) in the placebo group, 1 (0.8%) in the lixisenatide two-step titration group and 0 in the lixisenatide one-step titration group. No death was reported in this study. More patients in lixisenatide-treated group (5 [4.2%] for two-step titration; 3 [2.5%] for one-step titration) discontinued treatment than in the placebo group (1 [0.8%]), mainly due to gastrointestinal disorders.

Table 25 presents the incidences of TEAEs during the double-blind treatment occurring in at least 1% of patients in any treatment group. Nausea was the most frequently reported TEAE in the lixisenatide-treated group: 29 patients (24.2%) for two-step titration and 24 patients (20.2%) for one-step titration. Five placebo-treated patients (4.1%) reported nausea. The second most frequently reported TEAE in the lixisenatide-treated patients was headache (10 patients (8.3%) for two-step titration and 9 patients (7.6%) for one-step titration) followed by vomiting (9 patients [7.5%] for two-step titration and 8 patients [6.7%] for one-step titration). The corresponding number of patients (%) in the placebo group was 14 (11.5%) for headache and none for vomiting.

Table 17 - Overview of adverse event profile: treatment emergent adverse events – Safety population

	Placebo			Lixisenatide		
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Patients with any TEAE	25 (41.0%)	30 (49.2%)	55 (45.1%)	63 (52.5%)	65 (54.6%)	128 (53.6%)

	Placebo			Lixisenatide		
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Patients with any serious TEAE	3 (4.9%)	2 (3.3%)	5 (4.1%)	1 (0.8%)	0	1 (0.4%)
Patients with any TEAE leading to death	0	0	0	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	1 (1.6%)	0	1 (0.8%)	5 (4.2%)	3 (2.5%)	8 (3.3%)

TEAE: Treatment Emergent Adverse Event.
n (%) = number and percentage of patients with at least one adverse event

Table 18 - Number (%) of patients experiencing serious TEAE(s) presented by primary SOC, HLGT, HLT, and PT during on-treatment period – Safety population

	Placebo			Lixisenatide		
PRIMARY SYSTEM ORGAN CLASS HLGT:High Level Group Term HLT:High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Any class	3 (4.9%)	2 (3.3%)	5 (4.1%)	1 (0.8%)	0	1 (0.4%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (1.6%)	0	1 (0.8%)	0	0	0
HLGT:Gastrointestinal neoplasms malignant and unspecified	1 (1.6%)	0	1 (0.8%)	0	0	0
HLT:Colonic neoplasms malignant	1 (1.6%)	0	1 (0.8%)	0	0	0
Colon cancer stage III	1 (1.6%)	0	1 (0.8%)	0	0	0
ENDOCRINE DISORDERS	0	0	0	1 (0.8%)	0	1 (0.4%)
HLGT:Thyroid gland disorders	0	0	0	1 (0.8%)	0	1 (0.4%)
HLT:Thyroid disorders NEC	0	0	0	1 (0.8%)	0	1 (0.4%)
Goitre	0	0	0	1 (0.8%)	0	1 (0.4%)

	Placebo			Lixisenatide		
PRIMARY SYSTEM ORGAN CLASS HLGT:High Level Group Term HLT:High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
CARDIAC DISORDERS	1 (1.6%)	0	1 (0.8%)	0	0	0
HLGT:Coronary artery disorders	1 (1.6%)	0	1 (0.8%)	0	0	0
HLT:Ischaemic coronary artery disorders	1 (1.6%)	0	1 (0.8%)	0	0	0
Acute myocardial infarction	1 (1.6%)	0	1 (0.8%)	0	0	0
GASTROINTESTINAL DISORDERS	1 (1.6%)	0	1 (0.8%)	0	0	0
HLGT:Gastrointestinal stenosis and obstruction	1 (1.6%)	0	1 (0.8%)	0	0	0
HLT:Gastrointestinal stenosis and obstruction NEC	1 (1.6%)	0	1 (0.8%)	0	0	0
Ileus	1 (1.6%)	0	1 (0.8%)	0	0	0
INVESTIGATIONS	0	1 (1.6%)	1 (0.8%)	0	0	0
HLGT:Metabolic, nutritional and blood gas investigations	0	1 (1.6%)	1 (0.8%)	0	0	0
HLT:Carbohydrate tolerance analyses (incl diabetes)	0	1 (1.6%)	1 (0.8%)	0	0	0
Blood glucose increased	0	1 (1.6%)	1 (0.8%)	0	0	0

