Treatment of Diabetes Mellitus by long–acting formulations of insulins

The application relates to an aqueous pharmaceutical formulation for use in the treatment of Type I or Type II Diabetes Mellitus, wherein the treatment reduces the risk of nocturnal hypoglycemia, said formulation comprising 200 – 1000 U/mL [equimolar to 200 – 1000 IU human insulin] of insulin glargine, with the proviso that the concentration of said formulation is not 684 U/mL of insulin glargine.

Insulin glargine is 31^{B}-32^{B}-Di-Arg human insulin, an analogue of human insulin, with further substitution of asparagine in position A21 by glycine.

WO2008/013938 A2 discloses an aqueous pharmaceutical formulation comprising insulin glargine at a concentration of 684 U/mL.

Metformin is a biguanide hypoglycemic agent used in the treatment of non-insulin-dependent diabetes mellitus (diabetes mellitus type 2) not responding to dietary modification. Metformin improves glycemic control by improving insulin sensitivity and decreasing intestinal absorption of glucose. Metformin is usually administered orally.

Lantus® is an insulin product containing insulin glargine providing 24 hour basal insulin supply after single dose subcutaneous injection.

The glucodynamic effect of Lantus® is distinguished from other currently marketed insulin products by virtue of a delayed and predictable absorption of insulin glargine from the subcutaneous injection site resulting in a smooth, 24 hour time-concentration and action profile without a definite peak. Lantus® was developed to meet the medical need for a long-acting insulin product that can be administered as a single daily injection to yield normal or near-normal blood glucose control with a basal insulin profile that is as smooth as possible over a 24-hour period. Such a preparation provides good control of blood glucose all day, while minimizing the tendency to produce hypoglycemia seen with other insulin preparations with a more definite “peak” effect.

A considerable number of patients, in particular those with increased insulin resistance due to obesity, use large doses to control blood glucose. For example, a dose of 100 U

requires injection of 1 mL Lantus® U100, which may confer some discomfort; each mL Lantus® U100 contains 100 U (3.6378 mg) insulin glargine. To reduce the volume of injection, a formulation containing 300 U insulin glargine per mL has been developed.

The purpose of the multicenter, randomized, open-label, parallel-group study as described in Example 1 was to compare the efficacy and safety of insulin glargine U300 with that of Lantus, both given once-daily subcutaneous (S.C.) as part of a basal-bolus insulin regimen in patients with type 2 diabetes. Patients with type 2 diabetes and glycated hemoglobin A1c (HbA1c) in the range of 7% to 10% injecting at least 42 U Lantus U100 or equivalents of neutral protamine Hagedorn (NPH) insulin in a basal plus mealtime insulin regimen were eligible for the study. These patients on relative high doses of basal insulin benefited from the lower injection volume of a U300 insulin formulation as compared with U100 formulations.

Each mL insulin glargine U300 contains 300 U (10.9134 mg) insulin glargine. This formulation would allow patients to inject the same number of units of insulin glargine at one third the volume of injection. This formulation is also termed herein as HOE901-U300.

In the study described in Example 1, patients were stratified by their HbA1c (<8.0%; ≥ 8.0%). The primary efficacy analysis tested non-inferiority of insulin glargine U300 compared to Lantus in terms of change of HbA1c from baseline to endpoint (scheduled at month 6; non-inferiority margin 0.4 % HbA1c units). HbA1c reflects the average glycemia over several months and has strong predictive value for diabetes complications. The 6-months duration of study treatment is considered to be sufficient for achieving steady state conditions with insulin glargine U300 after changing over from Lantus or NPH insulin enabling an adequate assessment of time-dependent changes in HbA1c and the concomitant risk of hypoglycemia.

Main secondary endpoints included nocturnal hypoglycemia. Hypoglycemia is the critical limiting factor in the glycemic management of diabetes in both the short and long term. Despite steady improvements in the glycemic management of diabetes, population-based data indicate that hypoglycemia continues to be a major problem for people with both type 1 and type 2 diabetes (American diabetes association, workgroup

on hypoglycemia: Defining and Reporting Hypoglycemia in Diabetes. Diabetes Care 28(5), 2005, 1245-1249).

In the study described in Example 1, it was surprisingly found that by treatment of diabetes type 2 patients with an insulin glargine U300 formulation, the risk of a nocturnal hypoglycemic event can be significantly reduced compared with the treatment with Lantus® U100. The incidence of patients with at least one nocturnal severe and/or confirmed hypoglycemia between start of Week 9 and Month 6 was lower in the U300 group [136/404 (33.7%)] than in the Lantus group [180/400 (45.0%)] (see Table 6). Superiority of U300 versus Lantus was shown with a relative risk of 0.75 (95% CI [0.63, 0.89]) (p=0.0010).

Example 2 describes a clinical trial comparing the efficacy and safety of an insulin glargine U300 (HOE901-U300) formulation and Lantus® U 100, both in combination with oral antihyperglycemic drug(s) in patients with type 2 Diabetes Mellitus.

In Example 2, non-inferiority of U300 versus Lantus was demonstrated with the least square mean difference in HbA1c versus Lantus of -0.01% (95 % CI [-0.139; 0.119]) (Table 26). The least square mean change in pre-injection SMPG was similar in the U300 (-0.56 mmol/L) and Lantus groups (-0.51 mmol/L) (Table 28).

Example 2 confirmed that by treatment with an insulin glargine U300 formulation, the risk of a nocturnal hypoglycemic event can be significantly reduced compared with the treatment with Lantus® U100. In a different patient group, namely type 2 Diabetes Mellitus patients not adequate controlled with antihyperglycemic drug(s) alone, it was surprisingly found that the incidence of patients with at least one nocturnal severe and/or confirmed hypoglycemia between was lower in the U300 group [87/403 (21.6%)] than in the Lantus group [113/405 (27.9%)] (see Table 27). Superiority of U300 versus Lantus was shown with a relative risk of 0.77 (95% CI [0.61, 0.99]) (p=0.0380).

Example 3 compares adaptable dosing intervals with fixed dosing intervals of once-daily administration of an U300 insulin glargine formulation in combination with mealtime insulin. Example 3 is a substudy of the trial described in example 1. No negative effects were seen on HbA1c (Table 50) and on fasting plasma glucose (Table 51). The overall

incidence of hypoglycemia was similar in both regimens regardless of the category of hypoglycemia (Table 53).

Example 6 compares adaptable dosing intervals with fixed dosing intervals of once-daily administration of an U300 insulin glargine formulation in combination with oral antihyperglycemic drugs(s). Example 6 is a substudy of the trial described in example 2. No negative effects were seen on HbA1c (Table 67) and on fasting plasma glucose (Table 68). The overall incidence of hypoglycemia was similar in both regimens regardless of the category of hypoglycemia (Table 70).

An aspect of the present invention relates to an aqueous pharmaceutical formulation for use in the treatment of Type I or Type II Diabetes Mellitus, wherein the treatment reduces the risk of nocturnal hypoglycemia, said formulation comprising 200 – 1000 U/mL [equimolar to 200 – 1000 IU human insulin] of insulin glargine, with the proviso that the concentration of said formulation is not 684 U/mL of insulin glargine. The present invention relates to an aqueous pharmaceutical formulation for use in the reduction of the risk of nocturnal hypoglycemia.

The formulation of the present invention can reduce the incidence of nocturnal hypoglycemia when administered to a Diabetes Mellitus patient, as described herein. “Reduction of the incidence of nocturnal hypoglycemia” includes reduction of the number of nocturnal hypoglycemic events, and/or the severity of nocturnal hypoglycemia events. The formulation as described herein is suitable for use in the reduction of the incidence of nocturnal hypoglycemia.

The formulation of the present invention can prevent nocturnal hypoglycemia when administered to a Diabetes Mellitus patient, as described herein. “Prevention of nocturnal hypoglycemia” includes reduction of the number of nocturnal hypoglycemic events and/or the severity of nocturnal hypoglycemia events. The formulation as described herein is suitable for use in the prevention of nocturnal hypoglycemia.

The formulation of the present invention is suitable for use in the reduction of the number of nocturnal hypoglycemic events and/or the severity of nocturnal hypoglycemia events.

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

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

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

The definition of severe symptomatic hypoglycemia may include all episodes in which neurological impairment is severe enough to prevent self-treatment and which were

thus thought to place patients at risk for injury to themselves or others. The acute neurological impairment may be at least one selected from somnolence, psychiatric disorders, visual disorders, transient sensory defects, transient motor defects, confusion, convulsions, and coma. “Requires assistance” means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a “requires assistance” incident.

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

In the present invention, “documented symptomatic hypoglycemia” or “documented symptomatic hypoglycemic event” is an event during which typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (≤ 3.9 mmol/L), or less than or equal to 54 mg/dL (≤ 3.0 mmol/L). Clinical symptoms that are considered to result from a hypoglycemic episode are, e.g., increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, coma.

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

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

In the present invention, “relative hypoglycemia” or “relative hypoglycemic event” is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a

measured plasma glucose concentration greater than 70 mg/dL (or greater than 3.9 mmol/L).

In the present invention, "nocturnal hypoglycemia" or "nocturnal hypoglycemic event" is any hypoglycemia of the hypoglycema categories as described above that occurs night-time. "Nocturnal hypoglycemia" can be defined by the clock time. In particular, nocturnal hypoglycemia is a hypoglycemia that occurs between 00:00 and 05:59 a.m. hours. The patient can be awake or can wake up because of the event. The patient can also sleep during the event.

In the present invention, "daytime hypoglycemia" or "daytime hypoglycemic event" is in particular any hypoglycemia of the hypoglycema categories as described above that occurs between 06:00 a.m. and 23:59.

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

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

Example 3 and 6 demonstrate that occasional adaptation of injection intervals of insulin glargine U300 have no negative effects on HbA1c (Tables 50 and 67) and on fasting plasma glucose (Tables 51 and 69). The overall incidence of hypoglycemia was similar

in administration by adaptable dosing intervals and in administration by a fixed dosing interval regardless of the category of hypoglycemia (Tables 53 and 70).

An aspect of the present invention relates to an aqueous pharmaceutical formulation to be administered in adaptable time intervals. This aspect relates to an aqueous pharmaceutical formulation for use in the treatment of Type I or Type II Diabetes Mellitus, wherein the formulation is administered once daily to a patient, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h, said formulation comprising 200 – 1000 U/mL [equimolar to 200 – 1000 IU human insulin] of insulin glargine, with the proviso that the concentration of said formulation is not 684 U/mL of insulin glargine.

As used herein, the time interval from the previous administration is the time interval between two consecutive administrations, in particular injections.

It is preferred that the formulation comprises 300 U/ml insulin glargin.

In the treatment regimen, the formulation can be administered in a time range around a fixed time, for example around a fixed time in the evening or in the morning. The average time interval from the previous administration can about 24 h (see Table 46). An interval of “about 24 h” in particular refers to a range of 24 h +/-10 min, a range of 24 h +/-20 min, or range of 24 h +/-30 min. The average time interval can be calculated for example, on weekly basis, on monthly basis, or on the basis of two or three months, or can be calculated on a longer time basis.

Table 47 describes the dosing regimen compliance in the test group and control group patients in Example 3. The % of injections by patients in different dosing interval categories is described. In the control group (fixed dosing interval of 24 h), about 88 % of U300 doses were injected in an interval of 23 to 25 h from previous injection. About 12 % of doses were injected at an interval of less than 23 h or more than 25 h. Taking into account one injection per day, the patients dosed the U300 formulation at an interval of less than 23 h or more than 25 h at less than one day per week. In the test group (adaptable dosing interval), about 63 % of U300 doses were injected in an

interval of 23 to 25 h from previous injection. About 37 % of doses were injected at an interval of less than 23 h or more than 25 h. Taking into account one injection per day, the patients dosed the U300 formulation at an interval of less than 23 h or more than 25 h at two or three days per week.

The aqueous formulation can be administered with the time interval specified herein on at least two days per week, on at least three days per week, on at least four days per week or on at least five days per week. The aqueous formulation can be administered with the time interval specified herein on at the maximum five days per week, on at the maximum four days per week or on at the maximum three days per week. More particular, the aqueous formulation is administered with the time interval specified herein on two or three days per week, or on two to three days per week.

"Occasional adaptation" in particular means that the aqueous formulation is administered on two or three days per week with the time interval specified herein.

"Days per week", as indicated herein, can be calculated for example, on weekly basis, on monthly basis, or on the basis of two or three months, or can be calculated on a longer time basis.

"Adaptable injection intervals" means that the time interval from the previous injection is variable within a predetermined time range. The time interval from the previous administration can be in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h. In particular, the time interval from the previous administration is in the range of 25 h to 28 h or in the range of 20 h to 23 h.

The time interval from the previous administration can also be in the range of 25 h to 27 h or in the range of 21 h to 23 h.

The time interval from the previous administration can also be in the range of 25 h to 26.5 h or in the range of 21.5 h to 23 h.

In this aspect, the excipients of the formulation can be excipients as described herein. The patient to be treated can be a patient as described herein.

The treatment regimen of adaptable time intervals, as described herein, can be combined with the reduction of the risk of nocturnal hypoglycemia, as described herein.

The formulation for use in the treatment of Diabetes Mellitus Type 1 or 2 administered in adaptable time intervals, as described herein, can be combined with the use in the treatment of Diabetes Mellitus Type 1 or 2 with reduction of the risk of nocturnal hypoglycemia, as described herein.

In the present invention, normoglycemia may relate to a blood plasma concentration of glucose of from 70 mg/dL to 140 mg/dL (corresponding to 3.9 mmol/L to 7.8 mmol/L).

The patient to be treated by the formulation as described herein may be a Type I or Type II Diabetes Mellitus patient. Preferable, the patient is a Type II Diabetes Mellitus patient.

The pharmaceutical formulation of the present invention may be administered in combination with at least one antihyperglycemic agent. In particular, the at least one antihyperglycemic is metformin or/and a pharmaceutically acceptable salt thereof. Metformin is the international nonproprietary name of 1,1-dimethylbiguanide (CAS Number 657-24-9). In the present invention, the term "metformin" includes any pharmaceutically acceptable salt thereof.

In the present invention, metformin may be administered orally. The skilled person knows formulations of metformin suitable for treatment of diabetes mellitus by oral administration. Metformin may be administered to a patient in need thereof, in an amount sufficient to induce a therapeutic effect. Metformin may be administered in a dose of at least 1.0 g/day or at least 1.5 g/day. 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.

The formulation of the present invention and metformin may be administered by different administration routes. Metformin may be administered orally, and the formulation of the present invention may be administered parenterally.

The patient to be treated by the formulation of the present invention may be a patient suffering from Diabetes Mellitus type 2, wherein diabetes type 2 is not adequately controlled by treatment with at least one antihyperglycemic alone. The antihyperglycemic may be metformin, wherein administration does not adequately control Diabetes Mellitus type 2, for example after treatment for at least 2 or at least 3 months, for example with a dose of at least 1.0 g/day or at least 1.5 g/day of metformin.

In the present invention, a patient the diabetes type 2 is not adequately controlled if at least one physiological parameter describing blood glucose concentration (e.g. the HbA1c value, the pre-injection SMPG or/and the fasting plasma glucose concentration) exceeds normoglycemic values, as described herein. In particular, a patient the diabetes type 2 of which is not adequately controlled may have
(i) a HbA1c value in the range of 7 % to 10 % or even larger,
(ii) a pre-injection SMPG of at least 9 mmol/L, or/and
(iv) a fasting plasma glucose of at least 8.0 mmol/L.

The patient to be treated by the formulation as described herein may have a HbA1c value in the range of 7% to 10% at the onset of treatment. More particular, the patient to be treated may have a HbA1c value of at least 8%, or a HbA1c value in the range of 8% to 10% at the onset of treatment of the present invention.

The patient to be treated by the formulation as described herein may be an adult subject. The patient may have an age of at least 50 years, at least 57 years, at least 58 years, at least 59 years, at least 60 years, at least 65 years, at least 70 years, or at least 75 years at the onset of treatment of the present invention.

The patient to be treated by the formulation as described herein may be an obese subject at the onset of treatment of the present invention. In the present invention, an obese subject may have a body mass index (BMI) of at least 30 kg/m^2, at least 31 kg/m^2, at least 32 kg/m^2, at least 33 kg/m^2, at least 34 kg/m^2, at least 35 kg/m^2, at least

36 kg/m^2, at least 37 kg/m^2, at least 38 kg/m^2, at least 39 kg/m^2 or at least 40 kg/m^2 at the onset of treatment. It is preferred that the patient has a BMI of at least 34 kg/m^2 or of at least 36 kg/m^2 at the onset of treatment.

The patient to be treated by the formulation as described herein may have an increased risk of hypoglycemia, in particular a diabetes type 2 patient having experienced at least one hypoglycemic event.

The patient to be treated by the formulation as described herein may have received an insulin directly prior to the treatment as described herein. In particular, the patient may have received a basal insulin, for example in a dose of at least 32 U/day or at least 42 U/day. In the present invention, any pre-treatment with a basal insulin can be considered. In particular, the basal insulin can be selected from insulin Glargine, Detemir, NPH, Lente, Ultralente, Novolin, Humalog and mixtures thereof. The mixture may comprise two different basal insulins. For example, a mixture comprising Detemir and Glargine, or a mixture comprising NPH and Novolin, may be employed. Preferably, the basal insulin is insulin Glargin, or a mixture comprising insulin Glargine. In the present invention, “basal insulin” includes suitable pharmaceutically acceptable salts thereof.

The patient to be treated by the formulation as described herein may have received a mealtime short-acting insulin directly prior to the treatment as described herein. The mealtime short-acting insulin may be an insulin analogue, for example insulin glulisin, insulin lispro, or insulin aspart.

The formulation as described herein may be administered once or twice daily. In particular, the formulation as described herein may be administered once daily, for example in the evening. The formulation as described herein may be administered once daily in the evening at a predetermined time.

The patient may additionally receive a mealtime short-acting insulin. The mealtime short-acting insulin may be an insulin analogue, for example insulin glulisin, insulin lispro, or insulin aspart.

The patient to be treated by the formulation of the present invention may have a pre-injection self-monitored plasma glucose (SMPG) concentration of at least 9 mmol/L, at least 10 mmol/L, at least 10.5 mmol/L, or at least 11 mmol/L at the onset of treatment of the present invention. In the present invention, self-monitored plasma glucose can be a fasting SMPG or a pre-injection SMPG (for example, measured 30 minutes prior to injection of the formulation described herein).

The patient to be treated may have a fasting plasma glucose concentration of at least 7 mmol/L, at least 7.5 mmol/L, at least 8 mmol/L, at least 8.5 mmol/L or at least 9 mmol/L at the onset of treatment of the present invention.

Although the invention is not limited to a insulin glargine U 300 formulation but is effective with other higher concentrated formulations of insulin glargine as outlined in detail in the specification, the clinical study described herein were performed with a insulin glargine U 300 formulation.

1 mL of insulin glargine U 300 formulation contains 10.913 mg 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg human insulin [equimolar to 300 IU human insulin], 90 µg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, HCl and NaOH ad pH 4.0; specific gravity 1.006 g/mL

However, variations with regard to the kind of excipients and their concentrations are possible.

The pharmaceutical formulation contains 200 – 1000 U/mL of insulin glargine [equimolar to 200 – 1000 IU human insulin], wherein the concentration of said formulation is not 684 U/mL, preferably 250 - 500 U/mL of insulin glargine [equimolar to 250 – 500 IU human insulin], more preferred 270 – 330 U/mL of insulin glargine [equimolar to 270 – 330 IU human insulin], and even more preferred 300 U/mL of insulin glargine [equimolar to 300 IU human insulin].

Surfactants can be added to pharmaceutical formulation, for example, inter alia, non-ionic surfactants. In particular, pharmaceutically customary surfactants are preferred, such as, for example: partial and fatty acid esters and ethers of polyhydric alcohols such as of glycerol, sorbitol and the like (Span®, Tween®, in particular Tween® 20 and Tween®

80, Myrj®, Brij®), Cremophor® or poloxamers. The surfactants are present in the pharmaceutical composition in a concentration of 5 - 200 µg/ml, preferably of 5 – 120 µg/ml and particularly preferably of 20 – 75 µg/ml.

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

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

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

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

In the pharmaceutical formulation a buffer substance can be present in a concentration of 5 – 250 mmol/L.

A further subject of the invention is a pharmaceutical insulin formulation for use as described herein which contains further additives such as, for example, salts which delay the release of insulin. Mixtures of such delayed-release insulins with formulations described above are included therein.

A further subject of the invention is directed to a method for the production of such pharmaceutical formulations for use as described herein. For producing the formulations the ingredients are dissolved in water and the pH is adjusted by using HCl and / or NaOH. Likewise, a further subject of the invention is directed to the use of such formulations for the treatment of diabetes mellitus.

A further subject of the invention is directed to the use or the addition of surfactants as stabilizer during the process for the production of insulin, insulin analogs or insulin derivatives or their preparations.

The invention further relates to a formulation as described above which additionally comprises also a glucagon-like peptide-1 (GLP1) or an analogue or derivative thereof, or exendin-3 or -4 or an analogue or derivative thereof, preferably exendin-4.

The invention further relates to a formulation as described above in which an analogue of exendin-4 is selected from a group comprising
H-desPro^{36}-exendin-4-Lys$_6$-NH$_2$ (Lixisenatide, AVE0010),
H-des(Pro^{36,37})-exendin-4-Lys$_4$-NH$_2$ and
H-des(Pro^{36,37})-exendin-4-Lys$_5$-NH$_2$,
or a pharmacologically tolerable salt thereof.

The invention further relates to a formulation as described above in which an analogue of exendin-4 is selected from a group comprising
desPro^{36} [Asp^{28}]exendin-4 (1-39),
desPro^{36} [IsoAsp^{28}]exendin-4 (1-39),
desPro^{36} [Met(O)^{14}, Asp^{28}]exendin-4 (1-39),
desPro^{36} [Met(O)^{14}, IsoAsp^{28}]exendin-4 (1-39),
desPro^{36} [Trp(O$_2$)^{25}, Asp^{28}]exendin-2 (1-39),
desPro^{36} [Trp(O$_2$)^{25}, IsoAsp^{28}]exendin-2 (1-39),
desPro^{36} [Met(O)^{14}Trp(O$_2$)^{25}, Asp^{28}]exendin-4 (1-39) and
desPro^{36} [Met(O)^{14}Trp(O$_2$)^{25}, IsoAsp^{28}]exendin-4 (1-39),
or a pharmacologically tolerable salt thereof.

The invention further relates to a formulation as described in the preceding paragraph, in which the peptide -Lys_6-NH_2 is attached to the C termini of the analogues of exendin-4.