	Placebo			Lixisenatide		
PRIMARY SYSTEM ORGAN CLASS HLGT:High Level Group Term HLT:High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (1.6%)	1 (0.8%)	0	0	0
HLGT:Bone and joint injuries	0	1 (1.6%)	1 (0.8%)	0	0	0
HLT:Upper limb fractures and dislocations	0	1 (1.6%)	1 (0.8%)	0	0	0
Ulna fracture	0	1 (1.6%)	1 (0.8%)	0	0	0

TEAE: Treatment Emergent Adverse Event, SOC: System Organ Class, HLGT: High Level Group Term, HLT: High Level term, PT: Preferred Term.

On-treatment period = the time from the first dose of double-blind study medication up to 3 days after the last dose administration.

MedDRA version: 12.1

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

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

Table 19 - Number (%) of patients experiencing TEAE(s) leading to permanent treatment discontinuation by primary SOC, HLGT, HLT, and PT during on-treatment period – Safety population

	Placebo			Lixisenatide		
PRIMARY SYSTEM ORGAN CLASS HLGT:High Level Group Term HLT:High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Any class	1 (1.6%)	0	1 (0.8%)	5 (4.2%)	3 (2.5%)	8 (3.3%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (1.6%)	0	1 (0.8%)	0	0	0
HLGT:Gastrointestinal neoplasms malignant and unspecified	1 (1.6%)	0	1 (0.8%)	0	0	0
HLT:Colonic neoplasms malignant	1 (1.6%)	0	1 (0.8%)	0	0	0
Colon cancer stage III	1 (1.6%)	0	1 (0.8%)	0	0	0
METABOLISM AND NUTRITION DISORDERS	0	0	0	1 (0.8%)	0	1 (0.4%)
HLGT:Appetite and general nutritional disorders	0	0	0	1 (0.8%)	0	1 (0.4%)
HLT:Appetite disorders	0	0	0	1 (0.8%)	0	1 (0.4%)
Decreased appetite	0	0	0	1 (0.8%)	0	1 (0.4%)
VASCULAR DISORDERS	0	0	0	0	1 (0.8%)	1 (0.4%)
HLGT:Vascular hypertensive disorders	0	0	0	0	1 (0.8%)	1 (0.4%)
HLT:Vascular hypertensive disorders NEC	0	0	0	0	1 (0.8%)	1 (0.4%)
Hypertension	0	0	0	0	1 (0.8%)	1 (0.4%)

PRIMARY SYSTEM ORGAN CLASS HLGT:High Level Group Term HLT:High Level Term Preferred Term n (%)	Placebo			Lixisenatide		
	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
GASTROINTESTINAL DISORDERS	0	0	0	5 (4.2%)	3 (2.5%)	8 (3.3%)
HLGT:Gastrointestinal haemorrhages NEC	0	0	0	1 (0.8%)	0	1 (0.4%)
HLT:Non-site specific gastrointestinal haemorrhages	0	0	0	1 (0.8%)	0	1 (0.4%)
Haematochezia	0	0	0	1 (0.8%)	0	1 (0.4%)
HLGT:Gastrointestinal inflammatory conditions	0	0	0	1 (0.8%)	0	1 (0.4%)
HLT:Colitis (excl infective)	0	0	0	1 (0.8%)	0	1 (0.4%)
Colitis	0	0	0	1 (0.8%)	0	1 (0.4%)
HLGT:Gastrointestinal signs and symptoms	0	0	0	3 (2.5%)	3 (2.5%)	6 (2.5%)
HLT:Gastrointestinal and abdominal pains (excl oral and throat)	0	0	0	0	1 (0.8%)	1 (0.4%)
Abdominal pain upper	0	0	0	0	1 (0.8%)	1 (0.4%)
HLT:Nausea and vomiting symptoms	0	0	0	3 (2.5%)	3 (2.5%)	6 (2.5%)
Nausea	0	0	0	3 (2.5%)	3 (2.5%)	6 (2.5%)
Vomiting	0	0	0	1 (0.8%)	1 (0.8%)	2 (0.8%)