The invention further relates to a formulation as described above in which an analogue of exendin-4 is selected from a group comprising

H-$(Lys)_6$- des Pro^{36} [Asp^{28}]exendin-4(1-39)-Lys_6-NH_2

des $Asp^{28}Pro^{36}$, Pro^{37}, Pro_{38} exendin-4(1-39) -NH_2,

H-$(Lys)_6$- des Pro^{36}, Pro^{37}, Pro^{38} [Asp^{28}]exendin-4(1-39) -NH_2,

H-Asn-$(Glu)_5$ des Pro^{36}, Pro^{37}, Pro^{38} [Asp^{28}]exendin-4(1-39) -NH_2,

des Pro^{36}, Pro^{37}, Pro^{38} [Asp^{28}]exendin-4(1-39)-$(Lys)_6$-NH_2,

H-$(Lys)_6$- des Pro^{36}, Pro^{37}, Pro^{38} [Asp^{28}]exendin-4(1-39)-$(Lys)_6$-NH_2,

H-Asn-$(Glu)_5$- des Pro^{36}, Pro^{37}, Pro^{38} [Asp^{28}]exendin-4(1-39)-$(Lys)_6$-NH_2,

H-$(Lys)_6$- des Pro^{36} [$Trp(O_2)^{25}$, Asp^{28}]exendin-4(1-39)-Lys_6-NH_2,

H- des Asp^{28} Pro^{36}, Pro^{37}, Pro^{38} [$Trp(O_2)^{25}$]exendin-4(1-39) -NH_2,

H-$(Lys)_6$- des Pro^{36}, Pro^{37}, Pro^{38} [$Trp(O_2)^{25}$, Asp^{28}]exendin-4(1-39) -NH_2,

H-Asn-$(Glu)_5$- des Pro^{36}, Pro^{37}, Pro^{38} [$Trp(O_2)^{25}$, Asp^{28}]exendin-4(1-39) -NH_2,

des Pro^{36}, Pro^{37}, Pro^{38} [$Trp(O_2)^{25}$, Asp^{28}]exendin-4(1-39)-$(Lys)_6$-NH_2,

H-$(Lys)_6$- des Pro^{36}, Pro^{37}, Pro^{38} [$Trp(O_2)^{25}$, Asp^{28}]exendin-4(1-39)-$(Lys)_6$-NH_2,

H-Asn-$(Glu)_5$- des Pro^{36}, Pro^{37}, Pro^{38} [$Trp(O_2)^{25}$, Asp^{28}]exendin-4(1-39)-$(Lys)_6$-NH_2,

H-$(Lys)_6$- des Pro^{36} [$Met(O)^{14}$, Asp^{28}]exendin-4(1-39)-Lys_6-NH_2,

des $Met(O)^{14}$ Asp^{28} Pro ^{36}, Pro^{37}, Pro^{38} exendin-4(1-39) -NH_2,

H-$(Lys)_6$- des Pro^{36}, Pro ^{37}, Pro^{38} [$Met(O)^{14}$, Asp^{28}]exendin-4(1-39) -NH_2,

H-Asn-$(Glu)_5$- des Pro^{36}, Pro^{37}, Pro^{38} [$Met(O)^{14}$, Asp^{28}] exendin-4(1-39) -NH_2,

des Pro^{36}, Pro^{37}, Pro^{38} [$Met(O)^{14}$, Asp^{28}]exendin-4(1-39)-$(Lys)_6$-NH_2,

H-$(Lys)_6$- des Pro^{36}, Pro^{37}, Pro^{38} [$Met(O)^{14}$, Asp^{28}]exendin-4(1-39)-Lys_6-NH_2,

H-Asn-$(Glu)_5$ des Pro^{36}, Pro^{37}, Pro^{38} [$Met(O)^{14}$, Asp^{28}] exendin-4(1-39)-$(Lys)_6$-NH_2,

H-$(Lys)_6$- des Pro^{36} [$Met(O)^{14}$, $Trp(O_2)^{25}$, Asp^{28}]exendin-4(1-39)-Lys_6-NH_2,

des Asp^{28} Pro^{36}, Pro^{37}, Pro^{38} [$Met(O)^{14}$, $Trp(O_2)^{25}$]exendin-4(1-39) -NH_2,

H-$(Lys)_6$- des $Pro^{36,}$ Pro^{37}, Pro^{38} [$Met(O)^{14}$, $Trp(O_2)^{25}$, Asp^{28}]exendin-4(1-39) -NH_2,

H-Asn-$(Glu)_5$- des Pro^{36}, Pro^{37}, Pro^{38} [$Met(O)^{14}$, Asp^{28}] exendin-4(1-39) -NH_2,

des Pro^{36}, Pro^{37}, Pro^{38} [$Met(O)^{14}$, $Trp(O_2)^{25}$, Asp^{28}]exendin-4(1-39)-$(Lys)_6$-NH_2,

H-$(Lys)_6$- des $Pro^{36,}$ Pro^{37}, Pro^{38} [$Met(O)^{14}$, $Trp(O_2)^{25}$, Asp^{28}]exendin-4(1-39)-$(Lys)_6$-NH_2, H-Asn-$(Glu)_5$- des Pro^{36}, Pro^{37}, Pro^{38} [$Met(O)^{14}$, $Trp(O_2)^{25}$, Asp^{28}] exendin-4(1-39)-$(Lys)_6$-NH_2,
or a pharmacologically tolerable salt thereof.

The invention further relates to a formulation as described above which additionally comprises Arg^{34}, Lys^{26} (N^{ε}(γ-glutamyl(N^{α}-hexadecanoyl))) GLP-1 (7-37) [liraglutide] or a pharmacologically tolerable salt thereof.

In one embodiment, the present invention is directed to an aqueous pharmaceutical formulation for use as described herein comprising insulin glargine in the range of 200 – 1000 U/mL [equimolar to 200 – 1000 IU human insulin], preferably 200 U/ml to 650 U/mL, still preferably 700 U/mL to 1000 U/ml, more preferably 270 – 330 U/mL and most preferably in a concentration of 300 U/mL, with the proviso that the concentration of said formulation is not 684 U/mL of insulin glargine.

Additionally, the formulation can also comprise an analogue of exendin-4, such, for example, lixisentatide, exenatide and liraglutide. These exendin-4 analogues are present in the formulation in the range of 0.1 µg to 10 µg per U insulin glargine, preferably 0.2 to 1 µg per U insulin glargine, and more preferably 0.25 µg to 0.7 µg per U insulin glargine. Lixisenatide is preferred.

Additionally, the aqueous pharmaceutical formulation can comprise one or more excipients selected from a group comprising zinc, m-cresol, glycerol, polysorbate 20 and sodium. Specifically, the aqueous pharmaceutical formulation can comprise 90 µg/mL zinc, 2.7 mg/mL m-cresol and 20 mg/ml glycerol 85%. Optionally, the aqueous pharmaceutical formulation can comprise 20µg/mL polysorbate 20.

The pH of the aqueous pharmaceutical formulation as described herein can be 4.6 or lower, preferably 4.5 or lower.

The pH of the aqueous pharmaceutical formulation as described herein can also be in the range from 3.4 to 4.6, preferably in the range from 4 to 4.5.

Another aspect of the present invention is directed to a method for treating a disease or condition as described herein, in particular a method for treating Type I or Type II Diabetes Mellitus comprising administering to said patient the aqueous pharmaceutical composition of the present invention to a diabetic patient, wherein treatment reduces the risk of nocturnal hypoglycemia. The method preferably refers to treatment of Type II Diabetes Mellitus. Preferred among the various disclosed concentration ranges is a concentration of 300 U/mL. Further the aqueous pharmaceutical formulation also can comprise zinc, m-cresol, glycerol, polysorbate 20 and sodium and mixtures thereof in the ranges disclosed herein in relation to the aqueous pharmaceutical formulation of the present invention. In a preferred embodiment the aqueous pharmaceutical formulation also comprises 0.1 µg to 10 µg lixisenatide per U insulin glargine. The nocturnal hypoglycemia can be any nocturnal hypoglycemia, as defined herein. The patient can be any patient as defined herein.

The insulin is administered preferably once daily but can be administered twice daily as needed. Dosage requirements are a function of the needs of the individual patient determined by the achievement of normal or acceptable blood glucose levels.

The method can also be a method of treating Type I or Type II Diabetes Mellitus in a patient comprising administering to said patient an aqueous pharmaceutical composition as described herein, wherein the formulation is administered once daily, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h. The time interval can be a time interval as defined herein. The aqueous formulation can be administered on at least three days per week, on at least four days per week or on at least five days per week with the time interval specified herein. The method preferably refers to treatment of Type II Diabetes Mellitus. Preferred among the various disclosed concentration ranges is a concentration of 300 U/mL. Further the aqueous pharmaceutical formulation also can comprise zinc, m-cresol, glycerol, polysorbate 20 and sodium and mixtures thereof in the ranges disclosed herein in relation to the aqueous pharmaceutical formulation of the present invention. In a preferred embodiment the aqueous pharmaceutical formulation also comprises 0.1 µg to 10 µg lixisenatide per U insulin glargine. The patient can be any patient as defined herein.

The treatment method of Diabetes Mellitus Type 1 or 2 administered in adaptable time intervals, as described herein, can be combined with the method of treatment of Diabetes Mellitus Type 1 or 2 with reduction of the risk of nocturnal hypoglycemia, as described herein.

Yet another aspect of the present invention is directed to the use of an aqueous formulation as described herein for the manufacture of a medicament for the treatment of a disease or condition as described herein, in particular for the treatment of Type I or Type II Diabetes Mellitus, wherein the treatment reduces the risk of nocturnal hypoglycemia. The use preferably refers to treatment of Type II Diabetes Mellitus. Preferred among the various disclosed concentration ranges is a concentration of 300 U/mL. Further the aqueous pharmaceutical formulation also can comprise zinc, m-cresol, glycerol, polysorbate 20 and sodium and mixtures thereof in the ranges disclosed herein in relation to the aqueous pharmaceutical formulation of the present invention. In a preferred embodiment the aqueous pharmaceutical formulation also comprises 0.1 µg to 10 µg lixisenatide per U insulin glargine. The nocturnal hypoglycemia can be any nocturnal hypoglycemia, as defined herein. The patient can be any patient as defined herein.

The insulin is administered preferably once daily but can be administered twice daily as needed. Dosage requirements are a function of the needs of the individual patient determined by the achievement of normal or acceptable blood glucose levels.

Another aspect refers to the use of an aqueous formulation as described herein for the manufacture of a medicament for treating Type I or Type II Diabetes Mellitus in a patient comprising administering to said patient an aqueous pharmaceutical composition as described herein, wherein the formulation is administered once daily, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h. The time interval can be a time interval as defined herein. The aqueous formulation can be administered on at least three days per week, on at least four days per week or on at least five days per week with the time interval specified herein. The method preferably refers to treatment of

Type II Diabetes Mellitus. Preferred among the various disclosed concentration ranges is a concentration of 300 U/mL. Further the aqueous pharmaceutical formulation also can comprise zinc, m-cresol, glycerol, polysorbate 20 and sodium and mixtures thereof in the ranges disclosed herein in relation to the aqueous pharmaceutical formulation of the present invention. In a preferred embodiment the aqueous pharmaceutical formulation also comprises 0.1 µg to 10 µg lixisenatide per U insulin glargine. The patient can be any patient as defined herein.

The use for the manufacture of a medicament for the treatment of Diabetes Mellitus Type 1 or 2 administered in adaptable time intervals, as described herein, can be combined with the use for the manufacture of a medicament for the treatment of Diabetes Mellitus Type 1 or 2 with reduction of the risk of nocturnal hypoglycemia, as described herein.

The invention relates, inter alia, to the following items:

1. An aqueous pharmaceutical formulation for use in the treatment of Type I or Type II Diabetes Mellitus, wherein the treatment reduces the risk of nocturnal hypoglycemia, said formulation comprising 200 – 1000 U/mL [equimolar to 200 – 1000 IU human insulin] of insulin glargine, with the proviso that the concentration of said formulation is not 684 U/mL of insulin glargine.

2. The aqueous formulation for use of item 1 comprising 200 U/ml to 650 U/mL of insulin glargine.

3. The aqueous formulation for use of item 1 comprising 700 U/ml to 1000 U/mL of insulin glargine.

4. The aqueous formulation for use of item 2 comprising 270 – 330 U/mL of insulin glargine [equimolar to 270 – 330 IU human insulin].

5. The aqueous formulation for use of item 4 comprising 300 U/mL of insulin glargine [equimolar to 300 IU human insulin].

6. The aqueous pharmaceutical formulation for use of any of the foregoing items, wherein the nocturnal hypoglycemia is selected from symptomatic hypoglycemia, severe symptomatic hypoglycemia, documented symptomatic hypoglycemia, probable symptomatic hypoglycemia, relative symptomatic hypoglycemia, and asymptomatic hypoglycemia.

7. The aqueous pharmaceutical formulation for use of any of the foregoing items, wherein the patient to be treated has a HbA1c value of at least 8% at the onset of treatment.

8. The aqueous pharmaceutical formulation for use of any of the foregoing items, wherein the patient to be treated has an age of at least 60 years at the onset of treatment.

9. The aqueous pharmaceutical formulation for use of any of the foregoing items, wherein the patient to be treated has a BMI of at least 30 kg/m^2 at the onset of treatment.

10. The aqueous pharmaceutical formulation for use of any of the foregoing items, wherein the patient to be treated received a basal insulin directly prior to the treatment.

11. The aqueous pharmaceutical formulation for use of any of the foregoing items, wherein the patient to be treated received a mealtime short-acting insulin directly prior to the treatment.

12. The aqueous pharmaceutical formulation for use of item 10 or 11, wherein the patient to be treated has a pre-injection SMPG of at least 9 mmol/L at the onset of treatment.

13. The aqueous pharmaceutical formulation for use of item 10 or 11, wherein the patient to be treated has a fasting plasma glucose concentration of at least 8 mmol/L at the onset of treatment.

14. The aqueous pharmaceutical formulation for use of any of the foregoing items, wherein the formulation is administered once daily in the evening at a predetermined time.

15. The aqueous pharmaceutical formulation for use of any of the foregoing items, wherein the patient additionally receives a mealtime short-acting insulin.

16. The aqueous pharmaceutical formulation for use of any of the foregoing items comprising an analogue of exendin-4.

17. The aqueous formulation for use of item 16, wherein the analogue of exendin-4 is selected from a group comprising lixisentatide, exenatide and liraglutide.

18. The aqueous formulation for use of item 17 comprising 0.1 µg to 10 µg lixisenatide per U insulin glargine.

19. The aqueous formulation for use of item 18 comprising 0.2 to 1 µg lixisenatide per U insulin glargine.

20. The aqueous formulation for use of item 19 comprising 0.25 µg to 0.7 µg lixisenatide per U insulin glargine.

21. The aqueous formulation for use of any of the foregoing items comprising one or more excipients selected from a group comprising zinc, m-cresol, glycerol, polysorbate 20 and sodium.

22. The aqueous formulation for use of item 21 comprising 90 µg/mL zinc, 2.7 mg/mL m-cresol and 20 mg/ml glycerol 85%.

23. The aqueous formulation for use of item 21 comprising 90 µg/mL zinc, 2.7 mg/mL m-cresol, 20µg/mL polysorbate 20 and 20 mg/mL glycerol 85%.

24. The aqueous formulation for use of any of the foregoing items, wherein the pH is between 3.4 and 4.6.

25. The aqueous formulation for use of item 24, wherein the pH is 4.

26. The aqueous formulation for use of item 24, wherein the pH is 4.5.

27. The pharmaceutical formulation for use of any one of the items 1 to 26, wherein the Diabetes Mellitus is Type II Diabetes Mellitus.

28. The pharmaceutical formulation for use of item 27, wherein the Diabetes Mellitus Type II is not adequately controlled with at least one oral antihyperglycemic alone.

29. The pharmaceutical formulation for use of item 28, wherein the at least one oral antihyperglycemic is metformin.

30. The pharmaceutical formulation for use of item 29, wherein a treatment with at least 1.5 g/day of metformin does not adequately control the Diabetes Mellitus.

31. The aqueous pharmaceutical formulation for use of any of the items 27 to 30, administered in combination with at least one oral antihyperglycemic agent.

32. The aqueous pharmaceutical formulation for use of item 31, wherein the at least one antihyperglycemic agent is metformin.

33. The aqueous pharmaceutical formulation for use of any one of the preceding items, wherein the formulation is administered once daily, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h.

34. A method of treating Type I or Type II Diabetes Mellitus in a patient comprising administering to said patient an aqueous pharmaceutical composition comprising insulin glargine in a concentration of 300 U/mL, wherein the treatment reduces the risk of nocturnal hypoglycemia.

35. The method of item 34 wherein said pharmaceutical composition further comprises excipients selected from the group consisting of zinc, m-cresol, glycerol, polysorbate 20 and sodium.

36. The method of item 34 wherein said pharmaceutical composition further comprises 0.1 µg to 10 µg lixisenatide per U insulin glargine.

37. Use of an aqueous formulation according to any of the foregoing items for the manufacture of a medicament for the treatment of Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus, wherein the treatment reduces the risk of nocturnal hypoglycemia.

38. An aqueous pharmaceutical formulation for use in the treatment of Type I or Type II Diabetes Mellitus, wherein the formulation is administered once daily to a patient, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h, said formulation comprising 200 – 1000 U/mL [equimolar to 200 – 1000 IU human insulin] of insulin glargine, with the proviso that the concentration of said formulation is not 684 U/mL of insulin glargine.

39. The aqueous formulation of item 38 administered on at least three days per week with the time interval specified in item 38.

40. The aqueous formulation of item 38 administered on at least four days per week with the time interval specified in item 38.

41. The aqueous formulation of any one of the items 38 to 40, wherein the time interval from the previous administration is in the range of 25 h to 28 h or in the range of 20 h to 23 h.

42. The aqueous formulation of any one of the items 38 to 41, wherein the time interval from the previous administration is in the range of 25 h to 27 h or in the

range of 21 h to 23 h.

43. The aqueous formulation of any one of the items 38 to 42, wherein the time interval from the previous administration is in the range of 25 h to 26.5 h or in the range of 21.5 h to 23 h.

44. The aqueous formulation for use of any one of the items 38 to 43, comprising insulin glargine in an amount as defined in any one of the items 2 to 5.

45. The aqueous formulation for use of any one of the items 38 to 44, wherein the patient is defined as in any one of the items 7 to 15.

46. The aqueous formulation for use of any one of the items 38 to 45, further comprising an analogue of exendin-4, as defined in any one of the items 16 to 20.

47. The aqueous formulation for use of any one of the items 38 to 46, further comprising one or more excipients as defined in any one of the items 21 to 23.

48. The aqueous formulation for use of any one of the items 38 to 47, having a pH as defined in any one of the items 24 to 26.

49. The aqueous formulation for use of any one of the items 38 to 48, wherein the treatment reduces the risk of nocturnal hypoglycaemia.

50. The aqueous formulation for use of item 49, wherein the nocturnal hypoglycemia is selected from symptomatic hypoglycemia, severe symptomatic hypoglycemia, documented symptomatic hypoglycemia, probable symptomatic hypoglycemia, relative symptomatic hypoglycemia, and asymptomatic hypoglycemia.

51. The aqueous formulation for use of any one of the items 38 to 50, wherein the Diabetes Mellitus is Type II Diabetes Mellitus.

52. The aqueous formulation for use of item 51, wherein the Diabetes Mellitus type II

is not adequately controlled with a least one oral antihyperglycemic agent alone, as defined in any one of the items 28 to 32.

53. A method of treating Type I or Type II Diabetes Mellitus in a patient comprising administering to said patient an aqueous pharmaceutical composition comprising insulin glargine in a concentration of 300 U/mL, wherein the formulation is administered once daily, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h.

54. The method of item 53 wherein said pharmaceutical composition further comprises excipients selected from the group consisting of zinc, m-cresol, glycerol, polysorbate 20 and sodium.

55. The method of item 53 wherein said pharmaceutical composition further comprises 0.1 µg to 10 µg lixisenatide per U insulin glargine.

56. Use of an aqueous formulation according to any of the foregoing items for the manufacture of a medicament for the treatment of Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus, wherein the formulation is administered once daily, and wherein the time interval from the previous administration is in the range of 24.5 h to 28 h or in the range of 20 h to 23.5 h on at least two days per week, and wherein the average time interval from the previous administration is about 24 h.

57. An article of manufacture comprising a packaging material, an aqueous formulation according to any of the foregoing items, and a label or packaging material indicating that the formulation is administered once daily, and wherein the time interval from the previous administration is between 21 h and 27 h, and wherein the average time interval from the previous administration is about 24 h.

58. An article of manufacture comprising a packaging material, an aqueous formulation according to any of the foregoing items, and a label or packaging

material indicating that the formulation can be given together with other anti-hyperglyaemic medicinal products.

59. An article of manufacture comprising a packaging material, an aqueous formulation according to any of the foregoing items, and a label or packaging material indicating that changing from a once-daily administration of a basal insulin products to a once daily administration of the formulation can be done unit-to-unit based on the previous basal insulin dose; and changing from twice daily administration of a basal insulin product to once-daily administration of the formulation, the recommended initial dose of the formulation is 80% of the total daily dose of basal insulin that is being discontinued.

60. An article of manufacture comprising a packaging material, an aqueous formulation according to any of the foregoing items, and a label or packaging material indicating that in case the formulation is given together with a substance that may enhance the blood-glucose-lowering effect of the formulation selected from a group comprising anti-hyperglycaemic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics, a dose adjustment of the formulation may be needed.

61. An article of manufacture comprising a packaging material, an aqueous formulation according to any of the foregoing items, and a label or packaging material indicating that in case the formulation is given together with a substance that may reduce the blood-glucose-lowering effect of the formulation selected from a group comprising corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens, phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, atypical antipsychotic medicinal products (e.g. clozapine and olanzapine) and protease inhibitors a dose adjustment of the formulation may be needed.

The application is described below with the aid of the following figures and examples, which are in no way intended to act restrictively.

Legends

Figure 1 - Main efficacy analysis - Mean HbA1c (%) by visit during the main 6-month on-treatment period - mITT population (Example 1). BAS = Baseline, M6LOCF= last value during main 6-month on-treatment (LOCF). LOCF = Last observation carried forward.

Figure 2 - Other secondary efficacy endpoints - Mean average pre-injection SMPG (mmol/L) by visit during the main 6-month on-treatment period - mITT population (Example 1). BAS = Baseline, M6LOCF= last value during main 6-month on-treatment (LOCF). LOCF = Last observation carried forward.

Figure 3 - Other secondary efficacy endpoints - Mean 8-point SMPG profile (mmol/l) at baseline and Month 6 endpoint - mITT population (Example 1). LOCF = Last observation carried forward.

Figure 4 - Other secondary efficacy endpoints - Average daily basal insulin and mealtime insulin dose (U) by visit during the main 6-month on-treatment period - mITT population (Example 1). BAS = Baseline, M6LOCF= last value during main 6-month on-treatment (LOCF). LOCF = Last observation carried forward.

Figure 5 - Main efficacy analysis - Mean HbA1c (%) by visit during the main 6-month on-treatment period - mITT population (Example 2). BAS = Baseline, M6LOCF= Month-6 endpoint (LOCF), LOCF = Last observation carried forward. Note: For all patients rescued during the 6-month period, the last postbaseline HbA1c measurement before rescue and during the 6-month on-treatment period will be used as the HbA1c endpoint.

Figure 6 - Other secondary efficacy endpoints - Mean average pre-injection SMPG (mmol/L) by visit during the main 6-month on-treatment period - mITT population (Example 2). BAS = Baseline, M6LOCF= Month 6 endpoint (LOCF). SMPG = Self

Monitoring Plasma Glucose. LOCF = Last observation carried forward. Note: For all patients rescued during the 6-month period, the last postbaseline average pre-injection SMPG measurement before rescue and during the 6-month on-treatment period will be used as the average pre-injection SMPG endpoint.

Figure 7 - Other secondary efficacy endpoints - Mean 8-point SMPG profile (mmol/l) at baseline and Month 6 endpoint - mITT population (Example 2). LOCF = Last observation carried forward. SMPG=Self Monitoring Plasma Glucose. M6 (LOCF)= Month 6 endpoint LOCF. Note: For all patients rescued during the 6-month period, the last postbaseline 8-point profile SMPG measurement before rescue and during the 6-month on-treatment period will be used as the8-point profile SMPG endpoint.

Figure 8 - Other secondary efficacy endpoints - Average daily basal insulin dose (U) by visit during the main 6-month on-treatment period - mITT population (Example 2). BAS = Baseline, M6LOCF= last value during main 6-month on-treatment (LOCF). LOCF = Last observation carried forward. Note: For all patients rescued during the 6-month period, the last postbaseline insulin dose measurement before rescue and during the 6-month on-treatment period will be used as the insulin dose endpoint.

Figure 9 - Main efficacy analysis - Mean HbA1c (%) by visit during the 3-month comparative regimen period - mITT sub-study population. BASM6 = Baseline (month 6), M9LOCF= last value during the 3-month comparative regimen period (LOCF). LOCF = Last observation carried forward.

Figure 10 - Average daily basal (glargine) and mealtime insulin dose (U) by visit during the 3-month comparative regimen period - mITT sub-study population. BASM6 = Baseline (month 6), M9LOCF= last value during the 3-month comparative regimen period (LOCF). LOCF = Last observation carried forward.

Figure 11 - Plot of average glucose (mg/dL) by hour of day during entire treatment period – CGM population

Figure 12 - Plot of average glucose (mg/dL) by hour of day during entire morning injection period – CGM population

Figure 13 - Plot of average glucose (mg/dL) by hour of day during entire evening injection period – CGM population

Figure 14 - Main efficacy analysis - Mean HbA1c (%) by visit during the 3-month comparative regimen period - mITT sub-study population. BASM6 = Baseline (month 6), M9LOCF= last value during the 3-month comparative regimen period (LOCF). LOCF = Last observation carried forward. Note: For all patients rescued during the 3-month comparative regimen period, the last postbaseline HbA1c measurement before rescue and during sub-study 3-month on-treatment period will be used as the HbA1c endpoint.

Figure 15 - Average daily basal (glargine) insulin dose (U) by visit during the 3-month comparative regimen period - mITT sub-study population. BASM6 = Baseline (month 6), M9LOCF= last value during the 3-month comparative regimen period (LOCF). LOCF = Last observation carried forward. Note: For all patients rescued during the 3-month comparative regimen period, the last postbaseline insulin dose measurement before rescue and during sub-study 3-month on-treatment period will be used as the insulin dose endpoint.

Example 1: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period

SYNOPSIS

Phase of development: Phase 3

Objectives:

Primary Objective: To assess the effects on glycemic control of HOE901-U300 in comparison to Lantus when given as basal insulin in a regimen with mealtime insulin in terms of HbA_{1c} change over a period of 6 months in patients with type 2 diabetes mellitus.

Main secondary Objectives: To compare HOE901-U300 and Lantus in terms of occurrence of nocturnal hypoglycemia, change in preinjection plasma glucose, and change in variability of preinjection plasma glucose.

Further secondary objectives:

- To compare HOE901-U300 and Lantus in terms of reaching target HbA_{1c} values and controlled plasma glucose;
- To compare HOE901-U300 and Lantus in terms of treatment satisfaction of patients using the Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs) (not presented in KRM);
- To assess the safety and tolerability of HOE901-U300.

Methodology: The randomization was 1:1 (HOE901-U300 versus Lantus) and was stratified according to HbA_{1c} values at screening (<8.0%; ≥ 8.0%). The sample size (400 with HOE901-U300 and 400 with Lantus) was chosen to ensure sufficient power for the primary endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]) as well as to allow conclusions on the first main secondary endpoint (occurrence of nocturnal hypoglycemia).

Number of patients:	Planned: 800 (400 per treatment arm)		Randomized: 807
	Treated: 806		
Evaluated:	efficacy: 804	Safety: 806	

Diagnosis and criteria for inclusion: Inclusion criteria: Patients with type 2 diabetes mellitus as defined by WHO; signed written informed consent. Key exclusion criteria: Age < 18 years; HbA_{1c} < 7.0% or > 10% at screening; diabetes other than type 2 diabetes mellitus; less than 1 year on basal plus mealtime insulin and self-monitoring of

blood glucose; total daily dose insulin glargine < 42 U or equivalent dose of NPH in the last 4 weeks prior to the study (if NPH was used as basal insulin prior to the study).

Study treatments

Investigational medicinal products: Tested drug: HOE901-U300; Control drug: Lantus

Formulations: HOE901-U300 (insulin glargine 300 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution in a glass cartridge that has been assembled in a pen-injector (prefilled ie, disposable pen). Lantus (insulin glargine 100 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution supplied in the marketed Solostar® (prefilled ie, disposable pen).

Route of administration: subcutaneous injection

Dose regimen: Once daily injection in the evening. The injection time was fixed at the time of randomization and was to be maintained for the duration of the study.

HOE901-U300 or Lantus will be injected once daily subcutaneously in the evening, ie, anytime immediately prior to the evening meal until bedtime. The injection time will be always at the same time within this time window and will be fixed at randomization at the discretion of the patient/investigator. Patients will continue with their mealtime insulin analogue.

Starting dose: Patients on Lantus or NPH once daily prior to the baseline visit: the daily dose (U) of HOE901-U300 or Lantus was equal to the median of the total daily basal insulin doses in the last 3 days prior to the baseline visit.

Patients on NPH more than once daily prior to the baseline visit: the daily dose of for HOE901-U300 or Lantus (U) was to be approximately 20% less than the median of the total daily NPH insulin doses in the last 3 days prior to the baseline visit.

The basal insulin dose was adjusted once weekly to achieve fasting SMPG in the target range of 80 to 100 mg/dL (4.4 to 5.6 mmol/L):

- by + 3 U, if the median fasting SMPG of last 3 days was in the range of >100 mg/dL and <140 mg/dL (>5.6 and <7.8 mmol/L)
- by + 6 U, if the median fasting SMPG of last 3 days was ≥ 140 mg/dL (≥ 7.8 mmol/L)
- by - 3 U, if the median fasting SMPG of last 3 days was in the range of ≥ 60 mg/dL and <80 mg/dL (≥ 3.3 and <4.4 mmol/L).

Mealtime insulin doses were to be adjusted to optimize glycemic control after basal insulin doses have been optimized. Bolus insulin doses could be reduced as basal insulin doses were increased.

Noninvestigational medicinal products:
Patients in both treatment groups were to continue with their mealtime insulin analogue during the study. Patients on concomitant metformin treatment were to continue during the study on a stable dose as received prior to the study, unless safety concerns necessitated a dose reduction or discontinuation of metformin.

Duration of treatment: Up to 12 months

Duration of observation: up to 54 weeks (up to 2-week screening period + 6-month efficacy and safety period + 6-month safety extension period + 2-day safety follow-up).

The analysis period for efficacy and safety is the main 6-month on-treatment period. Results presented in the present KRM refer to this period.

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: change in HbA_{1c} from baseline to endpoint (Month 6).
Main secondary endpoints: incidence of patients (%) with at least one nocturnal hypoglycemia between start of Week 9 and endpoint (month 6), indicated as severe

and/or confirmed by plasma glucose ≤ 70 mg/dL (3.9 mmol/L); change in preinjection SMPG from baseline to endpoint (Month 6) and change in variability of preinjection SMPG from baseline to endpoint (Month 6).

Safety: Hypoglycemia, occurrence of adverse events particularly treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), injection site reactions and hypersensitivity reactions. Following information not presented in KRM: physical examination, other safety information including clinical laboratory data, vital signs (including body weight), 12-lead ECG and anti-insulin antibodies.

Statistical methods: The primary efficacy endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]) was analyzed using an analysis of covariance (ANCOVA) model with treatment, strata of screening HbA_{1c} (<8.0 and ≥ 8.0%), and country as fixed effects and using the HbA_{1c} baseline value as a covariate. Differences between HOE901-U300 and Lantus and two-sided 95% confidence intervals were estimated within the framework of ANCOVA.

A stepwise closed testing approach was used for the primary efficacy endpoint to assess non-inferiority and superiority sequentially. Step 1 assessed non inferiority of HOE901-U300 versus Lantus. To assess non-inferiority, the upper bound of the two sided 95% CI for the difference in the mean change in HbA1c from baseline to endpoint between HOE901-U300 and Lantus was compared with a predefined non inferiority margin of 0.4% for HbA1c. Non-inferiority would be demonstrated if the upper bound of the two-sided 95% CI of the difference between HOE901-U300 and Lantus on mITT population is <0.4%. Step 2 assessed superiority of HOE901-U300 versus Lantus only if non inferiority was demonstrated. The superiority of HOE901-U300 over Lantus was demonstrated if the upper bound of the two-sided 95%CI of the difference between HOE901-U300 and Lantus on mITT population was <0.

Only if non-inferiority of HOE901-U300 versus Lantus had been demonstrated for the primary endpoint, would testing for superiority of HOE901-U300 over Lantus on the

main secondary endpoints occur within the frame of a hierarchical testing procedure. Safety analyses were descriptive, based on the safety population.

Summary:

Population characteristics:

A total of 807 patients with type 2 diabetes were randomized to HOE901-U300 (n=404) or to Lantus (n=403); 806 patients were exposed to IMP (safety population). The mITT population (efficacy population) included 804 patients.

Overall, a comparable number of patients in each treatment group discontinued the study prematurely (HOE901-U300: 30/404, 7.4%; Lantus 31/403, 7.7%).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 60 years, 246/807 (30.4%) were ≥ 65 years. The mean BMI at baseline was 36.6 kg/m². The mean duration of diabetes prior to study start was 15.8 years, the mean duration of prior treatment with basal insulin was 6.6 years and the median total daily insulin dose was 1.1 U/kg body weight. In both treatment groups, mean HbA1c at baseline was 8.14%.

Efficacy results:

Primary endpoint: The LS mean change in HbA1c from baseline to endpoint (Month 6) was similar in both treatment groups (HOE901-U300: -0.83% (95% CI [-0.946;-0.709]); Lantus: -0.83% (95 %CI [-0.944;-0.706]). Non-inferiority of HOE901-U300 versus Lantus was demonstrated with the LS mean difference in HbA1c versus Lantus of -0.00% (95 % CI [-0.112; 0.107]) with the upper bound lower than the predefined non-inferiority margin of 0.4%. Superiority of HOE901-U300 versus Lantus was not demonstrated.

1st main secondary endpoint: The incidence of patients with at least one nocturnal severe and/or confirmed hypoglycemia between start of Week 9 and Month 6 was lower in the HOE901-U300 group [136/404 (33.7%)] than in the Lantus group [180/400 (45.0%)]. Superiority of HOE901-U300 versus Lantus was shown with a relative risk of 0.75 (95% CI [0.63, 0.89]) (p=0.0010).

2nd main secondary endpoint: The LS mean change in pre-injection SMPG from baseline to endpoint (Month 6) was similar in the HOE901-U300 (-0.90 mmol/L) and Lantus groups (-0.84 mmol/L). The difference between the treatment groups was not statistically significant (LS mean difference -0.06 (95% CI [-0.383, 0.255], p=0.6921).

3rd main secondary endpoint: As the superiority of HOE901-U300 versus Lantus was not demonstrated for the second main secondary endpoint, no further test was performed for the third main secondary endpoint (decrease in variability of pre-injection SMPG at Month 6, which was similar for both treatment groups).

Other secondary efficacy endpoints (Month 6): Both the proportion of patients having reached HbA1c <7% and the mean change in FPG were similar between treatment groups. Graphical presentation of the 8-point SMPG profiles of HOE901-U300- and Lantus-treated patients showed a marked decrease in plasma glucose at endpoint (Month 6) compared with baseline. The profiles of the 2 treatment groups are almost superimposable at both baseline and endpoint.

The increase of basal insulin dose in the HOE901-U300 group resulted in a mean daily dose of 103 U at Month 6 compared to Lantus group with a mean daily dose of 94 U (the mean basal insulin dose at baseline was 70 U in both treatment groups). The increase of the daily mealtime insulin dose was comparable between treatment groups with a small increase in the first two weeks. Thereafter, mealtime insulin doses remained stable.

Safety results:

Overall, hypoglycemia was reported by a consistently lower percentage of patients in the HOE901-U300 group than in the Lantus group. This difference was even more pronounced during the first 2 months of study treatment as well as for events of nocturnal hypoglycemia. During the main 6-month on-treatment period severe hypoglycemia was reported in 21/404 (5.2%) of HOE901-U300 treated patients and 23/402 (5.7%) of Lantus treated patients.

The percentages of patients with any TEAEs (HOE901-U300, 222/404 [55.0%]; Lantus: 215/402 [53.5%]) or with serious TEAEs (HOE901-U300, 25 [6.2%]; Lantus, 21 [5.2%]) were similar between both groups. A similar proportion of patients experienced serious cardiac TEAEs (SOC – cardiac disorders) in both treatment groups (HOE901-U300: n=5, 1.2%; Lantus: n=7; 1.7%).

Six patients died during the study, 3 (0.7%) in each treatment group. Of these, 4 patients died during the first 6 months, 2 (0.5%) in each treatment group. The events with fatal outcome in the three patients in the HOE901-U300 group included the following conditions: infected thrombosis and embolism in the heart, bronchogenic carcinoma with metastasis and - for the third patient - pulmonary emboli. The leading cause of the fatal events in the three patients in the Lantus group included: chronic depression and intoxication with medication, one patient had multitude of conditions including worsening of chronic heart failure (NYHA IV), chronic kidney failure stage 4 with acute decompensation, decompensated diabetes and diabetic nephropathy contributing to the fatal outcome and the last patient suffered acute cardiopulmonary arrest of unknown etiology. None of the deaths were considered related to study drug.

A similar number of patients in both treatment groups experienced TEAEs leading to permanent treatment discontinuation (HOE901-U300: n=6, 1.5%; Lantus: n=7, 1.7%).

Hypersensitivity reactions during the main 6-month on-treatment period were reported at a similar rate in both treatment groups (HOE901-U300: n=3, 0.7%; Lantus: n=2, 0.5%).

Overall injection site reactions during the main 6-month on-treatment period showed similar rate in both treatment groups (HOE901-U300: n=9, 2.2%; Lantus: n=6, 1.5%).

Conclusions:

In this study in 807 patients with T2DM on basal insulin in combination with mealtime insulin, the baseline characteristics and demographic characteristics were well balanced across treatment groups. Non-inferiority of HOE901-U300 versus Lantus was shown for the primary efficacy endpoint (change in HbA1c from baseline to endpoint [Month 6]). The incidence of patients (%) reporting nocturnal hypoglycemia (severe and/or confirmed by SMPG ≤ 70 mg/dL [3.9 mmol/L]) between start of Week 9 and Month 6 was significantly lower in the HOE901-U300 group than in the Lantus group (33.7% and 45% respectively, RR of 0.75, p-value 0.0010; 1st main secondary efficacy endpoint). Comparable results between the treatment groups were found for other secondary endpoints such as pre-injection plasma glucose, variability of pre-injection plasma glucose, number of patients reaching target HbA1c, mean change of FPG and 8-point profiles of plasma glucose.

Overall incidence of hypoglycemia (% of patients with at least one event) during the main 6-month on-treatment period was lower in the HOE901-U300 group than in the Lantus group regardless of the category of hypoglycemia.

HOE901-U300 was well tolerated during the main 6-month on-treatment period of the study and no specific safety concerns were observed.

Summary of the efficacy and safety results of the twelve month EDITION 1 extension study

- HbA1c: during the safety extension period (from the main study endpoint [Month 6] to the End of Treatment [Month 12]) HbA1c remained stable and was comparable in both treatment groups
- hypoglycemia: overall, similarly as during the main 6-month treatment period, during the whole study on-treatment period hypoglycemia occurred in a similar or lower percentage of patients in the HOE901-U300 group than in the Lantus group
- safety: HOE901-U300 was well tolerated during the study and no specific safety concerns were observed; during the whole treatment period, the percentages of patients with any TEAEs were similar in both groups (289/404 [71.5%] in the HOE901-U300 and 278/402 [69.2%] in the Lantus treatment group), with no specific SOC contributing. Serious TEAEs were reported by a similar number of patients: (53 [13.1%]) in the HOE901-U300 and 62 [15.4%] in the Lantus treatment group). Two (0.5%) patients in the HOE901-U300 and 4 (1.0%) patient in the Lantus treatment group had TEAE leading to death during the whole study on-treatment period
- body weight: in both treatment groups, during the whole study on-treatment period there was small increase in body weight (1.17 kg for HOE901-U300 and 1.40 kg for Lantus).

1 RESULTS

1.1 STUDY PATIENTS

1.1.1 Study disposition

Table 1 - Patient disposition - Randomized population

	HOE901-U300 (N=404)	Lantus (N=403)
Randomized and treated	404 (100%)	402 (99.8%)
Completed main 6-month treatment period	374 (92.6%)	371 (92.1%)
Permanently discontinued the treatment during the main 6-month period	30 (7.4%)	31 (7.7%)
Subject's request for treatment discontinuation	21 (5.2%)	20 (5.0%)

	HOE901-U300 (N=404)	Lantus (N=403)
Randomized and treated	404 (100%)	402 (99.8%)
Reason for treatment discontinuation during the main 6-month period		
Adverse event	9 (2.2%)	8 (2.0%)
Lack of efficacy	1 (0.2%)	1 (0.2%)
Poor compliance to protocol	2 (0.5%)	5 (1.2%)
Other reasons	18 (4.5%)	17 (4.2%)
Status at last study contact of patients who permanently discontinued the treatment during the main 6-month period		
Alive	27 (6.7%)	28 (6.9%)
Dead	3 (0.7%)	2 (0.5%)

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

Table 2 - Analysis populations

	HOE901-U300	Lantus	All
Randomized population	404 (100%)	403 (100%)	807 (100%)
Efficacy populations			
Modified Intent-to-Treat (mITT)	404 (100%)	400 (99.3%)	804 (99.6%)
Month 6 completers	374 (92.6%)	371 (92.1%)	745 (92.3%)
Safety population	404	402	806

Note: For the safety population, patients are tabulated according to treatment actually received (as treated)

For the other populations, patients are tabulated according to their randomized treatment

1.1.2 Demographics and baseline characteristics

Table 3 - Demographics and patient characteristics at baseline - Randomized population

	HOE901-U300 (N=404)	Lantus (N=403)	All (N=807)
Age (years)			
Number	404	403	807
Mean (SD)	60.1 (8.5)	59.8 (8.7)	60.0 (8.6)
Median	61.0	60.0	61.0
Min : Max	28 : 83	32 : 86	28 : 86
Age Group (years) [n(%)]			
Number	404	403	807
<65	277 (68.6%)	284 (70.5%)	561 (69.5%)
[65-75[	114 (28.2%)	105 (26.1%)	219 (27.1%)
≥ 75	13 (3.2%)	14 (3.5%)	27 (3.3%)
Gender [n (%)]			
Number	404	403	807
Male	217 (53.7%)	210 (52.1%)	427 (52.9%)
Female	187 (46.3%)	193 (47.9%)	380 (47.1%)
Race [n (%)]			
Number	404	403	807

	HOE901-U300 (N=404)	Lantus (N=403)	All (N=807)
Age (years)			
Caucasian/White	371 (91.8%)	374 (92.8%)	745 (92.3%)
Black	26 (6.4%)	21 (5.2%)	47 (5.8%)
Asian/Oriental	6 (1.5%)	5 (1.2%)	11 (1.4%)
Other	1 (0.2%)	3 (0.7%)	4 (0.5%)
Ethnicity [n (%)]			
Number	404	403	807
Hispanic	26 (6.4%)	25 (6.2%)	51 (6.3%)
Not Hispanic	378 (93.6%)	378 (93.8%)	756 (93.7%)
World region [n (%)]			
Number	404	403	807
Northern America	206 (51.0%)	207 (51.4%)	413 (51.2%)
Western Europe	33 (8.2%)	33 (8.2%)	66 (8.2%)
Eastern Europe	147 (36.4%)	141 (35.0%)	288 (35.7%)
Rest of the world	18 (4.5%)	22 (5.5%)	40 (5.0%)
Baseline weight (kg)			
Number	404	403	807
Mean (SD)	106.2 (21.5)	106.4 (20.0)	106.3 (20.8)
Median	104.3	104.1	104.1
Min : Max	60 : 197	62 : 164	60 : 197
Baseline BMI (kg/m^2)			
Number	404	403	807
Mean (SD)	36.6 (6.8)	36.6 (6.1)	36.6 (6.4)
Median	35.8	36.0	35.9
Min : Max	23 : 62	24 : 62	23 : 62
Baseline BMI categories (kg/m^2) [n(%)]			
Number	404	403	807
<25	5 (1.2%)	2 (0.5%)	7 (0.9%)
[25-30[	54 (13.4%)	47 (11.7%)	101 (12.5%)
[30-40[	241 (59.7%)	244 (60.5%)	485 (60.1%)
≥ 40	104 (25.7%)	110 (27.3%)	214 (26.5%)

	HOE901-U300 (N=404)	Lantus (N=403)	All (N=807)
Age (years)			
Baseline estimated GFR (mL/min/1.73m^2)			
Number	404	403	807
Mean (SD)	73.67 (19.32)	74.77 (21.38)	74.22 (20.37)
Median	73.62	75.63	74.41
Min : Max	19.9 : 144.2	15.0 : 141.5	15.0 : 144.2
Baseline estimated GFR categories (mL/min/1.73m^2) [n(%)]			
Number	404	403	807
≥ 90	75 (18.6%)	89 (22.1%)	164 (20.3%)
[60-90[	235 (58.2%)	221 (54.8%)	456 (56.5%)
[30-60[	92 (22.8%)	83 (20.6%)	175 (21.7%)
<30	2 (0.5%)	10 (2.5%)	12 (1.5%)
Randomization strata of screening HbA1c (%) [n(%)]			
Number	404	403	807
<8	144 (35.6%)	144 (35.7%)	288 (35.7%)
≥ 8	260 (64.4%)	259 (64.3%)	519 (64.3%)

BMI = Body Mass Index

GFR = Glomerular filtration rate

GFR is derived from MDRD formula

Table 4 - Summary of disease characteristics at baseline - Randomized population

	HOE901-U300 (N=404)	Lantus (N=403)	All (N=807)
Duration of T2D (years)			
Number	404	403	807
Mean (SD)	15.6 (7.2)	16.1 (7.8)	15.8 (7.5)
Median	15.2	15.2	15.2
Min : Max	2 : 43	2 : 44	2 : 44
Category of duration of T2D (years)			
Number	404	403	807
<10	90 (22.3%)	84 (20.8%)	174 (21.6%)

	HOE901-U300 (N=404)	Lantus (N=403)	All (N=807)
Duration of T2D (years)			
≥ 10	314 (77.7%)	319 (79.2%)	633 (78.4%)
Age at onset of T2D (years)			
Number	404	403	807
Mean (SD)	45.0 (8.8)	44.2 (9.5)	44.6 (9.2)
Median	44.9	44.4	44.7
Min : Max	18 : 78	15 : 73	15 : 78
Duration of basal insulin treatment (years)			
Number	404	403	807
Mean (SD)	6.71 (4.74)	6.48 (4.78)	6.59 (4.76)
Median	5.50	5.20	5.40
Min : Max	0.3 : 32.8	1.0 : 33.2	0.3 : 33.2
Previous basal insulin type [n(%)]			
Number	402	399	801
Insulin glargine	372 (92.5%)	365 (91.5%)	737 (92.0%)
NPH	30 (7.5%)	34 (8.5%)	64 (8.0%)
Previous basal insulin daily injection number[a] [n(%)]			
Number	403	399	802
Once daily	333 (82.6%)	334 (83.7%)	667 (83.2%)
Twice daily	70 (17.4%)	65 (16.3%)	135 (16.8%)
More than twice daily	0	0	0
Previous basal insulin daily dose[b] (U)			
Number	371	363	734
Mean (SD)	69.93 (30.42)	70.17 (28.31)	70.05 (29.38)
Median	60.00	60.00	60.00
Q1 : Q3	49.00 : 81.00	50.00 : 80.00	50.00 : 80.00
Min : Max	42.0 : 200.0	42.0 : 200.0	42.0 : 200.0
Previous basal insulin daily dose[b] (U/kg)			
Number	371	363	734
Mean (SD)	0.668 (0.264)	0.667 (0.240)	0.667 (0.252)
Median	0.598	0.609	0.601

	HOE901-U300 (N=404)	Lantus (N=403)	All (N=807)
Duration of T2D (years)			
Q1 : Q3	0.487 : 0.769	0.493 : 0.770	0.490 : 0.769
Min : Max	0.30 : 2.12	0.31 : 1.76	0.30 : 2.12
Previous mealtime insulin daily dose[b] (U)			
Number	396	397	793
Mean (SD)	57.11 (36.45)	58.42 (37.89)	57.77 (37.16)
Median	49.30	52.00	50.00
Q1 : Q3	32.00 : 72.80	31.70 : 75.00	32.00 : 73.70
Min : Max	5.0 : 350.0	3.6 : 280.0	3.6 : 350.0
Previous mealtime insulin daily dose[b] (U/kg)			
Number	396	397	793
Mean (SD)	0.537 (0.336)	0.540 (0.315)	0.538 (0.325)
Median	0.474	0.488	0.480
Q1 : Q3	0.332 : 0.670	0.329 : 0.687	0.330 : 0.685
Min : Max	0.06 : 3.08	0.03 : 2.30	0.03 : 3.08
Previous total insulin daily dose[b] (U)			
Number	366	361	727
Mean (SD)	126.00 (56.57)	127.78 (55.97)	126.88 (56.24)
Median	112.00	114.00	113.00
Q1 : Q3	88.00 : 149.10	87.00 : 154.90	87.90 : 152.00
Min : Max	47.0 : 530.0	52.4 : 384.0	47.0 : 530.0
Previous total insulin daily dose[b] (U/kg)			
Number	366	361	727
Mean (SD)	1.193 (0.484)	1.199 (0.447)	1.196 (0.465)
Median	1.085	1.101	1.096
Q1 : Q3	0.875 : 1.401	0.871 : 1.388	0.871 : 1.398
Min : Max	0.50 : 4.66	0.51 : 3.13	0.50 : 4.66
Prior use of Lantus[c]			
Number	404	403	807
Yes	373 (92.3%)	369 (91.6%)	742 (91.9%)
No	31 (7.7%)	34 (8.4%)	65 (8.1%)
Prior use of Metformin[c]			

	HOE901-U300 (N=404)	Lantus (N=403)	All (N=807)
Duration of T2D (years)			
Number	404	403	807
Yes	227 (56.2%)	234 (58.1%)	461 (57.1%)
No	177 (43.8%)	169 (41.9%)	346 (42.9%)

T2D = Type 2 diabetes

[a] Maximal injection number of the patient.