TEAE: Treatment Emergent Adverse Event, SOC: System Organ Class, HLGT: High Level Group Term, HLT: High Level term, PT: Preferred Term.

On-treatment period = the time from the first dose of double-blind study medication up to 3 days after the last dose administration.

MedDRA version: 12.1

n (%) = number and percentage of patients with at least one TEAE leading to permanent treatment discontinuation.

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

As shown in Table 20 below, a total of 6 cases of symptomatic hypoglycemia per protocol definition were observed (3 [2.5%] in the lixisenatide two-step titration group, 1 [0.8%] in the lixisenatide one-step titration group, and 2 [1.6%] in the placebo group), and none of them was severe.

Table 20 – Summary of symptomatic hypoglycemia – Safety population

	Placebo			Lixisenatide		
Type	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Exposure in patient years	13.80	13.37	27.17	26.66	26.64	53.30
Any symptomatic hypoglycemia						
Number of patients with events, n (%)[1]	1 (1.6%)	1 (1.6%)	2 (1.6%)	3 (2.5%)	1 (0.8%)	4 (1.7%)
Number of patients with events per 100 patient years of exposure[2]	7.2	7.5	7.4	11.3	3.8	7.5
< 60 mg/dL						
Number of patients with events, n (%)[1]	1 (1.6%)	1 (1.6%)	2 (1.6%)	2 (1.7%)	0	2 (0.8%)
Number of patients with events per 100 patient years of exposure[2]	7.2	7.5	7.4	7.5	0	3.8
No blood glucose reported						
Number of patients with events, n (%)[1]	0	0	0	1 (0.8%)	1 (0.8%)	2 (0.8%)
Number of patients with events per 100 patient years of exposure[2]	0	0	0	3.8	3.8	3.8

Symptomatic hypoglycemia = symptomatic hypoglycemia as defined per protocol.
[1]: Percents are calculated using the number of safety patients as the denominator.
[2]: Number of patients with events per 100 patient years of exposure = 100*(number of patients with events / exposure in patient years).

A total of 11 patients, all lixisenatide-treated patients (4 [3.3%] in two-step titration group and 7 [5.9%] in one-step titration group), reported injection site reactions. None of the reactions was serious or severe.

Table 21 - Number (%) of patients experiencing injection site reactions during on-treatment period – Safety population

	Placebo			Lixisenatide		
Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Any injection site reactions	0	0	0	4 (3.3%)	7 (5.9%)	11 (4.6%)
Injection site pruritus	0	0	0	2 (1.7%)	4 (3.4%)	6 (2.5%)
Injection site pain	0	0	0	1 (0.8%)	2 (1.7%)	3 (1.3%)
Injection site haematoma	0	0	0	1 (0.8%)	1 (0.8%)	2 (0.8%)
Injection site erythema	0	0	0	0	2 (1.7%)	2 (0.8%)
Injection site haemorrhage	0	0	0	1 (0.8%)	0	1 (0.4%)
Injection site rash	0	0	0	1 (0.8%)	0	1 (0.4%)

On-treatment period = the time from the first dose of double-blind study medication up to 3 days after the last dose administration.

A total of 3 cases of allergic reactions were reported by investigators in the lixisenatide one-step titration group during double-blind treatment period and 2 of them were confirmed by the allergic reaction assessment committee (ARAC).

Table 22 - Number (%) of patients with allergic reaction as adjudicated and confirmed by ARAC – Safety population

Relationship to study treatment (by ARAC)	MedDRA coded term (PT) for ARAC diagnosis	ARAC diagnosis	Placebo			Lixisenatide		
			Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
All	Allergic reaction as adjudicated and confirmed by ARAC		0	0	0	0	2 (1.7%)	2 (0.8%)
	Angioedema	ANGIOEDEMA	0	0	0	0	1 (0.8%)	1 (0.4%)
	Urticaria	URTICARIA (HIVES)	0	0	0	0	1 (0.8%)	1 (0.4%)
Related	Allergic reaction as adjudicated and confirmed by ARAC		0	0	0	0	2 (1.7%)	2 (0.8%)
	Angioedema	ANGIOEDEMA	0	0	0	0	1 (0.8%)	1 (0.4%)
	Urticaria	URTICARIA (HIVES)	0	0	0	0	1 (0.8%)	1 (0.4%)

ARAC = Allergic Reaction Assessment Committee.

The adverse event “lipase increased” reported in one patient in the placebo group Table 23 occurred on study Day 1 and presumably prior to the first injection of double-blind treatment according to the study protocol. No incidence of elevated lipase or amylase (≥ 3 ULN) was observed in any treatment group (Table 24) during the double-double treatment period.

Table 23 - Number (%) of patients with suspected pancreatitis – Safety population

	Placebo			Lixisenatide		
Preferred Term	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Any	0	1 (1.6%)	1 (0.8%)	0	0	0
Lipase increased	0	1 (1.6%)	1 (0.8%)	0	0	0

n (%) = number and percentage of patients with any cases reported on the AE form for suspected pancreatits along with complementary form.

Table 24 – Pancreatic enzymes: Number of patients with abnormalities (PCSA) in the on-treatment period according to baseline status – Safety population

	Placebo			Lixisenatide		
Laboratory criteria Baseline by PCSA criteria n/N1 (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Amylase						
Total*						
≥ 3 ULN	0/61	0/59	0/120	0/119	0/118	0/237
Normal/Missing						
≥ 3 ULN	0/61	0/59	0/120	0/119	0/118	0/237
> = 3 ULN						
≥ 3 ULN	0/0	0/0	0/0	0/0	0/0	0/0
Lipase						
Total*						
≥ 3 ULN	0/61	0/59	0/120	0/119	0/118	0/237

	Placebo			Lixisenatide		
Laboratory criteria Baseline by PCSA criteria n/N1 (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Normal/Missing ≥ 3 ULN	0/61	0/59	0/120	0/119	0/118	0/237
> = 3 ULN ≥ 3 ULN	0/0	0/0	0/0	0/0	0/0	0/0

PCSA: Potentially Clinically Significant Abnormalities.
On-treatment period = the time from the first dose of double-blind study medication up to 3 days after the last dose administration.
*Regardless of baseline.
Note: The number (n) represents the subset of the total number who met the criterion in question at least once during treatment.
The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline by baseline PCSA status.
For PCSA including condition based only on change from baseline, the denominator is restricted on patients having a baseline and a post-baseline values.

Table 25 - Number (%) of patients experiencing common TEAE(s) (PT ≥ 1% in the placebo combined group or any individual lixisenatide group) by primary SOC and HLGT, HLT and PT – Safety population

	Placebo			Lixisenatide		
Primary System Organ Class HLGT: High Level Group Term HLT: High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Any class	25 (41.0%)	30 (49.2%)	55 (45.1%)	63 (52.5%)	65 (54.6%)	128 (53.6%)
INFECTIONS AND INFESTATIONS	7 (11.5%)	10 (16.4%)	17 (13.9%)	17 (14.2%)	15 (12.6%)	32 (13.4%)
HLGT: Infections - pathogen unspecified	7 (11.5%)	8 (13.1%)	15 (12.3%)	16 (13.3%)	14 (11.8%)	30 (12.6%)
HLT: Abdominal and gastrointestinal infections	1 (1.6%)	2 (3.3%)	3 (2.5%)	1 (0.8%)	0	1 (0.4%)
Gastroenteritis	1 (1.6%)	2 (3.3%)	3 (2.5%)	1 (0.8%)	0	1 (0.4%)
HLT: Upper respiratory tract infections	5 (8.2%)	3 (4.9%)	8 (6.6%)	12 (10.0%)	12 (10.1%)	24 (10.0%)
Nasopharyngitis	3 (4.9%)	1 (1.6%)	4 (3.3%)	6 (5.0%)	5 (4.2%)	11 (4.6%)