[b] Mean of the patient from the basal / mealtime / total daily doses during the last 7 days prior to randomization

[c] Taken within 3 months before screening

1.2 EFFICACY EVALUATION

1.2.1 Primary efficacy endpoint

Table 5 - Main efficacy analysis - Mean change in HbA1c (%) from baseline to Month 6 endpoint using LOCF procedure - mITT population (Figure 1)

HbA1c (%)	HOE901-U300 (N=404)	Lantus (N=400)
Baseline		
Number	391	394
Mean (SD)	8.14 (0.78)	8.14 (0.76)
Median	8.10	8.10
Min : Max	6.5 : 10.6	6.4 : 10.3
Month 6 endpoint (LOCF)		
Number	391	394
Mean (SD)	7.25 (0.85)	7.28 (0.92)
Median	7.10	7.20
Min : Max	5.3 : 10.6	5.2 : 13.8
Change from baseline to Month 6 endpoint (LOCF)		
Number	391	394
Mean (SD)	-0.88 (0.81)	-0.86 (0.92)
Median	-0.90	-0.90
Min : Max	-3.4 : 1.8	-3.1 : 4.6
LS Mean (SE) [a]	-0.83 (0.060)	-0.83 (0.061)
95% CI	(-0.946 to -0.709)	(-0.944 to -0.706)

HbA1c (%)	HOE901-U300 (N=404)	Lantus (N=400)
Baseline		
LS Mean difference (SE) vs. Lantus [a]	-0.00 (0.056)	
95% CI	(-0.112 to 0.107)	

LOCF = Last observation carried forward.

[a]Analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥ 8.0%), and country as fixed effects and baseline HbA1c value as a covariate.

1.2.2 Main secondary endpoints

1.2.2.1 Nocturnal hypoglycemia

Table 6 - First main secondary efficacy endpoint - Number (%) of patients with at least one nocturnal hypoglycemia [00:00 to 05:59] occurring between start of Week 9 and Month 6 endpoint (using LOCF procedure), indicated as severe and/or confirmed by plasma glucose ≤ 3.9 mmol/L (70 mg/dL) - mITT population

	HOE901-U300 (N=404)	Lantus (N=400)
Severe and/or confirmed nocturnal hypoglycemia [00:00 to 05:59]		
n (%)	136 (33.7%)	180 (45.0%)
RR (95% CI) vs. Lantus [a]	0.75 (0.63 to 0.89)	-
p-value (CMH)	0.0010	-

n(%) = number and percentage of patients with at least one nocturnal hypoglycemia event, indicated as severe and/or confirmed by plasma glucose ≤ 3.9 mmol/L (70 mg/dL)

[a]Based on RR stratified by randomization strata of screening HbA1c (<8.0 or ≥ 8.0 %), using a CMH methodology

1.2.2.2 Pre-injection plasma glucose - Month 6 endpoint

Table 7 - Second main secondary efficacy endpoint - Mean change in average pre-injection SMPG (mmol/L) from baseline to Month 6 endpoint using LOCF procedure - mITT population (Figure 2)

Average pre-injection SMPG (mmol/L)	HOE901-U300 (N=404)	Lantus (N=400)

Baseline		
Number	365	360
Mean (SD)	10.31 (2.58)	10.44 (2.65)
Median	10.02	9.98
Min : Max	4.4 : 20.6	5.6 : 20.8
Month 6 endpoint (LOCF)		
Number	365	360
Mean (SD)	9.11 (2.42)	9.28 (2.45)
Median	8.77	8.69
Min : Max	3.8 : 20.3	4.8 : 19.1
Change from baseline to Month 6 endpoint (LOCF)		
Number	365	360
Mean (SD)	-1.20 (2.84)	-1.16 (2.70)
Median	-1.19	-1.24
Min : Max	-13.2 : 8.9	-11.3 : 7.5
LS Mean (SE) [b]	-0.90 (0.183)	-0.84 (0.183)
95% CI	(-1.260 to -0.543)	(-1.196 to -0.478)
LS Mean difference (SE) vs. Lantus [b]	-0.06 (0.162)	
95% CI	(-0.383 to 0.255)	
p-value(ANCOVA)	0.6921	

LOCF = Last observation carried forward.

SMPG=Self Monioring Plasma Glucose

[a] Average is assessed by the mean of at least 3 SMPG calculated over the 7 days preceding the given visit.

[b] Analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥ 8.0%), and country as fixed effects and baseline average pre-injection SMPG value as a covariate.

At V1 (week-2), the investigator or a member of the investigational staff will provide patients with a blood glucometer and the corresponding supplies (needles, control solutions, test strips etc.) and with diaries in order to perform self-measurement of plasma glucose and its recording. Patients will be shown how to accurately measure plasma glucose values with the blood glucometer. The investigator or a member of the investigational staff will explain the need to measure glucose at the times requested for profiles and to correctly record the values in the patient diaries. Training is repeated as often as necessary at the study visits and the investigational staff reviews the patient's

diary at each visit. Blood glucose values will be measured by the patient using the sponsor-provided blood glucose meter. Patients will document their SMPG data in the diary.

The patients will be instructed to bring the blood glucometers provided by the sponsor with them to each office visit. The blood glucometers should be calibrated according to instructions given in the package leaflet and the investigational site should also check regularly the glucometers using the provided control solutions for data validity.

Starting with V1 (screening visit), the diary includes sections for recording by patients of

- **Study treatment and mealtime insulin**: time and dose of HOE901-U300 or Lantus injections (Lantus or NPH injections during screening period) and mealtime/bolus insulin analogue injections;

- **SMPG**: time and value of SMPG;
  1. Fasting SMPG in the morning (prebreakfast)
  2. SMPG within 30 minutes prior to injection of basal insulin during 7 days before each visit
  3. 4-point profile and 8-point profile SMPG
  4. SMPG related to hypoglycemic events
  5. Any other SMPG (whatever the reason of measurement)

SMPG measurements are scheduled as follows:

- ***Fasting plasma glucose (SMPG):*** The fasting (prebreakfast) SMPG will be measured daily throughout the study. During the week before visit 3 (Day 1, Baseline) compliance to the fasting SMPG measurement schedule will be used to assess eligibility for entry in the randomized treatment period. During the study, when uptitration has been completed and fasting (prebreakfast) SMPG is stable in the target range, at least of 3 measurements per week should be performed.
- ***Plasma glucose within 30 minutes prior to injection of study drug (preinjection SMPG)***: Preinjection SMPG will be done within 30 min prior to the

injection of the IMP (HOE901-U300 or Lantus) on at least 7 days before baseline and before each on site visit throughout the study. At days when 4-point or 8-point profiles are done: if time of preinjection SMPG is the same as a time point of the 4-point or 8-point profile, the SMPG value has to be assigned by the patient in the diary to both (eg, preinjection PG; bedtime).

- ***4-point SMPG profiles (prebreakfast, prelunch, predinner, bedtime):*** During the week before baseline visit and during the first 12 weeks of treatment with IMP, patients will perform 4-point SMPG profiles at least on 3 days per week. Once the titration goal is reached, the number of 4-point SMPG profiles can be reduced according to the investigator's judgment but 4-point SMPG profiles at least on 3 days in the week before each visit are mandatory. It is, however, recommended to perform 4-point SMPG profiles daily throughout the study for optimal adjustment of the insulin regimen;
- ***8-point blood glucose profiles (starting with a measurement at 03:00 am at night; before and 2 hours after breakfast; before and 2 hours after lunch; before and 2 hours after dinner; at bedtime):*** Patients will perform 8-point SMPG profiles at least one day in the 5 days before each on-site visit. It is, however, recommended to perform 8-point SMPG profiles at least once weekly up to week 8, and once every second week thereafter. Special attention should be paid that the 3.00 a.m. SMPG value is recorded.
- **SMPG during episodes of symptomatic hypoglycemia:** Whenever the patients feel hypoglycemic symptoms, plasma glucose should be measured by the patient (or others, if applicable), if possible. Patients should be instructed to measure plasma glucose levels prior to the administration of glucose or carbohydrate intake whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose/carbohydrate rescue prior to confirmation.

The following SMPG values have to be copied into the eCRF:

During the week prior to baseline visit and during the first 12 weeks until Visit 8 (week 12):

- Fasting (prebreakfast) SMPG: daily
- Preinjection SMPG (within 30 minutes prior to injection of the basal insulin): at 7 days prior to each on-site visit

- 4-point profile SMPG: at 3 different days in each week until visit 8 (week 12)
- 8-point profile SMPG: 1 profile within 5 days before each on-site visit
- SMPG related to hypoglycemic event: whenever documented

Note: following phone call visits the following data at the minimum will be entered into the e-CRF: fasting (prebreakfast) SMPG over last 3 days, SMPG related to hypoglycemic event: whenever documented. The remaining SMPG data of the week prior to the phone call visits will be entered into the e-CRF at a subsequent on-site visit.

After Visit 8 (week 12):

- Fasting (prebreakfast) SMPG: during 7 days before each on-site visit
- Preinjection SMPG (within 30 minutes prior to injection of the basal insulin): at 7 days prior to each on-site visit
- 4-point profile SMPG: at 3 different days within 7 days before each on-site visit
- 8-point profile SMPG: at one day within 5 days before each on-site visit
- SMPG related to hypoglycemic event: whenever documented

All glucose values will be used by the investigator to monitor glycemia.

1.2.2.3 Variability of preinjection SMPG - Month 6 endpoint

Table 8 - Third main secondary efficacy endpoint - Mean change in variability of pre-injection SMPG from baseline to Month 6 endpoint using LOCF procedure - mITT population

Variability of pre-injection SMPG	HOE901-U300 (N=404)	Lantus (N=400)
Baseline		
Number	365	360
Mean (SD)	25.55 (12.41)	24.97 (11.82)
Median	23.92	24.34
Min : Max	0.0 : 82.8	1.7 : 74.3
Month 6 endpoint (LOCF)		
Number	365	360
Mean (SD)	22.23 (11.76)	21.57 (11.47)
Median	21.79	20.42
Min : Max	0.0 : 60.3	0.9 : 64.1
Change from baseline to Month 6 endpoint (LOCF)		

Variability of pre-injection SMPG	HOE901-U300 (N=404)	Lantus (N=400)
Baseline		
Number	365	360
Mean (SD)	-3.32 (14.59)	-3.40 (14.54)
Median	-2.88	-3.17
Min : Max	-62.5 : 48.1	-54.7 : 41.7
LS Mean (SE) [a]	-1.09 (1.222)	-1.11 (1.222)
95% CI	(-3.486 to 1.310)	(-3.508 to 1.292)
LS Mean difference (SE) vs. Lantus [a]	0.02 (1.087)	
95% CI	(-2.114 to 2.154)	

LOCF = Last observation carried forward.

SMPG=Self Monitoring Plasma Glucose

Variability is assessed by the mean of coefficient of variation calculated over at least 3 SMPG measured during the 7 days preceding the given visit

[a]Analysis of variance (ANOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥ 8.0%), and country as fixed effects

1.2.3 Other secondary efficacy endpoints

1.2.3.1 Percentage of patients with HbA1c <7% at Month 6

Table 9 - Other secondary efficacy endpoint - Number (%) of patients with HbA1c < 7% at Month 6 endpoint (using LOCF procedure) and Number (%) of patients with HbA1c < 7% at Month 6 endpoint (using LOCF procedure) having experienced no hypoglycemia indicated as severe and/or confirmed by plasma glucose < 3 mmol/L (54 mg/dL) during the last 3 months of the main 6-month treatment period – mITT population

	HOE901-U300 (N=404)	Lantus (N=400)
HbA1c < 7%		
Number	391	394
n (%)	155 (39.6%)	161 (40.9%)
RR (95% CI) vs. Lantus [a]	0.97 (0.83 to 1.14)	-
HbA1c < 7% and no severe and/or confirmed (<3.0 mmol/L;<54mg/dL) hypoglycemia		
Number	393	394

	HOE901-U300 (N=404)	Lantus (N=400)
HbA1c < 7%		
n (%)	99 (25.2%)	95 (24.1%)
RR (95% CI) vs. Lantus [a]	1.05 (0.82 to 1.33)	-

LOCF = Last observation carried forward.

RR=relative risk

[a] Based on RR stratified by randomization strata of screening HbA1c (<8.0 or ≥ 8.0 %), using a CMH methodology

1.2.3.2 Change in FPG from baseline to Month 6 endpoint

Table 10 - Other secondary efficacy endpoint - Mean change in FPG (mmol/L) from baseline to Month 6 endpoint using LOCF procedure - mITT population

FPG(mmol/L)	HOE901-U300 (N=404)	Lantus (N=400)
Baseline		
Number	378	385
Mean (SD)	8.72 (2.83)	8.90 (2.94)
Median	8.40	8.60
Min : Max	2.3 : 19.2	2.4 : 20.8
Month 6 endpoint (LOCF)		
Number	378	385
Mean (SD)	7.25 (2.56)	7.21 (2.40)
Median	6.80	6.90
Min : Max	2.4 : 18.2	2.7 : 17.6
Change from baseline to Month 6 endpoint (LOCF)		
Number	378	385
Mean (SD)	-1.47 (3.10)	-1.69 (3.21)
Median	-1.40	-1.70
Min : Max	-13.7 : 11.3	-12.5 : 9.0
LS Mean (SE) [a]	-1.29 (0.191)	-1.39 (0.191)
95% CI	(-1.661 to -0.910)	(-1.763 to -1.012)
LS Mean difference (SE) vs. Lantus [a]	0.10 (0.171)	
95% CI	(-0.234 to 0.437)	

FPG(mmol/L)	HOE901-U300 (N=404)	Lantus (N=400)
Baseline		
FPG=Fasting Plasma Glucose		
LOCF = Last observation carried forward.		
[a]Analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥8.0%), and country as fixed effects and baseline FPG value as a covariate.		

1.2.3.3 Eight-point SMPG profile

Figure 3 describes the mean 8-point SMPG profile (mmol/l) at baseline and Month 6 endpoint - mITT population

1.2.3.4 Basal and mealtime insulin dose

Figure 4 describes the average daily basal insulin and mealtime insulin dose (U) by visit during the main 6-month on-treatment period - mITT population

1.3 SAFETY EVALUATION

1.3.1 Extent of exposure

Table 11 - Exposure to investigational product for the main 6-month on-treatment period - Safety population

	HOE901-U300 (N=404)	Lantus (N=402)
Cumulative exposure to main 6-month treatment (patient years)	194.7	193.3
Duration of main 6-month study treatment (days)		
Number	404	401
Mean (SD)	176.0 (29.8)	176.0 (30.0)
Median	183.0	183.0
Min : Max	6 : 199	5 : 216
Duration of main 6-month study treatment by category [n(%)]		

	HOE901-U300 (N=404)	Lantus (N=402)
Cumulative exposure to main 6-month treatment (patient years)	194.7	193.3
up to 2 weeks	2 (0.5%)	5 (1.2%)
>2 to 4 weeks	3 (0.7%)	3 (0.7%)
>4 to 8 weeks	8 (2.0%)	2 (0.5%)
>8 to 12 weeks	5 (1.2%)	6 (1.5%)
>12 to 17 weeks	2 (0.5%)	3 (0.7%)
>17 to 26 weeks	129 (31.9%)	122 (30.4%)
>26 weeks	255 (63.1%)	260 (64.8%)
Cumulative duration of main 6-month study treatment by category [n(%)]		
≥ 1 days	404 (100%)	401 (100%)
>2 weeks	402 (99.5%)	396 (98.8%)
>4 weeks	399 (98.8%)	393 (98.0%)
>8 weeks	391 (96.8%)	391 (97.5%)
>12 weeks	386 (95.5%)	385 (96.0%)
>17 weeks	384 (95.0%)	382 (95.3%)
>26 weeks	255 (63.1%)	260 (64.8%)

Note: Patients are considered in the treatment group they actually received at randomization

1.3.2 Hypoglycemia

Table 12 Number (%) of patients with at least one emergent hypoglycemia event during the main 6-month on-treatment period – Safety population

	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)	
Type of hypoglycemia event n(%)	**HOE901-U300 (N=404)**	**Lantus (N=402)**	**HOE901-U300 (N=404)**	**Lantus (N=402)**
Any hypoglycemia event	336 (83.2%)	356 (88.6%)	183 (45.3%)	238 (59.2%)
Severe hypoglycemia	21 (5.2%)	23 (5.7%)	8 (2.0%)	10 (2.5%)
Documented symptomatic hypoglycemia ≤ 3.9 mmol/L (70 mg/dL)	282 (69.8%)	312 (77.6%)	145 (35.9%)	193 (48.0%)

Type of hypoglycemia event n(%)	All hypoglycemia HOE901-U300 (N=404)	All hypoglycemia Lantus (N=402)	Nocturnal hypoglycemia (00:00-05:59) HOE901-U300 (N=404)	Nocturnal hypoglycemia (00:00-05:59) Lantus (N=402)
Any hypoglycemia event	336 (83.2%)	356 (88.6%)	183 (45.3%)	238 (59.2%)
< 3.0 mmol/L (54 mg/dL)	157 (38.9%)	171 (42.5%)	55 (13.6%)	73 (18.2%)
Asymptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	255 (63.1%)	271 (67.4%)	84 (20.8%)	100 (24.9%)
< 3.0 mmol/L (54 mg/dL)	70 (17.3%)	73 (18.2%)	9 (2.2%)	15 (3.7%)
Probable symptomatic hypoglycemia	18 (4.5%)	28 (7.0%)	6 (1.5%)	9 (2.2%)
Relative hypoglycemia				
> 3.9 mmol/L (70 mg/dL)	56 (13.9%)	76 (18.9%)	15 (3.7%)	33 (8.2%)
Severe and/or confirmed[a] hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	329 (81.4%)	352 (87.6%)	180 (44.6%)	229 (57.0%)
< 3.0 mmol/L (54 mg/dL)	185 (45.8%)	202 (50.2%)	65 (16.1%)	84 (20.9%)

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

[a] Confirmed hypoglycemia = documented symptomatic hypoglycemia or asymptomatic hypoglycemia

Hypoglycemia events are categorized as follows (American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes. Diabetes Care 2005;28:1245-49):

Severe hypoglycemia

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma

glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others.

Note that "requires assistance" means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a "requires assistance" incident.

Severe symptomatic hypoglycemia will be qualified as an SAE only if it fulfills SAE criteria. All events of seizure, unconsciousness or coma must be reported as SAEs.

Documented symptomatic hypoglycemia

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L) (American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes. Diabetes Care 2005;28:1245-49).

Clinical symptoms that are considered to result from a hypoglycemic episode are, eg, increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, coma.

Asymptomatic hypoglycemia

Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L);

Probable symptomatic hypoglycemia

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

Relative hypoglycemia

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

Nocturnal hypoglycemia

Nocturnal hypoglycemia is any hypoglycemia of the above categories that occurs between 00:00 and 05:59 hours. Note: Relative nocturnal hypoglycemia will not be included in the analysis of the main secondary endpoint (patients with at least one nocturnal hypoglycemia).

In addition of the threshold of less than or equal to 70 mg/dL (3.9 mmol/L), hypoglycemia episodes with a plasma glucose of <54 mg/dL (3.0 mmol/L) will be analyzed separately (Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus. Draft. EMA, 20 January 2010).

The classification of hypoglycemia will be done on basis of the clock time: Hypoglycemia episodes will be analyzed by their diurnal distribution (0:00-24:00) and in addition by time of the day:

- nocturnal hypoglycemia defined by time of the day: any hypoglycemia of the above categories that occurs between 00:00 and 05:59 a.m. hours, regardless whether patient was awake or woke up because of the event);
- daytime hypoglycemia: any hypoglycemia of the above categories that occurs between 6:00 a.m. and 23:59.

Patients will be instructed to measure finger stick plasma glucose levels prior to the administration of carbohydrates whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose rescue prior to confirmation, and then a glucose measurement should be performed as soon as safe, with appropriate diary documentation.

Details on hypoglycemia episodes will be captured in the patient diaries, and patients will contact the sites as soon as possible following severe events to review the details and decide on any necessary measures to be taken.

All hypoglycemia episodes will be documented on the “hypoglycemia specific form” in the e-CRF. This includes all symptomatic hypoglycemia events and asymptomatic hypoglycemia. Hypoglycemia events fulfilling the criteria of a SAE will be documented on the SAE form in the e-CRF.

Incidences of hypoglycemia per patient year will be computed per patient as: 365.25 x (number of episodes of hypoglycemia)/(number of days exposed) and summarized by type of event and treatment group.