	Placebo			Lixisenatide		
Primary System Organ Class HLGT: High Level Group Term HLT: High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Pharyngitis	2 (3.3%)	1 (1.6%)	3 (2.5%)	2 (1.7%)	0	2 (0.8%)
Upper respiratory tract infection	0	0	0	2 (1.7%)	4 (3.4%)	6 (2.5%)
HLT: Urinary tract infections	0	2 (3.3%)	2 (1.6%)	2 (1.7%)	0	2 (0.8%)
Urinary tract infection	0	2 (3.3%)	2 (1.6%)	2 (1.7%)	0	2 (0.8%)
METABOLISM AND NUTRITION DISORDERS	1 (1.6%)	1 (1.6%)	2 (1.6%)	6 (5.0%)	6 (5.0%)	12 (5.0%)
HLGT: Appetite and general nutritional disorders	1 (1.6%)	0	1 (0.8%)	3 (2.5%)	5 (4.2%)	8 (3.3%)
HLT: Appetite disorders	1 (1.6%)	0	1 (0.8%)	3 (2.5%)	5 (4.2%)	8 (3.3%)
Decreased appetite	1 (1.6%)	0	1 (0.8%)	3 (2.5%)	5 (4.2%)	8 (3.3%)
HLGT: Glucose metabolism disorders (incl diabetes mellitus)	1 (1.6%)	1 (1.6%)	2 (1.6%)	4 (3.3%)	1 (0.8%)	5 (2.1%)
HLT: Hypoglycaemic conditions NEC	1 (1.6%)	1 (1.6%)	2 (1.6%)	4 (3.3%)	1 (0.8%)	5 (2.1%)
Hypoglycaemia	1 (1.6%)	1 (1.6%)	2 (1.6%)	4 (3.3%)	1 (0.8%)	5 (2.1%)
NERVOUS SYSTEM DISORDERS	9 (14.8%)	8 (13.1%)	17 (13.9%)	22 (18.3%)	15 (12.6%)	37 (15.5%)
HLGT: Headaches	9 (14.8%)	5 (8.2%)	14 (11.5%)	10 (8.3%)	9 (7.6%)	19 (7.9%)
HLT: Headaches NEC	9 (14.8%)	5 (8.2%)	14 (11.5%)	10 (8.3%)	9 (7.6%)	19 (7.9%)
Headache	9 (14.8%)	5 (8.2%)	14 (11.5%)	10 (8.3%)	9 (7.6%)	19 (7.9%)
HLGT: Neurological disorders NEC	1 (1.6%)	3 (4.9%)	4 (3.3%)	12 (10.0%)	6 (5.0%)	18 (7.5%)
HLT: Disturbances in consciousness NEC	0	0	0	2 (1.7%)	1 (0.8%)	3 (1.3%)
Somnolence	0	0	0	2 (1.7%)	1 (0.8%)	3 (1.3%)