Table 13 Number (%) of patients with at least one emergent hypoglycemia event during the main 6-month on-treatment period by study period - Safety population

Type of hypoglycemia event n(%)	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)	
	HOE901-U300 (N=404)	Lantus (N=402)	HOE901-U300 (N=404)	Lantus (N=402)
Any hypoglycemia event				
Overall	336 (83.2%)	356 (88.6%)	183 (45.3%)	238 (59.2%)
Treatment Start to Week 8	275 (68.1%)	310 (77.1%)	112 (27.7%)	153 (38.1%)
After Week 8 to Month 6	298 (73.8%)	304 (75.6%)	140 (34.7%)	181 (45.0%)
Severe hypoglycemia				
Overall	21 (5.2%)	23 (5.7%)	8 (2.0%)	10 (2.5%)
Treatment Start to Week 8	7 (1.7%)	12 (3.0%)	3 (0.7%)	3 (0.7%)
After Week 8 to Month 6	19 (4.7%)	13 (3.2%)	5 (1.2%)	7 (1.7%)
Documented symptomatic hypoglycemia ≤ 3.9 mmol/L (70 mg/dL)				
Overall	282 (69.8%)	312 (77.6%)	145 (35.9%)	193 (48.0%)
Treatment Start to Week 8	210 (52.0%)	250 (62.2%)	79 (19.6%)	109 (27.1%)
After Week 8 to Month 6	242 (59.9%)	242 (60.2%)	108 (26.7%)	146 (36.3%)
< 3.0 mmol/L (54 mg/dL)				
Overall	157 (38.9%)	171 (42.5%)	55 (13.6%)	73 (18.2%)
Treatment Start to Week 8	96 (23.8%)	113 (28.1%)	31 (7.7%)	39 (9.7%)
After Week 8 to Month 6	119 (29.5%)	115 (28.6%)	40 (9.9%)	47 (11.7%)
Asymptomatic hypoglycemia ≤ 3.9 mmol/L (70 mg/dL)				
Overall	255 (63.1%)	271 (67.4%)	84 (20.8%)	100 (24.9%)
Treatment Start to Week 8	187 (46.3%)	210 (52.2%)	44 (10.9%)	60 (14.9%)
After Week 8 to Month 6	203 (50.2%)	206 (51.2%)	57 (14.1%)	64 (15.9%)
< 3.0 mmol/L (54 mg/dL)				
Overall	70 (17.3%)	73 (18.2%)	9 (2.2%)	15 (3.7%)
Treatment Start to Week 8	34 (8.4%)	39 (9.7%)	6 (1.5%)	10 (2.5%)
After Week 8 to Month 6	52 (12.9%)	46 (11.4%)	4 (1.0%)	6 (1.5%)
Severe and/or confirmed[a] hypoglycemia ≤ 3.9 mmol/L (70 mg/dL)				

Type of hypoglycemia event n(%)	All hypoglycemia HOE901-U300 (N=404)	All hypoglycemia Lantus (N=402)	Nocturnal hypoglycemia (00:00-05:59) HOE901-U300 (N=404)	Nocturnal hypoglycemia (00:00-05:59) Lantus (N=402)
Any hypoglycemia event				
Overall	329 (81.4%)	352 (87.6%)	180 (44.6%)	229 (57.0%)
Treatment Start to Week 8	269 (66.6%)	299 (74.4%)	107 (26.5%)	139 (34.6%)
After Week 8 to Month 6	295 (73.0%)	303 (75.4%)	135 (33.4%)	180 (44.8%)
< 3.0 mmol/L (54 mg/dL)				
Overall	185 (45.8%)	202 (50.2%)	65 (16.1%)	84 (20.9%)
Treatment Start to Week 8	117 (29.0%)	131 (32.6%)	38 (9.4%)	48 (11.9%)
After Week 8 to Month 6	148 (36.6%)	146 (36.3%)	44 (10.9%)	51 (12.7%)

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

[a] Confirmed hypoglycemia = documented symptomatic hypoglycemia or asymptomatic hypoglycemia

1.3.3 Treatment-emergent adverse events

Table 14 - Treatment emergent adverse events during the main 6-month on-treatment period - Safety population

n (%)	HOE901-U300 (N=404)	Lantus (N=402)
Patients with any TEAE	222 (55.0%)	215 (53.5%)
Patients with any treatment emergent SAE	25 (6.2%)	21 (5.2%)
Patients with any TEAE leading to death	1 (0.2%)	2 (0.5%)
Patients with any TEAE leading to permanent treatment discontinuation	6 (1.5%)	7 (1.7%)

TEAE: Treatment emergent adverse event, SAE: Serious Adverse Event

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

Table 15 - Number (%) of patients with TEAE(s) that occurred with HLT ≥ 2% in any treatment group by Primary SOC, HLT and PT for the main 6-month on-treatment period - Safety population

PRIMARY SYSTEM ORGAN CLASS HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=404)	Lantus (N=402)
Any class	222 (55.0%)	215 (53.5%)
INFECTIONS AND INFESTATIONS	115 (28.5%)	121 (30.1%)
HLT: Abdominal and gastrointestinal infections	6 (1.5%)	12 (3.0%)
Abdominal wall abscess	1 (0.2%)	0
Diverticulitis	0	3 (0.7%)
Enteritis infectious	1 (0.2%)	0
Gastroenteritis	4 (1.0%)	9 (2.2%)
HLT: Ear infections	3 (0.7%)	9 (2.2%)
Ear infection	2 (0.5%)	6 (1.5%)
Otitis externa	1 (0.2%)	1 (0.2%)
Otitis media	0	2 (0.5%)
HLT: Influenza viral infections	8 (2.0%)	9 (2.2%)
Influenza	8 (2.0%)	9 (2.2%)
HLT: Lower respiratory tract and lung infections	18 (4.5%)	24 (6.0%)
Bronchitis	14 (3.5%)	19 (4.7%)
Bronchopneumonia	1 (0.2%)	1 (0.2%)
Lower respiratory tract infection	1 (0.2%)	0
Pneumonia	2 (0.5%)	4 (1.0%)
HLT: Upper respiratory tract infections	56 (13.9%)	51 (12.7%)
Acute sinusitis	0	3 (0.7%)
Acute tonsillitis	0	1 (0.2%)
Chronic tonsillitis	1 (0.2%)	0
Laryngitis	0	2 (0.5%)
Nasopharyngitis	19 (4.7%)	17 (4.2%)
Pharyngitis	3 (0.7%)	2 (0.5%)
Rhinitis	1 (0.2%)	0
Sinusitis	11 (2.7%)	10 (2.5%)
Upper respiratory tract infection	23 (5.7%)	19 (4.7%)
HLT: Urinary tract infections	10 (2.5%)	12 (3.0%)
Cystitis	2 (0.5%)	3 (0.7%)
Kidney infection	0	1 (0.2%)
Pyelonephritis	0	1 (0.2%)
Pyelonephritis acute	0	1 (0.2%)

PRIMARY SYSTEM ORGAN CLASS HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=404)	Lantus (N=402)
Urinary tract infection	8 (2.0%)	6 (1.5%)
HLT: Viral infections NEC	13 (3.2%)	12 (3.0%)
Bronchitis viral	1 (0.2%)	0
Gastroenteritis viral	7 (1.7%)	5 (1.2%)
Pneumonia viral	0	1 (0.2%)
Respiratory tract infection viral	1 (0.2%)	2 (0.5%)
Viral infection	3 (0.7%)	2 (0.5%)
Viral rhinitis	0	2 (0.5%)
Viral upper respiratory tract infection	3 (0.7%)	1 (0.2%)
NERVOUS SYSTEM DISORDERS	42 (10.4%)	40 (10.0%)
HLT: Headaches NEC	13 (3.2%)	11 (2.7%)
Headache	12 (3.0%)	10 (2.5%)
Sinus headache	1 (0.2%)	2 (0.5%)
VASCULAR DISORDERS	12 (3.0%)	13 (3.2%)
HLT: Vascular hypertensive disorders NEC	8 (2.0%)	10 (2.5%)
Hypertension	8 (2.0%)	10 (2.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	32 (7.9%)	32 (8.0%)
HLT: Breathing abnormalities	10 (2.5%)	4 (1.0%)
Dyspnoea	6 (1.5%)	2 (0.5%)
Dyspnoea exertional	3 (0.7%)	2 (0.5%)
Hyperventilation	1 (0.2%)	0
HLT: Upper respiratory tract signs and symptoms	10 (2.5%)	7 (1.7%)
Dysphonia	1 (0.2%)	0
Nasal discomfort	0	1 (0.2%)
Oropharyngeal pain	5 (1.2%)	5 (1.2%)
Rhinorrhoea	2 (0.5%)	1 (0.2%)
Throat irritation	1 (0.2%)	0
Upper respiratory tract congestion	1 (0.2%)	0
GASTROINTESTINAL DISORDERS	54 (13.4%)	48 (11.9%)
HLT: Diarrhoea (excl infective)	15 (3.7%)	15 (3.7%)
Diarrhoea	15 (3.7%)	15 (3.7%)
HLT: Nausea and vomiting symptoms	18 (4.5%)	18 (4.5%)

PRIMARY SYSTEM ORGAN CLASS ***HLT: High Level Term*** **Preferred Term n(%)**	**HOE901-U300** **(N=404)**	***Lantus*** **(N=402)**
Nausea	15 (3.7%)	11 (2.7%)
Vomiting	5 (1.2%)	10 (2.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	54 (13.4%)	61 (15.2%)
HLT: Joint related signs and symptoms	11 (2.7%)	16 (4.0%)
Arthralgia	8 (2.0%)	14 (3.5%)
Joint range of motion decreased	0	2 (0.5%)
Joint swelling	3 (0.7%)	0
HLT: Musculoskeletal and connective tissue pain and discomfort	22 (5.4%)	27 (6.7%)
Back pain	9 (2.2%)	14 (3.5%)
Flank pain	1 (0.2%)	0
Musculoskeletal chest pain	1 (0.2%)	2 (0.5%)
Musculoskeletal pain	5 (1.2%)	4 (1.0%)
Pain in extremity	7 (1.7%)	10 (2.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	42 (10.4%)	34 (8.5%)
HLT: Asthenic conditions	12 (3.0%)	8 (2.0%)
Asthenia	1 (0.2%)	1 (0.2%)
Fatigue	10 (2.5%)	6 (1.5%)
Malaise	1 (0.2%)	1 (0.2%)
HLT: Injection site reactions	9 (2.2%)	6 (1.5%)
Injection site discomfort	1 (0.2%)	0
Injection site erythema	0	1 (0.2%)
Injection site haematoma	4 (1.0%)	3 (0.7%)
Injection site haemorrhage	0	2 (0.5%)
Injection site induration	0	1 (0.2%)
Injection site pain	4 (1.0%)	0
Injection site pruritus	1 (0.2%)	0
HLT: Oedema NEC	15 (3.7%)	14 (3.5%)
Generalised oedema	1 (0.2%)	0
Oedema peripheral	14 (3.5%)	14 (3.5%)

TEAE: Treatment emergent adverse event, SOC: System organ class, HLT: High level term, PT: Preferred term MedDRA 15.1

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

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

Only HLT with at least one <HLT ≥ 2%> in at least one group are presented

1.3.4 Deaths, serious treatment-emergent adverse events

1.3.4.1 Death

Table 16 - Number (%) of patients who died by study period (on study, on-treatment, post-study)- Safety population

	HOE901-U300 (N=404)	Lantus (N=402)
Death on-study[a]	3 (0.7%)	3 (0.7%)
Death on-study during first 6 months	2 (0.5%)	2 (0.5%)
Death on-treatment[b]	0	2 (0.5%)
Death post-study[c]	0	0

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

[a] Includes all deaths that occurred after the start of treatment up to end of study (defined as last protocol planned visit or the resolution/stabilization of all treatment emergent SAE and adverse event of pre-specified monitoring)

[b] On-treatment is main 6-month on-treatment period

[c] Includes deaths that occurred after the end of the study (as defined in footnote a) and reported in the database

1.3.4.2 Serious adverse events

Table 17 - Number (%) of patients with treatment emergent SAEs by Primary SOC, HLGT, HLT and PT for the main 6-month on-treatment period - Safety population

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=404)	Lantus (N=402)
Any class	25 (6.2%)	21 (5.2%)
INFECTIONS AND INFESTATIONS	7 (1.7%)	5 (1.2%)
HLGT: Bacterial infectious disorders	1 (0.2%)	1 (0.2%)
HLT: Bacterial infections NEC	0	1 (0.2%)
Cellulitis	0	1 (0.2%)
HLT: Streptococcal infections	1 (0.2%)	0
Erysipelas	1 (0.2%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=404)	Lantus (N=402)
Any class	25 (6.2%)	21 (5.2%)
HLGT: Infections - pathogen unspecified	6 (1.5%)	5 (1.2%)
HLT: Abdominal and gastrointestinal infections	0	1 (0.2%)
Diverticulitis	0	1 (0.2%)
HLT: Bone and joint infections	2 (0.5%)	1 (0.2%)
Osteomyelitis	2 (0.5%)	1 (0.2%)
HLT: Cardiac infections	1 (0.2%)	0
Endocarditis	1 (0.2%)	0
HLT: Infections NEC	1 (0.2%)	0
Groin abscess	1 (0.2%)	0
HLT: Lower respiratory tract and lung infections	2 (0.5%)	2 (0.5%)
Bronchitis	1 (0.2%)	0
Bronchopneumonia	1 (0.2%)	0
Pneumonia	0	2 (0.5%)
HLT: Sepsis, bacteraemia, viraemia and fungaemia NEC	1 (0.2%)	1 (0.2%)
Sepsis	1 (0.2%)	1 (0.2%)
Septic embolus	1 (0.2%)	0
HLT: Urinary tract infections	0	1 (0.2%)
Pyelonephritis acute	0	1 (0.2%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	3 (0.7%)	1 (0.2%)
HLGT: Breast neoplasms malignant and unspecified (incl nipple)	1 (0.2%)	0
HLT: Breast and nipple neoplasms malignant	1 (0.2%)	0
Breast cancer	1 (0.2%)	0
HLGT: Leukaemias	0	1 (0.2%)
HLT: Leukaemias chronic myeloid	0	1 (0.2%)
Chronic myeloid leukaemia	0	1 (0.2%)
HLGT: Reproductive neoplasms male malignant and unspecified	1 (0.2%)	0
HLT: Prostatic neoplasms malignant	1 (0.2%)	0
Prostate cancer	1 (0.2%)	0
HLGT: Respiratory and mediastinal neoplasms malignant and unspecified	1 (0.2%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=404)	Lantus (N=402)
Any class	25 (6.2%)	21 (5.2%)
HLT: Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	1 (0.2%)	0
Metastatic bronchial carcinoma	1 (0.2%)	0
METABOLISM AND NUTRITION DISORDERS	1 (0.2%)	3 (0.7%)
HLGT: Electrolyte and fluid balance conditions	0	1 (0.2%)
HLT: Potassium imbalance	0	1 (0.2%)
Hyperkalaemia	0	1 (0.2%)
HLGT: Glucose metabolism disorders (incl diabetes mellitus)	1 (0.2%)	2 (0.5%)
HLT: Diabetes mellitus (incl subtypes)	0	1 (0.2%)
Diabetes mellitus inadequate control	0	1 (0.2%)
HLT: Hypoglycaemic conditions NEC	1 (0.2%)	1 (0.2%)
Hypoglycaemia	1 (0.2%)	1 (0.2%)
PSYCHIATRIC DISORDERS	0	1 (0.2%)
HLGT: Depressed mood disorders and disturbances	0	1 (0.2%)
HLT: Depressive disorders	0	1 (0.2%)
Depression	0	1 (0.2%)
NERVOUS SYSTEM DISORDERS	3 (0.7%)	2 (0.5%)
HLGT: Central nervous system vascular disorders	1 (0.2%)	0
HLT: Transient cerebrovascular events	1 (0.2%)	0
Transient ischaemic attack	1 (0.2%)	0
HLGT: Neurological disorders NEC	2 (0.5%)	1 (0.2%)
HLT: Disturbances in consciousness NEC	2 (0.5%)	1 (0.2%)
Hypoglycaemic unconsciousness	2 (0.5%)	0
Syncope	0	1 (0.2%)
HLGT: Peripheral neuropathies	0	1 (0.2%)
HLT: Acute polyneuropathies	0	1 (0.2%)
Guillain-Barre syndrome	0	1 (0.2%)
CARDIAC DISORDERS	5 (1.2%)	7 (1.7%)
HLGT: Cardiac arrhythmias	1 (0.2%)	2 (0.5%)

PRIMARY SYSTEM ORGAN CLASS **HLGT: High Level Group Term** **HLT: High Level Term** **Preferred Term n(%)**	**HOE901-U300** **(N=404)**	**Lantus** **(N=402)**
Any class	25 (6.2%)	21 (5.2%)
HLT: Cardiac conduction disorders	0	1 (0.2%)
Bundle branch block left	0	1 (0.2%)
HLT: Supraventricular arrhythmias	0	1 (0.2%)
Atrial fibrillation	0	1 (0.2%)
HLT: Ventricular arrhythmias and cardiac arrest	1 (0.2%)	0
Ventricular tachycardia	1 (0.2%)	0
HLGT: Cardiac valve disorders	0	1 (0.2%)
HLT: Aortic valvular disorders	0	1 (0.2%)
Aortic valve stenosis	0	1 (0.2%)
HLGT: Coronary artery disorders	4 (1.0%)	3 (0.7%)
HLT: Coronary artery disorders NEC	2 (0.5%)	1 (0.2%)
Coronary artery disease	2 (0.5%)	1 (0.2%)
HLT: Ischaemic coronary artery disorders	2 (0.5%)	2 (0.5%)
Acute coronary syndrome	1 (0.2%)	0
Angina pectoris	0	1 (0.2%)
Myocardial ischaemia	1 (0.2%)	1 (0.2%)
HLGT: Heart failures	0	2 (0.5%)
HLT: Heart failures NEC	0	2 (0.5%)
Cardiac failure	0	1 (0.2%)
Cardiac failure chronic	0	1 (0.2%)
VASCULAR DISORDERS	0	1 (0.2%)
HLGT: Arteriosclerosis, stenosis, vascular insufficiency and necrosis	0	1 (0.2%)
HLT: Aortic necrosis and vascular insufficiency	0	1 (0.2%)
Aortic stenosis	0	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.2%)	0
HLGT: Respiratory disorders NEC	1 (0.2%)	0
HLT: Breathing abnormalities	1 (0.2%)	0
Dyspnoea exertional	1 (0.2%)	0
GASTROINTESTINAL DISORDERS	1 (0.2%)	0
HLGT: Gastrointestinal stenosis and obstruction	1 (0.2%)	0

PRIMARY SYSTEM ORGAN CLASS **HLGT: High Level Group Term** **HLT: High Level Term** **Preferred Term n(%)**	**HOE901-U300** **(N=404)**	**Lantus** **(N=402)**
Any class	25 (6.2%)	21 (5.2%)
HLT: Gastrointestinal stenosis and obstruction NEC	1 (0.2%)	0
Ileus	1 (0.2%)	0
HEPATOBILIARY DISORDERS	0	1 (0.2%)
HLGT: Gallbladder disorders	0	1 (0.2%)
HLT: Cholecystitis and cholelithiasis	0	1 (0.2%)
Cholelithiasis	0	1 (0.2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.2%)	0
HLGT: Skin and subcutaneous tissue disorders NEC	1 (0.2%)	0
HLT: Skin and subcutaneous tissue ulcerations	1 (0.2%)	0
Diabetic foot	1 (0.2%)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.5%)	2 (0.5%)
HLGT: Joint disorders	1 (0.2%)	1 (0.2%)
HLT: Osteoarthropathies	1 (0.2%)	0
Osteoarthritis	1 (0.2%)	0
HLT: Spondyloarthropathies	0	1 (0.2%)
Spondylitis	0	1 (0.2%)
HLGT: Muscle disorders	1 (0.2%)	0
HLT: Myopathies	1 (0.2%)	0
Rhabdomyolysis	1 (0.2%)	0
HLGT: Musculoskeletal and connective tissue disorders NEC	0	1 (0.2%)
HLT: Musculoskeletal and connective tissue pain and discomfort	0	1 (0.2%)
Musculoskeletal chest pain	0	1 (0.2%)
RENAL AND URINARY DISORDERS	2 (0.5%)	3 (0.7%)
HLGT: Bladder and bladder neck disorders (excl calculi)	1 (0.2%)	0
HLT: Bladder neoplasms	1 (0.2%)	0

PRIMARY SYSTEM ORGAN CLASS **HLGT: High Level Group Term** **HLT: High Level Term** **Preferred Term n(%)**	**HOE901-U300** **(N=404)**	**Lantus** **(N=402)**
Any class	25 (6.2%)	21 (5.2%)
Urinary bladder polyp	1 (0.2%)	0
HLGT: Nephropathies	0	1 (0.2%)
HLT: Nephropathies and tubular disorders NEC	0	1 (0.2%)
Diabetic nephropathy	0	1 (0.2%)
HLGT: Renal disorders (excl nephropathies)	1 (0.2%)	2 (0.5%)
HLT: Renal failure and impairment	1 (0.2%)	2 (0.5%)
Renal failure acute	1 (0.2%)	0
Renal failure chronic	0	2 (0.5%)
HLGT: Urolithiases	0	1 (0.2%)
HLT: Renal lithiasis	0	1 (0.2%)
Nephrolithiasis	0	1 (0.2%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.2%)	0
HLGT: Menstrual cycle and uterine bleeding disorders	1 (0.2%)	0
HLT: Menstruation and uterine bleeding NEC	1 (0.2%)	0
Metrorrhagia	1 (0.2%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.2%)	1 (0.2%)
HLGT: General system disorders NEC	1 (0.2%)	1 (0.2%)
HLT: Pain and discomfort NEC	1 (0.2%)	1 (0.2%)
Non-cardiac chest pain	1 (0.2%)	1 (0.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.5%)	4 (1.0%)
HLGT: Bone and joint injuries	1 (0.2%)	0
HLT: Limb injuries NEC (incl traumatic amputation)	1 (0.2%)	0
Meniscus lesion	1 (0.2%)	0
HLGT: Exposures, chemical injuries and poisoning	0	1 (0.2%)
HLT: Poisoning and toxicity	0	1 (0.2%)
Toxicity to various agents	0	1 (0.2%)
HLGT: Injuries NEC	1 (0.2%)	2 (0.5%)
HLT: Cerebral injuries NEC	0	1 (0.2%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=404)	Lantus (N=402)
Any class	25 (6.2%)	21 (5.2%)
Subdural haematoma	0	1 (0.2%)
HLT: Non-site specific injuries NEC	1 (0.2%)	1 (0.2%)
Fall	1 (0.2%)	1 (0.2%)
HLT: Site specific injuries NEC	0	1 (0.2%)
Head injury	0	1 (0.2%)
HLGT: Procedural related injuries and complications NEC	0	1 (0.2%)
HLT: Anaesthetic complications	0	1 (0.2%)
Airway complication of anaesthesia	0	1 (0.2%)

SAE: Serious adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term

MedDRA 15.1

n (%) = number and percentage of patients with at least one treatment emergent SAE

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

1.3.5 Adverse events leading to withdrawal

Table 18 - Number (%) of patients with TEAE(s) leading to permanent treatment discontinuation by Primary SOC, HLGT, HLT and PT for the main 6-month on-treatment period - Safety population

PRIMARY SYSTEM ORGAN CLASS **HLGT: High Level Group Term** **HLT: High Level Term** **Preferred Term n(%)**	**HOE901-U300** **(N=404)**	**Lantus** **(N=402)**
Any class	6 (1.5%)	7 (1.7%)
INFECTIONS AND INFESTATIONS	0	2 (0.5%)
HLGT: Infections - pathogen unspecified	0	2 (0.5%)
HLT: Infections NEC	0	1 (0.2%)
Wound infection	0	1 (0.2%)
HLT: Upper respiratory tract infections	0	1 (0.2%)
Acute sinusitis	0	1 (0.2%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.2%)	1 (0.2%)
HLGT: Leukaemias	0	1 (0.2%)
HLT: Leukaemias chronic myeloid	0	1 (0.2%)
Chronic myeloid leukaemia	0	1 (0.2%)
HLGT: Respiratory and mediastinal neoplasms malignant and unspecified	1 (0.2%)	0
HLT: Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	1 (0.2%)	0
Metastatic bronchial carcinoma	1 (0.2%)	0
METABOLISM AND NUTRITION DISORDERS	0	1 (0.2%)
HLGT: Glucose metabolism disorders (incl diabetes mellitus)	0	1 (0.2%)
HLT: Diabetes mellitus (incl subtypes)	0	1 (0.2%)
Diabetes mellitus inadequate control	0	1 (0.2%)
PSYCHIATRIC DISORDERS	1 (0.2%)	1 (0.2%)
HLGT: Anxiety disorders and symptoms	1 (0.2%)	1 (0.2%)
HLT: Anxiety symptoms	1 (0.2%)	0
Anxiety	1 (0.2%)	0
HLT: Stress disorders	0	1 (0.2%)
Burnout syndrome	0	1 (0.2%)
NERVOUS SYSTEM DISORDERS	0	1 (0.2%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=404)	Lantus (N=402)
Any class	6 (1.5%)	7 (1.7%)
HLGT: Central nervous system vascular disorders	0	1 (0.2%)
HLT: Central nervous system haemorrhages and cerebrovascular accidents	0	1 (0.2%)
Cerebral ischaemia	0	1 (0.2%)
HLGT: Peripheral neuropathies	0	1 (0.2%)
HLT: Chronic polyneuropathies	0	1 (0.2%)
Diabetic neuropathy	0	1 (0.2%)
CARDIAC DISORDERS	1 (0.2%)	2 (0.5%)
HLGT: Cardiac arrhythmias	1 (0.2%)	0
HLT: Ventricular arrhythmias and cardiac arrest	1 (0.2%)	0
Ventricular tachycardia	1 (0.2%)	0
HLGT: Coronary artery disorders	0	1 (0.2%)
HLT: Ischaemic coronary artery disorders	0	1 (0.2%)
Myocardial ischaemia	0	1 (0.2%)
HLGT: Heart failures	0	1 (0.2%)
HLT: Heart failures NEC	0	1 (0.2%)
Cardiac failure chronic	0	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (0.2%)
HLGT: Pulmonary vascular disorders	0	1 (0.2%)
HLT: Pulmonary thrombotic and embolic conditions	0	1 (0.2%)
Pulmonary embolism	0	1 (0.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.2%)	1 (0.2%)
HLGT: Joint disorders	1 (0.2%)	1 (0.2%)
HLT: Osteoarthropathies	1 (0.2%)	0
Osteoarthritis	1 (0.2%)	0
HLT: Spondyloarthropathies	0	1 (0.2%)
Spondylitis	0	1 (0.2%)
RENAL AND URINARY DISORDERS	0	1 (0.2%)
HLGT: Nephropathies	0	1 (0.2%)

PRIMARY SYSTEM ORGAN CLASS **HLGT: High Level Group Term** **HLT: High Level Term** **Preferred Term n(%)**	**HOE901-U300** **(N=404)**	**Lantus** **(N=402)**
Any class	6 (1.5%)	7 (1.7%)
HLT: Nephropathies and tubular disorders NEC	0	1 (0.2%)
Diabetic nephropathy	0	1 (0.2%)
HLGT: Renal disorders (excl nephropathies)	0	1 (0.2%)
HLT: Renal failure and impairment	0	1 (0.2%)
Renal failure chronic	0	1 (0.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (0.2%)
HLGT: General system disorders NEC	0	1 (0.2%)
HLT: Pain and discomfort NEC	0	1 (0.2%)
Non-cardiac chest pain	0	1 (0.2%)
INVESTIGATIONS	2 (0.5%)	0
HLGT: Metabolic, nutritional and blood gas investigations	1 (0.2%)	0
HLT: Carbohydrate tolerance analyses (incl diabetes)	1 (0.2%)	0
Blood glucose decreased	1 (0.2%)	0
HLGT: Physical examination and organ system status topics	1 (0.2%)	0
HLT: Physical examination procedures and organ system status	1 (0.2%)	0
Weight increased	1 (0.2%)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	2 (0.5%)
HLGT: Exposures, chemical injuries and poisoning	0	1 (0.2%)
HLT: Poisoning and toxicity	0	1 (0.2%)
Toxicity to various agents	0	1 (0.2%)
HLGT: Procedural related injuries and complications NEC	0	1 (0.2%)
HLT: Anaesthetic complications	0	1 (0.2%)
Airway complication of anaesthesia	0	1 (0.2%)

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

MedDRA 15.1

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 by alphabetic order

1.3.6 Other significant adverse events

1.3.6.1 Hypersensitivity reaction

Table 19 - Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term - Hypersensitivity reactions during the main 6-month on-treatment period - Safety population

Preferred Term	HOE901-U300 (N=404)	Lantus (N=402)
Any hypersensitivity reactions	3 (0.7%)	2 (0.5%)
Blister	2 (0.5%)	2 (0.5%)
Skin exfoliation	1 (0.2%)	0
Drug eruption	0	1 (0.2%)

MedDRA 15.1

TEAE: Treatment emergent adverse event

n (%) = number and percentage of patients with at least one hypersensitivity reaction event

1.3.6.2 Injection site reactions

Table 20 - Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term - Injection site reactions during the main 6-month on-treatment period - Safety population

Preferred Term	HOE901-U300 (N=404)	Lantus (N=402)
Any injection site reaction	9 (2.2%)	6 (1.5%)
Injection site haematoma	4 (1.0%)	3 (0.7%)
Injection site pain	4 (1.0%)	0
Injection site discomfort	1 (0.2%)	0
Injection site pruritus	1 (0.2%)	0
Injection site erythema	0	1 (0.2%)
Injection site haemorrhage	0	2 (0.5%)
Injection site induration	0	1 (0.2%)

MedDRA 15.1

TEAE: Treatment emergent adverse event

n (%) = number and percentage of patients with at least one local tolerability at injection site event

Example 2: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® both in combination with oral antihyperglycemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period)

Synopsis

Study center(s): Multicenter

Phase of development: 3

Objectives:

Primary Objective: To assess the effects on glycemic control of HOE901-U300 in comparison to Lantus when given as basal insulin in a regimen with oral antihyperglycemic drug(s) in terms of HbA1c change over a period of 6 months in patients with type 2 diabetes mellitus.