	Placebo			Lixisenatide		
Primary System Organ Class HLGT: High Level Group Term HLT: High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
HLT: Neurological signs and symptoms NEC	1 (1.6%)	2 (3.3%)	3 (2.5%)	9 (7.5%)	4 (3.4%)	13 (5.4%)
Dizziness	1 (1.6%)	2 (3.3%)	3 (2.5%)	9 (7.5%)	4 (3.4%)	13 (5.4%)
CARDIAC DISORDERS	1 (1.6%)	1 (1.6%)	2 (1.6%)	2 (1.7%)	5 (4.2%)	7 (2.9%)
HLGT: Cardiac disorder signs and symptoms	0	0	0	1 (0.8%)	3 (2.5%)	4 (1.7%)
HLT: Cardiac signs and symptoms NEC	0	0	0	1 (0.8%)	3 (2.5%)	4 (1.7%)
Palpitations	0	0	0	1 (0.8%)	3 (2.5%)	4 (1.7%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (1.6%)	4 (6.6%)	5 (4.1%)	3 (2.5%)	5 (4.2%)	8 (3.3%)
HLGT: Respiratory disorders NEC	1 (1.6%)	3 (4.9%)	4 (3.3%)	3 (2.5%)	5 (4.2%)	8 (3.3%)
HLT: Coughing and associated symptoms	1 (1.6%)	1 (1.6%)	2 (1.6%)	1 (0.8%)	2 (1.7%)	3 (1.3%)
Cough	1 (1.6%)	1 (1.6%)	2 (1.6%)	1 (0.8%)	2 (1.7%)	3 (1.3%)
HLT: Upper respiratory tract signs and symptoms	0	3 (4.9%)	3 (2.5%)	2 (1.7%)	3 (2.5%)	5 (2.1%)
Oropharyngeal pain	0	3 (4.9%)	3 (2.5%)	1 (0.8%)	2 (1.7%)	3 (1.3%)
GASTROINTESTINAL DISORDERS	7 (11.5%)	10 (16.4%)	17 (13.9%)	39 (32.5%)	37 (31.1%)	76 (31.8%)
HLGT: Dental and gingival conditions	1 (1.6%)	2 (3.3%)	3 (2.5%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
HLT: Dental pain and sensation disorders	1 (1.6%)	1 (1.6%)	2 (1.6%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
Toothache	1 (1.6%)	1 (1.6%)	2 (1.6%)	1 (0.8%)	1 (0.8%)	2 (0.8%)

	Placebo			Lixisenatide		
Primary System Organ Class HLGT: High Level Group Term HLT: High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
HLGT: Gastrointestinal motility and defaecation conditions	2 (3.3%)	2 (3.3%)	4 (3.3%)	7 (5.8%)	6 (5.0%)	13 (5.4%)
HLT: Diarrhoea (excl infective)	1 (1.6%)	2 (3.3%)	3 (2.5%)	3 (2.5%)	4 (3.4%)	7 (2.9%)
Diarrhoea	1 (1.6%)	2 (3.3%)	3 (2.5%)	3 (2.5%)	4 (3.4%)	7 (2.9%)
HLT: Gastrointestinal atonic and hypomotility disorders NEC	1 (1.6%)	0	1 (0.8%)	4 (3.3%)	2 (1.7%)	6 (2.5%)
Constipation	1 (1.6%)	0	1 (0.8%)	4 (3.3%)	2 (1.7%)	6 (2.5%)
HLGT: Gastrointestinal signs and symptoms	4 (6.6%)	4 (6.6%)	8 (6.6%)	33 (27.5%)	29 (24.4%)	62 (25.9%)
HLT: Dyspeptic signs and symptoms	1 (1.6%)	0	1 (0.8%)	2 (1.7%)	2 (1.7%)	4 (1.7%)
Dyspepsia	1 (1.6%)	0	1 (0.8%)	2 (1.7%)	2 (1.7%)	4 (1.7%)
Eructation	0	0	0	0	2 (1.7%)	2 (0.8%)
HLT: Flatulence, bloating and distension	0	0	0	2 (1.7%)	3 (2.5%)	5 (2.1%)
Abdominal distension	0	0	0	1 (0.8%)	3 (2.5%)	4 (1.7%)
HLT: Gastrointestinal and abdominal pains (excl oral and throat)	0	2 (3.3%)	2 (1.6%)	5 (4.2%)	2 (1.7%)	7 (2.9%)
Abdominal pain	0	2 (3.3%)	2 (1.6%)	2 (1.7%)	0	2 (0.8%)
Abdominal pain upper	0	0	0	4 (3.3%)	2 (1.7%)	6 (2.5%)
HLT: Gastrointestinal signs and symptoms NEC	0	0	0	0	2 (1.7%)	2 (0.8%)
Abdominal discomfort	0	0	0	0	2 (1.7%)	2 (0.8%)

	Placebo			Lixisenatide		
Primary System Organ Class HLGT: High Level Group Term HLT: High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
HLT: Nausea and vomiting symptoms	3 (4.9%)	2 (3.3%)	5 (4.1%)	29 (24.2%)	25 (21.0%)	54 (22.6%)
Nausea	3 (4.9%)	2 (3.3%)	5 (4.1%)	29 (24.2%)	24 (20.2%)	53 (22.2%)
Vomiting	0	0	0	9 (7.5%)	8 (6.7%)	17 (7.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (1.6%)	0	1 (0.8%)	3 (2.5%)	5 (4.2%)	8 (3.3%)
HLGT: Epidermal and dermal conditions	0	0	0	1 (0.8%)	4 (3.4%)	5 (2.1%)
HLT: Rashes, eruptions and exanthems NEC	0	0	0	0	2 (1.7%)	2 (0.8%)
Rash	0	0	0	0	2 (1.7%)	2 (0.8%)
HLGT: Skin appendage conditions	1 (1.6%)	0	1 (0.8%)	2 (1.7%)	0	2 (0.8%)
HLT: Apocrine and eccrine gland disorders	1 (1.6%)	0	1 (0.8%)	2 (1.7%)	0	2 (0.8%)
Hyperhidrosis	1 (1.6%)	0	1 (0.8%)	2 (1.7%)	0	2 (0.8%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.6%)	5 (8.2%)	6 (4.9%)	8 (6.7%)	4 (3.4%)	12 (5.0%)
HLGT: Muscle disorders	0	0	0	3 (2.5%)	1 (0.8%)	4 (1.7%)
HLT: Muscle related signs and symptoms NEC	0	0	0	2 (1.7%)	0	2 (0.8%)
Muscle spasms	0	0	0	2 (1.7%)	0	2 (0.8%)
HLGT: Musculoskeletal and connective tissue disorders NEC	1 (1.6%)	5 (8.2%)	6 (4.9%)	4 (3.3%)	2 (1.7%)	6 (2.5%)
HLT: Musculoskeletal and connective tissue pain and discomfort	1 (1.6%)	5 (8.2%)	6 (4.9%)	4 (3.3%)	2 (1.7%)	6 (2.5%)
Back pain	0	2 (3.3%)	2 (1.6%)	4 (3.3%)	1 (0.8%)	5 (2.1%)

	Placebo			Lixisenatide		
Primary System Organ Class HLGT: High Level Group Term HLT: High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
Musculoskeletal chest pain	0	2 (3.3%)	2 (1.6%)	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (1.6%)	1 (1.6%)	2 (1.6%)	9 (7.5%)	11 (9.2%)	20 (8.4%)
HLGT: Administration site reactions	0	0	0	4 (3.3%)	7 (5.9%)	11 (4.6%)
HLT: Injection site reactions	0	0	0	4 (3.3%)	7 (5.9%)	11 (4.6%)
Injection site erythema	0	0	0	0	2 (1.7%)	2 (0.8%)
Injection site pain	0	0	0	1 (0.8%)	2 (1.7%)	3 (1.3%)
Injection site pruritus	0	0	0	2 (1.7%)	4 (3.4%)	6 (2.5%)
HLGT: General system disorders NEC	1 (1.6%)	1 (1.6%)	2 (1.6%)	5 (4.2%)	6 (5.0%)	11 (4.6%)
HLT: Asthenic conditions	1 (1.6%)	1 (1.6%)	2 (1.6%)	5 (4.2%)	5 (4.2%)	10 (4.2%)
Asthenia	0	1 (1.6%)	1 (0.8%)	1 (0.8%)	3 (2.5%)	4 (1.7%)
Fatigue	1 (1.6%)	0	1 (0.8%)	4 (3.3%)	1 (0.8%)	5 (2.1%)
HLT: Feelings and sensations NEC	0	0	0	0	2 (1.7%)	2 (0.8%)
Chills	0	0	0	0	2 (1.7%)	2 (0.8%)