Main secondary Objectives: To compare HOE901-U300 and Lantus in terms of occurrence of nocturnal hypoglycemia, change in preinjection plasma glucose, and change in variability of preinjection plasma glucose.

Further secondary objectives:

- To compare HOE901-U300 and Lantus in terms of reaching target HbA_{1c} values and controlled plasma glucose;
- To compare HOE901-U300 and Lantus in terms of treatment satisfaction of patients using the Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs) (not presented in KRM);

- To assess the safety and tolerability of HOE901-U300.

Methodology: The randomization was 1:1 (HOE901-U300 versus Lantus) and was stratified according to HbA_{1c} values at screening (<8.0%; ≥ 8.0%). The sample size (400 with HOE901-U300 and 400 with Lantus) was chosen to ensure sufficient power for the primary endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]) as well as to allow conclusions on the first main secondary endpoint (occurrence of nocturnal hypoglycemia).

Number of patients:

Planned: 800 (400 per treatment arm)	Randomized: 811	Treated: 809
Evaluated:	Efficacy: 808	Safety: 809

Diagnosis and criteria for inclusion: Inclusion criteria: Patients with type 2 diabetes mellitus as defined by WHO diagnosed for at least 1 year at the time of the screening visit; signed written informed consent. Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >10% at screening; diabetes other than type 2 diabetes mellitus; Less than 6 months on basal insulin treatment together with oral antihyperglycemic drugs and self-monitoring of blood glucose; total daily dose insulin glargine <42 U or equivalent dose of NPH in the last 4 weeks prior to the study (if NPH was used as basal insulin prior to the study).

Study treatments

Investigational medicinal products: Tested drug: HOE901-U300; Control drug: Lantus

Formulations: HOE901-U300 (insulin glargine 300 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution in a glass cartridge that has been assembled in a pen-injector (prefilled ie, disposable pen). Lantus (insulin glargine 100 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution supplied in the marketed Solostar® (prefilled ie, disposable pen).

Route of administration: subcutaneous injection

Dose regimen: Once daily injection in the evening. The injection time was fixed at the time of randomization and was to be maintained for the duration of the study.

Starting dose: Patients on Lantus or NPH once daily prior to the baseline visit: the daily dose (U) of HOE901-U300 or Lantus was equal to the median of the total daily basal insulin doses in the last 3 days prior to the baseline visit.

Patients on NPH more than once daily prior to the baseline visit: the daily dose of for HOE901-U300 or Lantus (U) was to be approximately 20% less than the median of the total daily NPH insulin doses in the last 3 days prior to the baseline visit.

The basal insulin dose was adjusted once weekly to achieve fasting SMPG in the target range of 80 to 100 mg/dL (4.4 to 5.6 mmol/L):

- by + 3 U, if the median fasting SMPG of last 3 days was in the range of >100 mg/dL and <140 mg/dL (>5.6 and <7.8 mmol/L)
- by + 6 U, if the median fasting SMPG of last 3 days was ≥ 140 mg/dL (≥ 7.8 mmol/L)
- by - 3 U, if the median fasting SMPG of last 3 days was in the range of ≥ 60 mg/dL and <80 mg/dL (≥ 3.3 and <4.4 mmol/L).

Rescue treatment:

If the basal insulin adjustment failed to decrease FPG/HbA1c under the threshold values of 11.1 mmol/L (200 mg/dL) for FPG and 8% for HbA1c at week 12 or later and no apparent reason for insufficient control was identified, intensification of the treatment was to be considered. The choice of the anti-diabetic treatment to be added to the basal insulin and oral antihyperglycemic background therapy was based on Investigator's decision and local labeling documents.

Noninvestigational medicinal products:

Patients in both treatment groups were to continue with their oral antihyperglycemic background therapy at a stable dose during the study, except sulfonylurea which were prohibited within 2 months before the screening visit and during the study. Rescue therapy was also considered as noninvestigational medicinal product.

Duration of treatment: Up to 12 months

Duration of observation: up to 58 weeks (up to 2-week screening period + 6-month efficacy and safety period + 6-month safety extension period + a 4-week post-treatment follow up period)

The analysis period for efficacy and safety is the main 6-month on-treatment period. Results presented in the present KRM refer to this period.

For all patients requiring rescue therapy during the 6-month treatment period, the last post-baseline efficacy measurement before the start of rescue therapy was used as the efficacy endpoint. These patients were excluded from efficacy analyses after initiation of rescue treatment. For safety endpoints; the analysis period is the main 6-month on-treatment period regardless of the use of rescue therapy.

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: change in HbA_{1c} from baseline to endpoint (Month 6).

Main secondary endpoints: incidence of patients (%) with at least one nocturnal hypoglycemia between start of Week 9 and endpoint (month 6), indicated as severe and/or confirmed by plasma glucose ≤70 mg/dL (3.9 mmol/L); change in preinjection SMPG from baseline to endpoint (Month 6) and change in variability of preinjection SMPG from baseline to endpoint (Month 6).

Safety: Hypoglycemia, occurrence of adverse events particularly treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), TEAEs leading to withdrawal and TEAEs leading to death, injection site reactions and hypersensitivity reactions. Following information not presented in this KRM: physical examination, other safety information including clinical laboratory data, vital signs, 12-lead ECG and anti-insulin antibodies.

Following information not presented in this KRM: physical examination, other safety information including clinical laboratory data, vital signs, 12-lead ECG and anti-insulin antibodies.

Statistical methods: The primary efficacy endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]) was analyzed using an analysis of covariance (ANCOVA) model with treatment, strata of screening HbA_{1c} (<8.0 and ≥ 8.0%), and country as fixed effects and using the HbA_{1c} baseline value as a covariate. Differences between HOE901-U300 and Lantus and two-sided 95% confidence intervals were estimated within the framework of ANCOVA.

A stepwise closed testing approach was used for the primary efficacy endpoint to assess non-inferiority and superiority sequentially. Step 1 assessed non inferiority of HOE901-U300 versus Lantus. To assess non-inferiority, the upper bound of the two sided 95% CI for the difference in the mean change in HbA1c from baseline to endpoint between HOE901-U300 and Lantus was compared with a predefined non inferiority margin of 0.4% for HbA1c. Non-inferiority would be demonstrated if the upper bound of the two-sided 95% CI of the difference between HOE901-U300 and Lantus on mITT population is <0.4%. Step 2 assessed superiority of HOE901-U300 versus Lantus only if non inferiority was demonstrated. The superiority of HOE901-U300 over Lantus was demonstrated if the upper bound of the two-sided 95%CI of the difference between HOE901-U300 and Lantus on mITT population was <0.

Only if non-inferiority of HOE901-U300 versus Lantus had been demonstrated for the primary endpoint, would testing for superiority of HOE901-U300 over Lantus on the main secondary endpoints occur within the frame of a hierarchical testing procedure. Safety analyses were descriptive, based on the safety population.

Summary:

Population characteristics:

A total of 811 patients with type 2 diabetes mellitus were randomized to HOE901-U300 (n=404) or to Lantus (n=407); 809 patients were exposed to IMP (safety population). The mITT population (efficacy population) included 808 patients.

Overall, a comparable number of patients in each treatment group discontinued the study treatment prematurely (HOE901-U300: 36/404, 8.9%; Lantus 38/407, 9.3%). A total of 344 (85.1%) patients in the HOE901-U300 arm and 349 (85.7%) in the Lantus arm completed the main 6-month treatment period (patients who received rescue medication were excluded from the completers population).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 58.2 years, 190/811 (23.4%) were ≥ 65 years. The mean BMI at baseline was 34.8 kg/m². There were slightly more patients with a BMI above 40 kg/m² in the HOE901-U300 group (21.5%) than in the Lantus group (16.7%). The mean duration of diabetes prior to study start was 12.6 years; the mean duration of prior treatment with basal insulin was 3.8 years. The majority of patients took insulin glargine (78.8% vs. NPH 21.2%) on the 7 days before start of study treatment; more patients from the Lantus group were on insulin glargine (82.8%) compared to the HOE901-U300 group (74.9%). The median daily basal insulin dose at baseline was 0.614 U/kg body weight.

Mean HbA1c at baseline was similar in both treatment groups (HOE901-U300: 8.28 % and Lantus: 8.22%; for evaluable patients, i.e. who had a baseline and at least one post-baseline HbA1c assessment).

Efficacy results:

Primary endpoint: The LS mean change in HbA1c from baseline to endpoint (Month 6) was similar in both treatment groups (HOE901-U300: -0.57% (95% CI [-0.756;-0.387]); Lantus: -0.56% (95 %CI [-0.744;-0.379]). Non-inferiority of HOE901-U300 versus Lantus was demonstrated with the LS mean difference in HbA1c versus Lantus of -0.01% (95 % CI [-0.139; 0.119]) with the upper bound lower than the predefined non-inferiority margin of 0.4%. Non-inferiority was also the case with the non-inferiority margin of 0.3%. Superiority of HOE901-U300 versus Lantus was not demonstrated.

1st main secondary endpoint: The incidence of patients with at least one nocturnal severe and/or confirmed hypoglycemia between start of Week 9 and Month 6 was lower in the HOE901-U300 group [87/403 (21.6%)] than in the Lantus group [113/405 (27.9%)]. Superiority of HOE901-U300 versus Lantus was shown with a relative risk of 0.77 (95% CI [0.61, 0.99]) (p=0.0380).

2nd main secondary endpoint: The LS mean change in pre-injection SMPG from baseline to endpoint (Month 6) was similar in the HOE901-U300 (-0.56 mmol/L) and Lantus groups (-0.51 mmol/L). The difference between the treatment groups was not statistically significant (LS mean difference -0.04 (95% CI [-0.438, 0.350], p=0.8279).

3rd main secondary endpoint: As the superiority of HOE901-U300 versus Lantus was not demonstrated for the second main secondary endpoint, no further test was performed for the third main secondary endpoint (decrease in variability of pre-injection SMPG at Month 6, which was numerically larger in the HOE901-U300 group (-2.34) compared to the Lantus group (-0.53).

Other secondary efficacy endpoints (Month 6): The proportion of patients having reached HbA1c <7% was similar between treatment groups (30.6% in the HOE901-U300; 30.4% in the Lantus). For the mean change in FPG, a similar decrease was shown for the two treatment groups. Graphical presentation of the 8-point SMPG profiles showed in both treatment groups a comparable, marked decrease in plasma glucose at endpoint (Month 6) compared with baseline.

At month 6, the mean daily insulin dose in the HOE901-U300 group was 91 U (0.92 U/kg) and 82 U (0.84 U/kg) in the Lantus group.

A similar number of patients in both treatment groups received a rescue therapy during the main 6-month treatment period (5.7% for HOE901-U300, 4.9% for Lantus.

Safety results:

Overall, hypoglycemia was reported by a consistently lower percentage of patients in the HOE901-U300 group than in the Lantus group. This difference was even more

pronounced during the first 2 months of study treatment as well as for events of nocturnal hypoglycemia. During the main 6-month on-treatment period severe hypoglycemia was reported in 4/403 (1%) of HOE901-U300 treated patients and 6/406 (1.5%) of Lantus treated patients.

The percentages of patients with any TEAEs (HOE901-U300, 236/403 [58.6%]; Lantus: 206/406 [50.7%]) was higher for the patients in the HOE901-U300 treatment group than in the Lantus group, with no specific SOC contributing. Serious TEAEs were reported by a similar number of patients in both treatment groups (HOE901-U300, 15 [3.7%]; Lantus, 15 [3.7%]).

Two (0.5%) patients in the HOE901-U300 and 1 (0.2%) patient in the Lantus treatment group died during the 6-months on-treatment period.

The events with fatal outcome in the two patients in the HOE901-U300 group included myocardial infarction and sudden cardiac death due to advanced coronary artery disease. Both patients suffered from pre-existing significant cardiovascular pathology and had multiple risk factors contributing to the fatal outcome. The patient in the Lantus group experienced exacerbation of chronic pyelonephritis with fatal outcome. None of the deaths occurred during the 6 months treatment period were considered related to study drug.

A similar number of patients in both treatment groups experienced TEAEs leading to permanent treatment discontinuation (HOE901-U300: n=6, 1.5%; Lantus: n=4, 1.0%).

Hypersensitivity reactions during the main 6-month on-treatment period were reported at a similar rate in both treatment groups (HOE901-U300: n=13, 3.2%; Lantus: n=16, 3.9%).

Overall injection site reactions during the main 6-month on-treatment period showed higher rate of reporting in the Lantus treatment group than in the HOE901-U300 group (Lantus: n=12, 3.0%; HOE901-U300: n=4, 1.0%).

In both treatment groups, there was no apparent change in body weight (0.08 kg for HOE901-U300 and 0.66 kg for Lantus).

Conclusions:

In this study in 811 patients with T2DM on basal insulin in combination with oral antidiabetic drug(s), the baseline characteristics and demographic characteristics were well balanced across treatment groups. Non-inferiority of HOE901-U300 versus Lantus was shown for the primary efficacy endpoint (change in HbA1c from baseline to endpoint [Month 6]). The incidence of patients (%) reporting nocturnal hypoglycemia (severe and/or confirmed by SMPG ≤70 mg/dL [3.9 mmol/L]) between start of Week 9 and Month 6 was significantly lower in the HOE901-U300 group than in the Lantus group (21.6% and 27.9% respectively, RR of 0.77, p-value 0.0380; 1st main secondary efficacy endpoint). Comparable results between the treatment groups were found for the other secondary endpoints of pre-injection plasma glucose, variability of pre-injection plasma glucose, number of patients reaching target HbA1c and mean change of FPG, change of 8-point SMPG profile and variability of 24-hour average plasma glucose.

Overall incidence of hypoglycemia (% of patients with at least one event) during the main 6-month on-treatment period was consistently lower in the HOE901-U300 group than in the Lantus group regardless of the category of hypoglycemia. This difference in favor of HOE901-U300 was even more pronounced for nocturnal hypoglycemia of all categories.

HOE901-U300 was well tolerated during the main 6-month on-treatment period of the study and no specific safety concerns were observed.

Summary of the efficacy and safety results of the twelve month EDITION 2 extension study

- HbA1c: during the safety extension period (from the main study endpoint [Month 6] to the End of Treatment [Month 12]) HbA1c remained stable and was comparable in both treatment groups
- rescue: during the whole treatment period, the percentages of patients requiring a rescue therapy was similar in both treatment groups (8.2% for HOE901-U300, 10.1%

for Lantus). During the 6-month safety extension period rescue therapy was started in lower percentage of patients in the HOE901-U300 treatment group than in the Lantus group (2.5% for HOE901-U300, 5.4% for Lantus)

- hypoglycemia: overall, similarly as during the main 6-month treatment period, during the whole study on-treatment period hypoglycemia occurred in a lower percentage of patients in the HOE901-U300 group than in the Lantus, regardless of category of hypoglycemia
- safety: HOE901-U300 was well tolerated during the study and no specific safety concerns were observed; during the whole treatment period, the percentages of patients with any TEAEs was higher for the patients in the HOE901-U300 treatment group than in the Lantus group (278/403 [69.0%] and 244/406 [60.1%], respectively), with no specific SOC contributing. Serious TEAEs were reported by a similar number of patients (30 [7.4%]) in both treatment groups. Four (1.0%) patients in the HOE901-U300 and 2 (0.5%) patient in the Lantus treatment group had TEAE leading to death during the whole study on-treatment period
- body weight: in both treatment groups, during the whole study on-treatment period there was small increase in body weight (0.41 kg for HOE901-U300 and 1.15 kg for Lantus).

2 RESULTS

2.1 STUDY PATIENTS

2.1.1 Study disposition

Table 21 ***- Patient disposition - Randomized population***

	HOE901-U300 (N=404)	**Lantus (N=407)**
Randomized and treated	403 (99.8%)	406 (99.8%)
Completed main 6-month treatment period	344 (85.1%)	349 (85.7%)
Permanently discontinued the treatment during the main 6-month period [a]	36 (8.9%)	38 (9.3%)
Rescue intake during the main 6-month period	23 (5.7%)	20 (4.9%)
Subject's request for treatment discontinuation	24 (5.9%)	23 (5.7%)

	HOE901-U300 (N=404)	Lantus (N=407)
Reason for treatment discontinuation during the main 6-month period		
Adverse event	6 (1.5%)	4 (1.0%)
Lack of efficacy	2 (0.5%)	0
Poor compliance to protocol	4 (1.0%)	4 (1.0%)
Other reasons	24 (5.9%)	30 (7.4%)
Status at last study contact of patients who permanently discontinued the treatment during the main 6-month period		
Alive	34 (8.4%)	35 (8.6%)
Dead	2 (0.5%)	1 (0.2%)

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

Patients who completed the main 6-month treatment period are patients who did not permanently discontinue study treatment and who did not take any rescue medication

[a] Two subjects in the Lantus arm had their study status after the cut-off date

Table 22 ***- Analysis populations***

	HOE901-U300	Lantus	All
Randomized population	404 (100%)	407 (100%)	811 (100%)
Efficacy populations			
Modified Intent-to-Treat (mITT)	403 (99.8%)	405 (99.5%)	808 (99.6%)
Month 6 completers	344 (85.1%)	349 (85.7%)	693 (85.5%)
Safety population	403	406	809

Note: For the safety population, patients are tabulated according to treatment actually received (as treated)

For the other populations, patients are tabulated according to their randomized treatment

Table 23 ***- Number (%) of patients requiring rescue therapy during the main 6-month on-treatment period - mITT population***

	HOE901-U300 (N=403)	Lantus (N=405)

	HOE901-U300 (N=403)	Lantus (N=405)
Rescue medication		
Number	403	405
n (%)	23 (5.7%)	20 (4.9%)
RR (95% CI) vs. Lantus [a]	1.16 (0.65 to 2.07)	-

RR=relative risk

[a] Based on RR stratified by randomization strata of screening HbA1c (<8.0 or ≥ 8.0 %)., using a CHM methodology

2.1.2 Demographics and baseline characteristics

Table 24 ***- Demographics and patient characteristics at baseline - Randomized population***

	HOE901-U300 (N=404)	Lantus (N=407)	All (N=811)
Age (years)			
Number	404	407	811
Mean (SD)	57.9 (9.1)	58.5 (9.2)	58.2 (9.2)
Median	59.0	59.0	59.0
Min : Max	24 : 84	27 : 80	24 : 84
Age Group (years) [n(%)]			
Number	404	407	811
<65	317 (78.5%)	304 (74.7%)	621 (76.6%)
[65-75[	80 (19.8%)	88 (21.6%)	168 (20.7%)
≥ 75	7 (1.7%)	15 (3.7%)	22 (2.7%)
Gender [n (%)]			
Number	404	407	811
Male	187 (46.3%)	185 (45.5%)	372 (45.9%)
Female	217 (53.7%)	222 (54.5%)	439 (54.1%)
Race [n (%)]			
Number	404	407	811
Caucasian/White	378 (93.6%)	383 (94.1%)	761 (93.8%)
Black	20 (5.0%)	16 (3.9%)	36 (4.4%)
Asian/Oriental	3 (0.7%)	7 (1.7%)	10 (1.2%)
Other	3 (0.7%)	1 (0.2%)	4 (0.5%)

	HOE901-U300 (N=404)	Lantus (N=407)	All (N=811)
Ethnicity [n (%)]			
Number	404	407	811
Hispanic	102 (25.2%)	91 (22.4%)	193 (23.8%)
Not Hispanic	302 (74.8%)	316 (77.6%)	618 (76.2%)
World region [n (%)]			
Number	404	407	811
North America	175 (43.3%)	194 (47.7%)	369 (45.5%)
Western Europe	40 (9.9%)	43 (10.6%)	83 (10.2%)
Eastern Europe	122 (30.2%)	103 (25.3%)	225 (27.7%)
Rest of the world	67 (16.6%)	67 (16.5%)	134 (16.5%)
Baseline weight (kg)			
Number	404	407	811
Mean (SD)	98.7 (22.3)	98.0 (20.8)	98.3 (21.6)
Median	94.4	95.0	95.0
Min : Max	48 : 209	48 : 188	48 : 209
Baseline BMI (kg/m^2)			
Number	404	407	811
Mean (SD)	34.8 (6.6)	34.8 (6.1)	34.8 (6.4)
Median	33.6	34.0	33.8
Min : Max	20 : 63	21 : 59	20 : 63
Baseline BMI categories (kg/m^2) [n(%)]			
Number	404	407	811
<25	11 (2.7%)	5 (1.2%)	16 (2.0%)
[25-30[	91 (22.5%)	90 (22.1%)	181 (22.3%)
[30-40[	215 (53.2%)	244 (60.0%)	459 (56.6%)
≥ 40	87 (21.5%)	68 (16.7%)	155 (19.1%)
Baseline estimated GFR ($mL/min/1.73m^2$)			
Number	404	407	811
Mean (SD)	82.01 (21.73)	80.47 (20.89)	81.23 (21.31)
Median	81.11	78.69	79.84
Min : Max	22.7 : 155.3	25.1 : 158.8	22.7 : 158.8

	HOE901-U300 (N=404)	Lantus (N=407)	All (N=811)
Baseline estimated GFR categories (mL/min/1.73m^2) [n(%)]			
Number	404	407	811
≥ 90	134 (33.2%)	132 (32.4%)	266 (32.8%)
[60-90[	213 (52.7%)	218 (53.6%)	431 (53.1%)
[30-60[	55 (13.6%)	55 (13.5%)	110 (13.6%)
<30	2 (0.5%)	2 (0.5%)	4 (0.5%)
Randomization strata of screening HbA1c (%) [n(%)]			
Number	404	407	811
<8	144 (35.6%)	146 (35.9%)	290 (35.8%)
≥ 8	260 (64.4%)	261 (64.1%)	521 (64.2%)

BMI = Body Mass Index

GFR = Glomerular filtration rate

GFR is derived from MDRD formula

Table 25 ***- Summary of disease characteristics at baseline - Randomized population***

	HOE901-U300 (N=404)	Lantus (N=407)	All (N=811)
Duration of T2D (years)			
Number	403	407	810
Mean (SD)	12.7 (7.1)	12.5 (7.0)	12.6 (7.0)
Median	11.6	11.7	11.7
Min : Max	1 : 54	1 : 51	1 : 54
Category of duration of T2D (years)			
Number	403	407	810
<10	149 (37.0%)	160 (39.3%)	309 (38.1%)
≥ 10	254 (63.0%)	247 (60.7%)	501 (61.9%)
Age at onset of T2D (years)			
Number	403	407	810
Mean (SD)	45.7 (9.8)	46.5 (9.7)	46.1 (9.7)
Median	45.7	46.2	45.9
Min : Max	13 : 69	18 : 73	13 : 73

	HOE901-U300 (N=404)	Lantus (N=407)	All (N=811)
Duration of basal insulin treatment (years)			
Number	404	407	811
Mean (SD)	3.78 (3.73)	3.83 (3.34)	3.80 (3.54)
Median	2.60	2.70	2.70
Min : Max	0.5 : 30.6	0.4 : 24.5	0.4 : 30.6
Previous basal insulin type[a] [n(%)]			
Number	402	401	803
Insulin glargine	301 (74.9%)	332 (82.8%)	633 (78.8%)
NPH	101 (25.1%)	69 (17.2%)	170 (21.2%)
Previous basal insulin daily injection number[a] [n(%)]			
Number	402	402	804
Once daily	315 (78.4%)	322 (80.1%)	637 (79.2%)
Twice daily	83 (20.6%)	76 (18.9%)	159 (19.8%)
More than twice daily	4 (1.0%)	4 (1.0%)	8 (1.0%)
Previous basal insulin daily dose[b] (U)			
Number	378	382	760
Mean (SD)	64.08 (25.60)	65.69 (26.14)	64.89 (25.87)
Median	58.00	56.00	57.55
Q1 : Q3	47.00 : 70.00	47.10 : 77.30	47.10 : 74.00
Min : Max	32.0 : 218.6	41.9 : 200.0	32.0 : 218.6
Previous basal insulin daily dose[b] (U/kg)			
Number	378	382	760
Mean (SD)	0.660 (0.221)	0.681 (0.253)	0.671 (0.238)
Median	0.617	0.609	0.614
Q1 : Q3	0.505 : 0.767	0.504 : 0.796	0.504 : 0.777
Min : Max	0.31 : 1.83	0.30 : 2.02	0.30 : 2.02

	HOE901-U300 (N=404)	Lantus (N=407)	All (N=811)
Prior use of Lantus[c]			
Number	404	407	811
Yes	304 (75.2%)	337 (82.8%)	641 (79.0%)
No	100 (24.8%)	70 (17.2%)	170 (21.0%)

T2D = Type 2 diabetes

[a] Previous basal insulin type and maximal injection number of the patient during the last 7 days prior to randomization.

[b] Mean of the patient from the basal daily doses during the last 7 days prior to randomization

[c] Taken within 3 months before screening

2.2 EFFICACY EVALUATION

2.2.1 Primary efficacy endpoint

Table 26 ***- Main efficacy analysis - Mean change in HbA1c (%) from baseline to Month 6 endpoint using LOCF procedure - mITT population***

HbA1c (%)	HOE901-U300 (N=403)	Lantus (N=405)
Baseline		
Number	386	392
Mean (SD)	8.28 (0.87)	8.22 (0.77)
Median	8.20	8.10
Min : Max	6.0 : 12.6	6.7 : 10.4
Month 6 endpoint (LOCF)		
Number	386	392
Mean (SD)	7.57 (1.02)	7.56 (1.04)
Median	7.40	7.50
Min : Max	5.4 : 14.2	5.3 : 12.0
Change from baseline to Month 6 endpoint (LOCF)		
Number	386	392
Mean (SD)	-0.71 (1.05)	-0.66 (0.90)
Median	-0.70	-0.70
Min : Max	-3.9 : 5.3	-3.4 : 3.1
LS Mean (SE) [a]	-0.57 (0.094)	-0.56 (0.093)
95% CI	(-0.756 to -0.387)	(-0.744 to -0.379)

HbA1c (%)	HOE901-U300 (N=403)	Lantus (N=405)
LS Mean difference (SE) vs. Lantus [a]	-0.01 (0.066)	
95% CI	(-0.139 to 0.119)	

LOCF = Last observation carried forward.

[a]Analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥ 8.0%) and country as fixed effects and baseline HbA1c value as covariate.

Note: For all patients rescued during the 6-month period, the last postbaseline HbA1c measurement before rescue and during the 6-month on-treatment period will be used as the HbA1c endpoint.

The data of Table 26 are summarized in Figure 5.

2.2.2 Main secondary endpoints

2.2.2.1 Nocturnal hypoglycemia

Table 27 ***- First main secondary efficacy endpoint - Number (%) of patients with at least one nocturnal hypoglycemia [00:00 to 05:59] occuring between start of Week 9 and Month 6 endpoint (using LOCF procedure), indicated as severe and/or confirmed by plasma glucose ≤ 3.9 mmol/L (70 mg/dL) - mITT population***

	HOE901-U300 (N=403)	Lantus (N=405)
Severe and/or confirmed nocturnal hypoglycemia [00:00 to 05:59]		
n (%)	87 (21.6%)	113 (27.9%)
RR (95% CI) vs. Lantus [a]	0.77 (0.61 to 0.99)	-
p-value (CMH)	0.0380	-

n(%) = number and percentage of patients with at least one nocturnal hypoglycemia event, indicated as severe and/or confirmed by plasma glucose ≤ 3.9 mmol/L (70 mg/dL)

[a] Based on RR stratified by randomization strata of screening HbA1c (<8.0 or ≥ 8.0 %), using a CMH methodology

2.2.2.2 Pre-injection plasma glucose - Month 6 endpoint

Table 28 ***- Second main secondary efficacy endpoint - Mean change in average pre-injection SMPG (mmol/L) from baseline to Month 6 endpoint using LOCF procedure - mITT population***

Average pre-injection SMPG (mmol/L)	HOE901-U300 (N=403)	Lantus (N=405)

Average pre-injection SMPG (mmol/L)	HOE901-U300 (N=403)	Lantus (N=405)
Baseline		
Number	353	350
Mean (SD)	11.01 (2.92)	10.84 (2.79)
Median	10.55	10.48
Min : Max	5.0 : 21.8	4.8 : 18.8
Month 6 endpoint (LOCF)		
Number	353	350
Mean (SD)	10.23 (3.03)	10.28 (3.05)
Median	9.77	9.52
Min : Max	5.1 : 25.1	5.1 : 20.4
Change from baseline to Month 6 endpoint (LOCF)		
Number	353	350
Mean (SD)	-0.78 (3.10)	-0.57 (3.01)
Median	-0.82	-0.72
Min : Max	-9.6 : 9.9	-8.8 : 10.9
LS Mean (SE) [b]	-0.56 (0.278)	-0.51 (0.275)
95% CI	(-1.101 to -0.010)	(-1.052 to 0.028)
LS Mean difference (SE) vs. Lantus [b]	-0.04 (0.201)	
95% CI	(-0.438 to 0.350)	
p-value(ANCOVA)	0.8279	

LOCF = Last observation carried forward.

SMPG=Self Monitoring Plasma Glucose

[a] Average is assessed by the mean of at least 3 SMPG calculated over the 7 days preceding the given visit.

[b] Analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥ 8.0%) and country as fixed effects and baseline average pre-injection SMPG value as covariate.

Note: For all patients rescued during the 6-month period, the last postbaseline average pre-injection SMPG measurement before rescue and during the 6-month on-treatment period will be used as the average pre-injection SMPG endpoint.

The data of Table 28 are summarized in Figure 6.

2.2.2.3 Variability of preinjection SMPG - Month 6 endpoint

Table 29 ***- Third main secondary efficacy endpoint - Mean change in variability of pre-injection SMPG from baseline to Month 6 endpoint using LOCF procedure - mITT population***

Variability of pre-injection SMPG	**HOE901-U300 (N=403)**	**Lantus (N=405)**
Baseline		
Number	353	350
Mean (SD)	22.44 (11.73)	20.89 (10.46)
Median	21.77	20.04
Min : Max	0.0 : 86.6	0.0 : 57.0
Month 6 endpoint (LOCF)		
Number	353	350
Mean (SD)	19.84 (10.40)	20.37 (11.65)
Median	18.95	18.89
Min : Max	2.3 : 58.0	1.2 : 73.5
Change from baseline to Month 6 endpoint (LOCF)		
Number	353	350
Mean (SD)	-2.60 (14.00)	-0.52 (13.32)
Median	-1.69	-0.54
Min : Max	-66.6 : 46.4	-37.8 : 67.1
LS Mean (SE) [a]	-2.34 (1.425)	-0.53 (1.408)
95% CI	(-5.142 to 0.452)	(-3.297 to 2.231)
LS Mean difference (SE) vs. Lantus [a]	-1.81 (1.029)	
95% CI	(-3.833 to 0.210)	

LOCF = Last observation carried forward.

SMPG=Self Monitoring Plasma Glucose

Variability is assessed by the mean of coefficient of variation calculated over at least 3 SMPG measured during the 7 days preceding the given visit

[a]Analysis of variance (ANOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥ 8.0%) and country as fixed effects

Note: For all patients rescued during the 6-month period, the last postbaseline variability of pre-injection SMPG measurement before rescue and during the 6-month on-treatment period will be used as the variability of pre-injection SMPG endpoint.

2.2.3 Other secondary efficacy endpoints

2.2.3.1 Percentage of patients with HbA1c <7% at Month 6

Table 30 ***- Other secondary efficacy endpoint - Number (%) of patients with HbA1c < 7% at Month 6 endpoint (using LOCF procedure) and Number (%) of patients with HbA1c < 7% at Month 6 endpoint (using LOCF procedure) having experienced no hypoglycemia indicated as severe and/or confirmed by plasma glucose < 3 mmol/L (54 mg/dL) during the last 3 months of the main 6-month treatment period – mITT population***

	HOE901-U300 (N=403)	**Lantus (N=405)**
HbA1c < 7%		
Number	386	392
n (%)	118 (30.6%)	119 (30.4%)
RR (95% CI) vs. Lantus [a]	1.02 (0.83 to 1.25)	-
HbA1c < 7% and no emergent severe or confirmed (<3.0 mmol/L;<54mg/dL) hypoglycemia		
Number	387	396
n (%)	93 (24.0%)	94 (23.7%)
RR (95% CI) vs. Lantus [a]	1.02 (0.80 to 1.31)	-
HbA1c < 7% and no nocturnal [00:00 – 05:59] emergent severe or confirmed (<3.0 mmol/L;<54mg/dL) hypoglycemia		
Number	386	394
n (%)	107 (27.7%)	113 (28.7%)
RR (95% CI) vs. Lantus [a]	0.98 (0.78 to 1.22)	-

LOCF = Last observation carried forward.

RR=relative risk

[a] Based on RR stratified by randomization strata of screening HbA1c (<8.0 or ≥ 8.0 %), using a CMH methodology

Note: For all patients rescued during the 6-month period, the last postbaseline HbA1c measurement before rescue and during the 6-month on-treatment period will be used as the HbA1c endpoint.

2.2.3.2 Change in FPG from baseline to Month 6 endpoint

Table 31 ***- Other secondary efficacy endpoint - Mean change in FPG (mmol/L) from baseline to Month 6 endpoint using LOCF procedure - mITT population***

FPG (mmol/L)	HOE901-U300 (N=403)	Lantus (N=405)
Baseline		
Number	375	379
Mean (SD)	8.24 (2.97)	7.89 (2.67)
Median	7.80	7.40
Min : Max	2.7 : 20.1	2.9 : 16.6
Month 6 endpoint (LOCF)		
Number	375	379
Mean (SD)	7.09 (2.47)	6.83 (2.37)
Median	6.70	6.30
Min : Max	2.9 : 24.4	2.8 : 17.9
Change from baseline to Month 6 endpoint (LOCF)		
Number	375	379
Mean (SD)	-1.14 (3.42)	-1.06 (3.02)
Median	-0.90	-0.90
Min : Max	-13.1 : 11.0	-11.2 : 10.5
LS Mean (SE) [a]	-1.03 (0.242)	-1.21 (0.241)
95% CI	(-1.501 to -0.551)	(-1.687 to -0.741)
LS Mean difference (SE) vs. Lantus [a]	0.19 (0.171)	
95% CI	(-0.148 to 0.524)	

FPG=Fasting Plasma Glucose

LOCF = Last observation carried forward.

[a]Analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥ 8.0%) and country as fixed effects and baseline FPG value as covariate.

Note: For all patients rescued during the 6-month period, the last postbaseline FPG measurement before rescue and during the 6-month on-treatment period will be used as the FPG endpoint.

2.2.3.3 Eight-point SMPG profile

The mean 8-point SMPG profile (mmol/l) at baseline and Month 6 endpoint (mITT population) is described in Figure 7.

2.2.3.4 Basal insulin dose

The average daily basal insulin dose (U) by visit during the main 6-month on-treatment period (mITT population) is described in Figure 8.

2.3 SAFETY EVALUATION

2.3.1 Extent of exposure

Table 32 ***- Exposure to investigational product for the main 6-month on-treatment period - Safety population***

	HOE901-U300 (N=403)	**Lantus (N=406)**
Cumulative exposure to main 6-month treatment (patient years)	191.1	193.6
Duration of main 6-month study treatment (days)		
Number	402	406
Mean (SD)	173.7 (35.7)	174.2 (33.0)
Median	183.0	183.0
Min : Max	1 : 208	4 : 228
Duration of main 6-month study treatment by category [n(%)]		
up to 2 weeks	6 (1.5%)	2 (0.5%)
>2 to 4 weeks	4 (1.0%)	6 (1.5%)
>4 to 8 weeks	7 (1.7%)	6 (1.5%)
>8 to 12 weeks	6 (1.5%)	7 (1.7%)
>12 to 17 weeks	2 (0.5%)	5 (1.2%)
>17 to 26 weeks	117 (29.1%)	110 (27.1%)
>26 weeks	260 (64.7%)	270 (66.5%)

	HOE901-U300 (N=403)	Lantus (N=406)
Cumulative duration of main 6-month study treatment by category [n(%)]		
≥ 1 days	402 (100%)	406 (100%)
>2 weeks	396 (98.5%)	404 (99.5%)
>4 weeks	392 (97.5%)	398 (98.0%)
>8 weeks	385 (95.8%)	392 (96.6%)
>12 weeks	379 (94.3%)	385 (94.8%)
>17 weeks	377 (93.8%)	380 (93.6%)
>26 weeks	260 (64.7%)	270 (66.5%)

Note: Patients are considered in the treatment group they actually received at randomization

2.3.2 Hypoglycemia

Table 33 ***- Number (%) of patients with at least one emergent hypoglycemia event during the main 6-month on-treatment period – Safety population***

	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)	
Type of hypoglycemia event n(%)	**HOE901-U300 (N=403)**	**Lantus (N=406)**	**HOE901-U300 (N=403)**	**Lantus (N=406)**
Any hypoglycemia event	288 (71.5%)	322 (79.3%)	123 (30.5%)	169 (41.6%)
Severe hypoglycemia	4 (1.0%)	6 (1.5%)	0	2 (0.5%)
Documented symptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	200 (49.6%)	233 (57.4%)	91 (22.6%)	126 (31.0%)
< 3.0 mmol/L (54 mg/dL)	83 (20.6%)	109 (26.8%)	33 (8.2%)	47 (11.6%)
Asymptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	200 (49.6%)	238 (58.6%)	43 (10.7%)	77 (19.0%)
< 3.0 mmol/L (54 mg/dL)	43 (10.7%)	59 (14.5%)	10 (2.5%)	9 (2.2%)
Probable symptomatic hypoglycemia	6 (1.5%)	10 (2.5%)	3 (0.7%)	3 (0.7%)
Relative hypoglycemia				
> 3.9 mmol/L (70 mg/dL)	23 (5.7%)	45 (11.1%)	9 (2.2%)	23 (5.7%)

Type of hypoglycemia event n(%)	All hypoglycemia HOE901-U300 (N=403)	All hypoglycemia Lantus (N=406)	Nocturnal hypoglycemia (00:00-05:59) HOE901-U300 (N=403)	Nocturnal hypoglycemia (00:00-05:59) Lantus (N=406)
Severe and/or confirmed[a] hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	282 (70.0%)	314 (77.3%)	114 (28.3%)	162 (39.9%)
< 3.0 mmol/L (54 mg/dL)	110 (27.3%)	143 (35.2%)	40 (9.9%)	54 (13.3%)

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

[a] Severe and/or confirmed hypoglycemia= severe and/or confirmed by plasma glucose ≤ 3.9 mmol/L (70 mg/dL) (resp. ≤ 3.0 mmol/L (54 mg/dL))

Table 34 ***- Number (%) of patients with at least one emergent hypoglycemia event during the main 6-month on-treatment period by study period - Safety population***

Type of hypoglycemia event n(%)	All hypoglycemia HOE901-U300 (N=403)	All hypoglycemia Lantus (N=406)	Nocturnal hypoglycemia (00:00-05:59) HOE901-U300 (N=403)	Nocturnal hypoglycemia (00:00-05:59) Lantus (N=406)
Any hypoglycemia event				
Overall	288 (71.5%)	322 (79.3%)	123 (30.5%)	169 (41.6%)
Treatment Start to Week 8	198 (49.1%)	258 (63.5%)	58 (14.4%)	109 (26.8%)
From start of week 9 to Month 6	241 (59.8%)	267 (65.8%)	94 (23.3%)	119 (29.3%)
Severe hypoglycemia				
Overall	4 (1.0%)	6 (1.5%)	0	2 (0.5%)
Treatment Start to Week 8	1 (0.2%)	2 (0.5%)	0	0
From start of week 9 to Month 6	3 (0.7%)	5 (1.2%)	0	2 (0.5%)
Documented symptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)				
Overall	200 (49.6%)	233 (57.4%)	91 (22.6%)	126 (31.0%)
Treatment Start to Week 8	119 (29.5%)	158 (38.9%)	34 (8.4%)	79 (19.5%)
From start of week 9 to Month 6	163 (40.4%)	180 (44.3%)	77 (19.1%)	90 (22.2%)
< 3.0 mmol/L (54 mg/dL)				
Overall	83 (20.6%)	109 (26.8%)	33 (8.2%)	47 (11.6%)

Type of hypoglycemia event n(%)	All hypoglycemia HOE901-U300 (N=403)	All hypoglycemia Lantus (N=406)	Nocturnal hypoglycemia (00:00-05:59) HOE901-U300 (N=403)	Nocturnal hypoglycemia (00:00-05:59) Lantus (N=406)
Treatment Start to Week 8	35 (8.7%)	55 (13.5%)	10 (2.5%)	26 (6.4%)
From start of week 9 to Month 6	64 (15.9%)	81 (20.0%)	27 (6.7%)	35 (8.6%)
Asymptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)				
Overall	200 (49.6%)	238 (58.6%)	43 (10.7%)	77 (19.0%)
Treatment Start to Week 8	131 (32.5%)	171 (42.1%)	22 (5.5%)	46 (11.3%)
From start of week 9 to Month 6	163 (40.4%)	195 (48.0%)	25 (6.2%)	50 (12.3%)
< 3.0 mmol/L (54 mg/dL)				
Overall	43 (10.7%)	59 (14.5%)	10 (2.5%)	9 (2.2%)
Treatment Start to Week 8	22 (5.5%)	30 (7.4%)	7 (1.7%)	5 (1.2%)
From start of week 9 to Month 6	26 (6.5%)	40 (9.9%)	4 (1.0%)	5 (1.2%)
Severe and/or confirmed[a] hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)				
Overall	282 (70.0%)	314 (77.3%)	114 (28.3%)	162 (39.9%)
Treatment Start to Week 8	190 (47.1%)	244 (60.1%)	53 (13.2%)	100 (24.6%)
From start of week 9 to Month 6	239 (59.3%)	264 (65.0%)	89 (22.1%)	117 (28.8%)
< 3.0 mmol/L (54 mg/dL)				
Overall	110 (27.3%)	143 (35.2%)	40 (9.9%)	54 (13.3%)
Treatment Start to Week 8	52 (12.9%)	79 (19.5%)	16 (4.0%)	29 (7.1%)
From start of week 9 to Month 6	82 (20.3%)	107 (26.4%)	29 (7.2%)	39 (9.6%)

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

[a] Severe and/or confirmed hypoglycemia= severe and/or confirmed by plasma glucose ≤ 3.9 mmol/L (70 mg/dL) (resp. ≤ 3.0 mmol/L (54 mg/dL))

2.3.3 Treatment-emergent adverse events

Table 35 ***- Treatment emergent adverse events during the main 6-month on-treatment period - Safety population***

n (%)	HOE901-U300 (N=403)	Lantus (N=406)
Patients with any TEAE	236 (58.6%)	206 (50.7%)
Patients with any treatment emergent SAE	15 (3.7%)	15 (3.7%)
Patients with any TEAE leading to death	2 (0.5%)	1 (0.2%)
Patients with any TEAE leading to permanent treatment discontinuation	6 (1.5%)	4 (1.0%)

TEAE: Treatment emergent adverse event, SAE: Serious Adverse Event

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

Table 36 ***- Number (%) of patients with TEAE(s) that occurred with HLT ≥ 2% in any treatment group by Primary SOC, HLT and PT for the main 6-month on-treatment period - Safety population***

PRIMARY SYSTEM ORGAN CLASS HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=403)	Lantus (N=406)
Any class	236 (58.6%)	206 (50.7%)
INFECTIONS AND INFESTATIONS	133 (33.0%)	129 (31.8%)
HLT: Influenza viral infections	11 (2.7%)	11 (2.7%)
Influenza	11 (2.7%)	11 (2.7%)
HLT: Lower respiratory tract and lung infections	20 (5.0%)	18 (4.4%)
Bronchitis	19 (4.7%)	14 (3.4%)
Lower respiratory tract infection	0	1 (0.2%)
Pneumonia	1 (0.2%)	3 (0.7%)
HLT: Upper respiratory tract infections	72 (17.9%)	72 (17.7%)
Acute sinusitis	2 (0.5%)	2 (0.5%)
Acute tonsillitis	1 (0.2%)	0
Chronic sinusitis	1 (0.2%)	0
Laryngitis	1 (0.2%)	0
Nasopharyngitis	39 (9.7%)	27 (6.7%)
Pharyngitis	4 (1.0%)	10 (2.5%)
Pharyngotonsillitis	0	2 (0.5%)
Sinusitis	7 (1.7%)	9 (2.2%)
Tonsillitis	2 (0.5%)	0

PRIMARY SYSTEM ORGAN CLASS HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=403)	Lantus (N=406)
Tracheitis	1 (0.2%)	0
Upper respiratory tract infection	17 (4.2%)	28 (6.9%)
HLT: Urinary tract infections	13 (3.2%)	11 (2.7%)
Pyelonephritis acute	1 (0.2%)	0
Pyelonephritis chronic	0	1 (0.2%)
Urinary tract infection	12 (3.0%)	10 (2.5%)
HLT: Viral infections NEC	13 (3.2%)	10 (2.5%)
Conjunctivitis viral	1 (0.2%)	0
Gastroenteritis viral	5 (1.2%)	3 (0.7%)
Gastrointestinal viral infection	0	1 (0.2%)
Respiratory tract infection viral	0	3 (0.7%)
Viral infection	1 (0.2%)	0
Viral pharyngitis	1 (0.2%)	0
Viral upper respiratory tract infection	5 (1.2%)	3 (0.7%)
NERVOUS SYSTEM DISORDERS	47 (11.7%)	38 (9.4%)
HLT: Headaches NEC	20 (5.0%)	16 (3.9%)
Headache	19 (4.7%)	16 (3.9%)
Sinus headache	1 (0.2%)	0
Tension headache	1 (0.2%)	0
VASCULAR DISORDERS	14 (3.5%)	15 (3.7%)
HLT: Vascular hypertensive disorders NEC	11 (2.7%)	6 (1.5%)
Hypertension	11 (2.7%)	6 (1.5%)
GASTROINTESTINAL DISORDERS	44 (10.9%)	34 (8.4%)
HLT: *Diarrhoea (excl infective)*	15 (3.7%)	9 (2.2%)
Diarrhoea	15 (3.7%)	9 (2.2%)
HLT: Nausea and vomiting symptoms	14 (3.5%)	9 (2.2%)
Nausea	9 (2.2%)	4 (1.0%)
Vomiting	5 (1.2%)	5 (1.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	44 (10.9%)	41 (10.1%)
HLT: Musculoskeletal and connective tissue pain and discomfort	20 (5.0%)	22 (5.4%)
Back pain	9 (2.2%)	12 (3.0%)