	Placebo			Lixisenatide		
Primary System Organ Class HLGT: High Level Group Term HLT: High Level Term Preferred Term n (%)	Two-step Titration (N=61)	One-step Titration (N=61)	Combined (N=122)	Two-step Titration (N=120)	One-step Titration (N=119)	Combined (N=239)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (3.3%)	2 (3.3%)	4 (3.3%)	3 (2.5%)	2 (1.7%)	5 (2.1%)
HLGT: Injuries NEC	2 (3.3%)	2 (3.3%)	4 (3.3%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
HLT: Non-site specific injuries NEC	1 (1.6%)	2 (3.3%)	3 (2.5%)	0	1 (0.8%)	1 (0.4%)
Fall	1 (1.6%)	2 (3.3%)	3 (2.5%)	0	0	0

TEAE: Treatment emergent adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term

On-treatment period = the time from the first dose of double-blind study medication up to 3 days after the last dose administration.

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

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

Only SOC with at least one PT ≥ 1% in the placebo combined group or any lixisenatide one- or two-step titration group are presented.

Claims

1. Use of desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of diabetes mellitus type 2, for inducing weight loss in diabetes type 2 patients or/and for preventing weight gain in diabetes type 2 patients.

2. The use according to claim 1, wherein the subject to be treated is obese.

3. The use according to claim 1 or 2, wherein the subject to be treated has a body mass index of at least 30 kg/m^2.

4. The use according to any of the preceding claims, wherein the subject to be treated is an adult subject.

5. The use according to any of the claims 1 to 4, wherein the subject to be treated does not receive an antidiabetic treatment.

6. The use of any of the preceding claims, wherein in the subject to be treated, diabetes mellitus type 2 has been diagnosed at least 1 year or at least 2 years before onset of therapy.

7. The use of any of the preceding claims, wherein the subject to be treated has a HbA_{1c} value of about 7 to about 10%.

8. The use of any of the preceding claims, wherein the subject to be treated has a fasting plasma glucose concentration of at least 8 mmol/L.

9. The use of any of the preceding claims, wherein the subject to be treated has a 2 hours postprandial plasma glucose concentration of at least 10 mmol/L, at least 12 mmol/L, or at least 14 mmol/L.

10. The use of any of the preceding claims, wherein the subject to be treated has a glucose excursion of at least 2 mmol/L, at least 3 mmol/L, at least 4 mmol/L or at least 5 mmol/L, wherein the glucose excursion is the difference of the 2 hours postprandial plasma glucose concentration and plasma glucose concentration 30 minutes prior to a meal test.

11. The use of any of the preceding claims, wherein the desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and the pharmaceutically acceptable salt thereof is administered parenterally.

12. The use according to any of the preceding claims, wherein the desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and the pharmaceutically acceptable salt thereof is prepared for administration in a daily dose selected from the range of 10 µg to 20 µg.

13. A pharmaceutical composition comprising desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof, and optionally comprising pharmaceutically acceptable carriers, adjuvants, or/and auxiliary substances.

14. The composition of claim 10 for use in the treatment of diabetes mellitus type 2, for use in inducing weight loss in diabetes type 2 patients or/and for use in preventing weight gain in diabetes type 2 patients.

15. The composition of claim 10 or 11 for use in the treatment of a subject as defined in any one of the claims 2 to 10.

16. A method for the treatment of diabetes mellitus type 2 comprising administering desPro^{36}Exendin-4(1-39)-Lys$_6$-NH$_2$ or/and a pharmaceutically acceptable salt thereof to a subject in need thereof.

17. The method of claim 13, wherein the subject is the subject defined in any one of the claims 2 to 10.