PRIMARY SYSTEM ORGAN CLASS HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=403)	Lantus (N=406)
Flank pain	1 (0.2%)	0
Musculoskeletal chest pain	0	1 (0.2%)
Musculoskeletal discomfort	0	1 (0.2%)
Musculoskeletal pain	4 (1.0%)	2 (0.5%)
Neck pain	3 (0.7%)	3 (0.7%)
Pain in extremity	5 (1.2%)	3 (0.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	28 (6.9%)	29 (7.1%)
HLT: Injection site reactions	4 (1.0%)	12 (3.0%)
Injection site atrophy	0	1 (0.2%)
Injection site bruising	0	2 (0.5%)
Injection site erythema	0	2 (0.5%)
Injection site haemorrhage	2 (0.5%)	5 (1.2%)
Injection site induration	0	3 (0.7%)
Injection site inflammation	1 (0.2%)	0
Injection site irritation	0	1 (0.2%)
Injection site pain	1 (0.2%)	4 (1.0%)
Injection site reaction	1 (0.2%)	1 (0.2%)
Injection site swelling	0	1 (0.2%)
HLT: Oedema NEC	6 (1.5%)	12 (3.0%)
Oedema peripheral	6 (1.5%)	12 (3.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	34 (8.4%)	21 (5.2%)
HLT: Muscle, tendon and ligament injuries	11 (2.7%)	3 (0.7%)
Epicondylitis	0	1 (0.2%)
Ligament rupture	1 (0.2%)	0
Ligament sprain	7 (1.7%)	0
Muscle strain	2 (0.5%)	1 (0.2%)
Post-traumatic neck syndrome	1 (0.2%)	1 (0.2%)

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

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

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

Only HLT with at least one HLT ≥ 2% in at least one group are presented

2.3.4 Deaths, serious treatment-emergent adverse events

2.3.4.1 Death

Table 37 ***- Number (%) of patients who died by study period (on study, on-treatment, post-study)- Safety population***

	HOE901-U300 (N=403)	Lantus (N=406)
Death on-study[a]	3 (0.7%)	2 (0.5%)
Death on-study during first 6 months	2 (0.5%)	1 (0.2%)
Death on-treatment[b]	2 (0.5%)	1 (0.2%)
Death post-study[c]	0	0

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

[a] Includes all deaths that occurred after the start of treatment up to end of study (defined as last protocol planned visit or the resolution/stabilization of all treatment emergent SAE and adverse event of pre-specified monitoring)

[b] On-treatment is main 6-month on-treatment period

[c] Includes deaths that occurred after the end of the study (as defined in footnote a) and reported in the database

2.3.4.2 Serious adverse events

Table 38 ***- Number (%) of patients with treatment emergent SAEs by Primary SOC, HLGT, HLT and PT for the main 6-month on-treatment period - Safety population***

PRIMARY SYSTEM ORGAN CLASS **HLGT: High Level Group Term** **HLT: High Level Term** **Preferred Term n(%)**	**HOE901-U300 (N=403)**	**Lantus (N=406)**
Any class	15 (3.7%)	15 (3.7%)
INFECTIONS AND INFESTATIONS	2 (0.5%)	7 (1.7%)
HLGT: Infections - pathogen unspecified	2 (0.5%)	7 (1.7%)
HLT: Infections NEC	1 (0.2%)	2 (0.5%)
Infected bites	0	1 (0.2%)
Localised infection	0	1 (0.2%)
Wound infection	1 (0.2%)	0
HLT: Lower respiratory tract and lung infections	0	1 (0.2%)
Pneumonia	0	1 (0.2%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=403)	Lantus (N=406)
HLT: Upper respiratory tract infections	1 (0.2%)	1 (0.2%)
Chronic sinusitis	1 (0.2%)	0
Upper respiratory tract infection	0	1 (0.2%)
HLT: Urinary tract infections	0	3 (0.7%)
Pyelonephritis chronic	0	1 (0.2%)
Urinary tract infection	0	2 (0.5%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.2%)	1 (0.2%)
HLGT: Leukaemias	1 (0.2%)	0
HLT: Myelodysplastic syndromes	1 (0.2%)	0
Myelodysplastic syndrome	1 (0.2%)	0
HLGT: Skin neoplasms malignant and unspecified	0	1 (0.2%)
HLT: Skin melanomas (excl ocular)	0	1 (0.2%)
Malignant melanoma	0	1 (0.2%)
METABOLISM AND NUTRITION DISORDERS	0	1 (0.2%)
HLGT: Glucose metabolism disorders (incl diabetes mellitus)	0	1 (0.2%)
HLT: Hypoglycaemic conditions NEC	0	1 (0.2%)
Hypoglycaemia	0	1 (0.2%)
NERVOUS SYSTEM DISORDERS	1 (0.2%)	3 (0.7%)
HLGT: Central nervous system vascular disorders	0	2 (0.5%)
HLT: Central nervous system haemorrhages and cerebrovascular accidents	0	2 (0.5%)
Ischaemic stroke	0	2 (0.5%)
HLGT: Neurological disorders NEC	1 (0.2%)	1 (0.2%)
HLT: Neurological signs and symptoms NEC	1 (0.2%)	0
Cerebrospinal fluid leakage	1 (0.2%)	0
HLT: Sensory abnormalities NEC	0	1 (0.2%)
Hypoaesthesia	0	1 (0.2%)

PRIMARY SYSTEM ORGAN CLASS HLGT: *High Level Group Term* HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=403)	Lantus (N=406)
CARDIAC DISORDERS	6 (1.5%)	1 (0.2%)
HLGT: Cardiac arrhythmias	0	1 (0.2%)
HLT: Rate and rhythm disorders NEC	0	1 (0.2%)
Nodal rhythm	0	1 (0.2%)
HLGT: Cardiac disorder signs and symptoms	2 (0.5%)	0
HLT: Cardiac disorders NEC	2 (0.5%)	0
Cardiac disorder	1 (0.2%)	0
Cardiovascular disorder	1 (0.2%)	0
HLGT: Coronary artery disorders	2 (0.5%)	0
HLT: Ischaemic coronary artery disorders	2 (0.5%)	0
Acute myocardial infarction	1 (0.2%)	0
Myocardial infarction	1 (0.2%)	0
HLGT: Heart failures	2 (0.5%)	0
HLT: Heart failures NEC	2 (0.5%)	0
Cardiac failure	1 (0.2%)	0
Cardiac failure congestive	1 (0.2%)	0
VASCULAR DISORDERS	0	1 (0.2%)
HLGT: Decreased and nonspecific blood pressure disorders and shock	0	1 (0.2%)
HLT: Vascular hypotensive disorders	0	1 (0.2%)
Hypotension	0	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.2%)	0
HLGT: Bronchial disorders (excl neoplasms)	1 (0.2%)	0
HLT: Bronchospasm and obstruction	1 (0.2%)	0
Asthma	1 (0.2%)	0
GASTROINTESTINAL DISORDERS	1 (0.2%)	0
HLGT: Gastrointestinal haemorrhages NEC	1 (0.2%)	0
HLT: Non-site specific gastrointestinal haemorrhages	1 (0.2%)	0
Lower gastrointestinal haemorrhage	1 (0.2%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=403)	Lantus (N=406)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.2%)	1 (0.2%)
HLGT: Angioedema and urticaria	1 (0.2%)	0
HLT: Urticarias	1 (0.2%)	0
Urticaria	1 (0.2%)	0
HLGT: Skin and subcutaneous tissue disorders NEC	0	1 (0.2%)
HLT: Skin and subcutaneous tissue ulcerations	0	1 (0.2%)
Skin ulcer	0	1 (0.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (0.2%)
HLGT: Joint disorders	0	1 (0.2%)
HLT: Osteoarthropathies	0	1 (0.2%)
Osteoarthritis	0	1 (0.2%)
RENAL AND URINARY DISORDERS	0	1 (0.2%)
HLGT: Urolithiases	0	1 (0.2%)
HLT: Urinary tract lithiasis (excl renal)	0	1 (0.2%)
Calculus urinary	0	1 (0.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.2%)	0
HLGT: Fatal outcomes	1 (0.2%)	0
HLT: Death and sudden death	1 (0.2%)	0
Sudden cardiac death	1 (0.2%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=403)	Lantus (N=406)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.2%)	0
HLGT: Injuries NEC	1 (0.2%)	0
HLT: Skin injuries NEC	1 (0.2%)	0
Contusion	1 (0.2%)	0

SAE: Serious adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term

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n (%) = number and percentage of patients with at least one treatment emergent SAE

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

2.3.5 Adverse events leading to withdrawal

Table 39 ***- Number (%) of patients with TEAE(s) leading to permanent treatment discontinuation by Primary SOC, HLGT, HLT and PT for the main 6-month on-treatment period - Safety population***

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=403)	Lantus (N=406)
Any class	6 (1.5%)	4 (1.0%)
INFECTIONS AND INFESTATIONS	0	1 (0.2%)
HLGT: Infections - pathogen unspecified	0	1 (0.2%)
HLT: Urinary tract infections	0	1 (0.2%)
Pyelonephritis chronic	0	1 (0.2%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.2%)	0
HLGT: Leukaemias	1 (0.2%)	0
HLT: Myelodysplastic syndromes	1 (0.2%)	0
Myelodysplastic syndrome	1 (0.2%)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.2%)	0
HLGT: White blood cell disorders	1 (0.2%)	0
HLT: Neutropenias	1 (0.2%)	0
Neutropenia	1 (0.2%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=403)	Lantus (N=406)
METABOLISM AND NUTRITION DISORDERS	0	1 (0.2%)
HLGT: Glucose metabolism disorders (incl diabetes mellitus)	0	1 (0.2%)
HLT: Hypoglycaemic conditions NEC	0	1 (0.2%)
Hypoglycaemia	0	1 (0.2%)
PSYCHIATRIC DISORDERS	0	2 (0.5%)
HLGT: Manic and bipolar mood disorders and disturbances	0	1 (0.2%)
HLT: Bipolar disorders	0	1 (0.2%)
Bipolar disorder	0	1 (0.2%)
HLGT: Sleep disorders and disturbances	0	1 (0.2%)
HLT: Disturbances in initiating and maintaining sleep	0	1 (0.2%)
Insomnia	0	1 (0.2%)
NERVOUS SYSTEM DISORDERS	1 (0.2%)	0
HLGT: Cranial nerve disorders (excl neoplasms)	1 (0.2%)	0
HLT: Eye movement disorders	1 (0.2%)	0
IIIrd nerve paralysis	1 (0.2%)	0
CARDIAC DISORDERS	1 (0.2%)	0
HLGT: Coronary artery disorders	1 (0.2%)	0
HLT: Ischaemic coronary artery disorders	1 (0.2%)	0
Myocardial infarction	1 (0.2%)	0
RENAL AND URINARY DISORDERS	1 (0.2%)	0
HLGT: Nephropathies	1 (0.2%)	0
HLT: Nephropathies and tubular disorders NEC	1 (0.2%)	0
Diabetic nephropathy	1 (0.2%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 (N=403)	Lantus (N=406)
GENERAL DISORDERS AND ADMINISTRATION		
SITE CONDITIONS	1 (0.2%)	0
HLGT: Fatal outcomes	1 (0.2%)	0
HLT: Death and sudden death	1 (0.2%)	0
Sudden cardiac death	1 (0.2%)	0

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

MedDRA 16.0

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 HLGT, HLT, PT by alphabetic order

2.3.6 Other significant adverse events

2.3.6.1 Hypersensitivity reaction

Table 40 ***- Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term - Hypersensitivity reactions during the main 6-month on-treatment period - Safety population***

Preferred Term	HOE901-U300 (N=403)	Lantus (N=406)
Any hypersensitivity reactions	13 (3.2%)	16 (3.9%)
Asthma	2 (0.5%)	3 (0.7%)
Allergic cough	1 (0.2%)	0
Allergy to chemicals	1 (0.2%)	0
Bronchial hyperreactivity	1 (0.2%)	0
Dermatitis infected	1 (0.2%)	0
Drug hypersensitivity	1 (0.2%)	1 (0.2%)
Eczema	1 (0.2%)	0
Rash	1 (0.2%)	3 (0.7%)
Rhinitis allergic	1 (0.2%)	2 (0.5%)
Seasonal allergy	1 (0.2%)	1 (0.2%)
Sneezing	1 (0.2%)	0
Urticaria	1 (0.2%)	0
Asthmatic crisis	0	1 (0.2%)

Preferred Term	HOE901-U300 (N=403)	Lantus (N=406)
Blister	0	1 (0.2%)
Erythema	0	3 (0.7%)
Neurodermatitis	0	1 (0.2%)

MedDRA 16.0

TEAE: Treatment emergent adverse event

n (%) = number and percentage of patients with at least one hypersensitivity reaction event

2.3.6.2 Injection site reactions

Table 41 ***- Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term - Injection site reactions during the main 6-month on-treatment period - Safety population***

Preferred Term	HOE901-U300 (N=403)	Lantus (N=406)
Any injection site reaction	4 (1.0%)	12 (3.0%)
Injection site haemorrhage	2 (0.5%)	5 (1.2%)
Injection site inflammation	1 (0.2%)	0
Injection site pain	1 (0.2%)	4 (1.0%)
Injection site reaction	1 (0.2%)	1 (0.2%)
Injection site atrophy	0	1 (0.2%)
Injection site bruising	0	2 (0.5%)
Injection site erythema	0	2 (0.5%)
Injection site induration	0	3 (0.7%)
Injection site irritation	0	1 (0.2%)
Injection site swelling	0	1 (0.2%)

MedDRA 16.0

TEAE: Treatment emergent adverse event

n (%) = number and percentage of patients with at least one local tolerability at injection site event

2.3.7 Body Weight

Table 42 ***- Vital signs - Descriptive statistics - Mean change in Weight (kg) from baseline to Month 6 endpoint using LOCF procedure during the main 6-month on-treatment period - Safety population***

Weight (kg)	HOE901-U300 (N=403)	Lantus (N=406)

Weight (kg)	HOE901-U300 (N=403)	Lantus (N=406)
Baseline		
Number	400	403
Mean (SD)	98.78 (22.37)	98.17 (20.73)
Median	94.50	95.10
Min : Max	48.0 : 208.6	55.0 : 187.7
Month 6 endpoint (LOCF)		
Number	400	403
Mean (SD)	98.86 (22.09)	98.84 (20.63)
Median	94.70	96.00
Min : Max	46.5 : 213.2	57.9 : 189.1
Change from baseline to Month 6 endpoint (LOCF)		
Number	400	403
Mean (SD)	0.08 (3.44)	0.66 (3.01)
Median	0.00	0.64
Min : Max	-22.1 : 12.4	-23.3 : 9.9

LOCF = Last observation carried forward.

Example 3: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period - Administration Sub-study Comparing Adaptable Dosing Intervals with Fixed dosing intervals

1 SYNOPSIS

Phase of development: 3

Objectives:

Primary Objective: To compare the efficacy of HOE901-U300 injected once daily every 24 hours and HOE901-U300 injected once daily at intervals of 24 ± 3 hours in terms of change of HbA1c from month 6 of the main study (=baseline of sub-study) to month 9 of the main study (=endpoint of sub-study) in patients with type 2 diabetes mellitus.

Main secondary Objectives: To compare the safety of the two injection regimens for HOE901-U300 in terms of occurrence of hypoglycemia.

Methodology: Patients randomized on HOE901-U300 and having received HOE901-U300 in the 6-month main study period are randomized 1:1 to administer HOE901-U300 once daily either every 24 hours (fixed dosing intervals) or every 24 ± 3 hours (adaptable dosing intervals).

Patients on HOE901-U300 completing the 6 months main study period (see Example 1) and meeting the eligibility criteria for the sub-study were eligible for the sub-study. No specific sample size was requested for the primary analysis that is descriptive.

Number of patients:	Planned: up to 300 (150 pre-treatment arm)	
	Randomized: 110	
	Treated: 110	
Evaluated:	Efficacy: 109	Safety: 110

Diagnosis and criteria for inclusion: Inclusion criteria: Completion of the 6-month study period in main study described in Example 1 (Visit 10), Randomized and treated with HOE901-U300 during the 6-month treatment period (Baseline – month 6), Signed written informed consent for sub-study obtained.

Key exclusion criteria: Patient not willing to use the adaptable injection intervals of 24 ± 3 hours on at least two days per week; In the investigator's opinion, not able to comply with an adaptable dosing schedule; Health condition which precludes further participation of the patient in the study.

Study treatments

Investigational medicinal product: Tested drug: HOE901-U300

Formulation: HOE901-U300 (insulin glargine 300 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution in a glass cartridge assembled in a pen-injector (prefilled, disposable pen).

Route of administration: subcutaneous injection

Tested regimen:
Adaptable dosing intervals: HOE901-U300 administered once daily every 24 ± 3 hours.

The injection time may have been adapted according to individual needs by up to 3 hours earlier or later than the daily injection time in the evening fixed at the start of the main study. The maximum intervals, ie, 3 hours earlier or 3 hours later than the fixed daily injection time was to be used on at least 2 days of the week at the patients' choice. The injection time fixed at start of the main study was to be maintained as reference time for the variation.

Control regimen:
Fixed dosing intervals: HOE901-U300, once daily injection every 24 hours.

Patients continued to inject HOE901-U300 once daily every 24 hours at the injection time fixed at start of the main study.

Dose:
The dose of HOE901-U300 was to be titrated as needed to achieve or maintain fasting plasma glucose in the target range of 80 to 100 mg/dL (4.4mmol/L to 5.6mmol/L) without hypoglycemia. Changes in the insulin dose were based on fasting self-monitored capillary plasma glucose (SMPG) measurements.

Non-investigational medicinal products
Patients in both treatment groups were to continue with their mealtime insulin analogue during the sub-study.

Patients on concomitant metformin treatment were to continue during the sub-study on a stable dose, unless safety concerns necessitated a dose reduction or discontinuation of metformin

Duration of treatment: The sub-study consisted of a 3 month comparative efficacy and safety treatment period starting at completion of the 6-month main study period and ending at completion of Month 9 of the main study.

After completion, patients on the adaptable dosing arm may have continued this regimen up to the end of the main study (Month 12). Patients injecting HOE901-U300 every 24 hours continued with their treatment regimen up to the end of the study.

Duration of observation: The analysis period for efficacy and safety is the 3-month study period starting at Month 6 of the main study and ending at Month 9 of the main study. Results presented in the present KRM refer to this period.

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: change in HbA_{1c} from baseline (Month 6) to endpoint (Month 9).

Secondary endpoints: FPG (central laboratory) change from baseline (Month 6) to endpoint (Month 9), daily dose of basal insulin and mealtime insulin.

Safety: Hypoglycemia, occurrence of adverse events particularly treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), injection site reactions and hypersensitivity reactions. Following information not presented in KRM: other safety information including vital signs and overdose.

Statistical methods:

For this 3-month sub-study, Baseline is defined as Month 6 of the main study period; the Endpoint is month 9 of the Main study.

The primary efficacy endpoint (change in HbA_{1c} from baseline [Month 6] to endpoint [Month 9]) was analyzed using an analysis of covariance (ANCOVA) model with treatment regimen and country as fixed effects and using the HbA_{1c} baseline value as a covariate. Differences between HOE901-U300 adaptable dosing regimen and HOE901-U300 fixed dosing regimen and two-sided 95% confidence intervals were estimated within the framework of ANCOVA.

All continuous secondary efficacy variables (except for change in variability of pre-injection SMPG) were analyzed using an ANCOVA model with treatment regimen and

country as fixed effects and using the corresponding baseline value as a covariate.

Change in variability of pre-injection SMPG from baseline (month 6) to endpoint (month 9) is analyzed using an analysis of variance (ANOVA) model with treatment regimen and country as fixed effects.

Safety analyses were descriptive, based on the safety population.

Summary:

Population characteristics:

A total of 110 patients with type 2 diabetes were randomized to the sub-study: 56 patients to the HOE901-U300 adaptable dosing interval regimen and 54 patients the to HOE901-U300 fixed dosing interval regimen; 110 patients were exposed to IMP (safety population). The mITT sub-study population (efficacy population) included 109 patients.

One patient (1/56, 1.8%) randomized to HOE901-U300 adaptable dosing intervals discontinued the sub-study prematurely and also discontinued the extension period of the main study (HOE901-U300 fixed dosing intervals: 0/54, 0%).

Demographics and patient characteristics at baseline (Month 6) were well-balanced between both regimen groups. The mean age of the sub-study population was 60 years; 35 of 110 (31.8%) patients were ≥ 65 years.

During the sub-study, on average 23.0% of the injections in patients in the adaptable dosing interval group were taken at the extreme intervals of <21.5 hours or >26.5 hours from previous injection versus 3.9% of injections in patients in the fixed dosing interval group. On average 13.5% of the injections in patients in the adaptable dosing interval group were taken in the intermediate interval (between 21.5-23 hours or between 25-26.5 hours after the previous injection) versus 8.2% of injections in patients in the fixed dosing interval group. Fewer injections by patients in the adaptable dosing interval group (63.4%) were taken within 23-25 hours after previous injection, compared with the fixed dosing interval group (88.0%).

A total of 34.5% of patients in the adaptable dosing group took less than 20% of their

injections outside the 23-25 hours interval after previous injection and therefore around 65% of patients were considered to be compliant with the adaptable dosing interval regimen. In the fixed dosing interval group, 78.8% of patients took more than 80% of injections within 23-25 hours from the previous injection and therefore can be considered to be compliant with the fixed dosing interval regimen.

The compliance with either regimen was similar when intervals were calculated from the reference injection time as scheduled at the main study baseline.

Efficacy results:

Primary endpoint: The LS mean change in HbA_{1c} from baseline (Month 6) to endpoint (Month 9) was similar in the groups of adaptable dosing intervals (0.22% [95% CI: -0.006 to 0.436]) and fixed dosing intervals (0.14% [95 %CI: -0.099 to 0.380]) with the LS mean difference of 0.07% [95 % CI: -0.169 to 0.318].

Secondary efficacy endpoints (Month 9):

- FPG (adaptable dosing interval 1.40 mmol/L [95% CI: 0.624 to 2.177]; fixed dosing interval (1.18 mmol/L [95% CI: 0.350 to 2.015]; LS mean difference 0.22 mmol/L [95% CI:-0.634 to 1.070]).
- Pre-injection SMPG, variability of pre-injection SMPG:
  Adaptation of the injection intervals for HOE901-U300 resulting in shorter and longer intervals than the regular 24-hour interval may have an impact on the secondary efficacy endpoints pre-injection SMPG and variability of pre-injection SMPG. Therefore in addition to the overall analysis per dosing interval regimen showing the mean of the average by patient over up to 7 days prior to the visit, a breakdown of the SMPG data by injection intervals will be presented in the CSR.

In both dosing interval regimen groups, the average basal and mealtime insulin daily doses remained stable during the 3-month comparative regimen period.

***Safety*:**

During the 3-month comparative regimen period, hypoglycemia events, both overall and for each category of hypoglycemia, were reported by a similar percentage of patients in theHOE901-U300 adaptable dosing interval and HOE901-U300 fixed dosing interval regimens.

The percentages of patients with any TEAE (adaptable dosing intervals 15/56 [26.8%]; fixed dosing intervals 15/54 [27.8%]) or with a serious TEAE (adaptable dosing intervals 4/56 [7.1%]; fixed dosing intervals 5/56 [9.3%]) were comparable between the regimens.

No TEAEs leading to treatment discontinuation, leading to death, or linked to injection site reactions were observed in either dosing interval regimen during the 3-month sub-study period. One patient [1.9%] in the fixed dosing interval regimen had a TEAE linked to hypersensitivity reaction.

Conclusions:

The majority of patients in both dosing interval regimen groups followed the injection schedule as randomized and used either adaptable dosing intervals (HOE901-U300 once daily every 24 hours ± 3 hours on at least 2 days a week) or fixed dosing intervals (HOE901-U300 once daily every 24 hours). This allows a comparison of the two dosing interval regimens for efficacy and safety analyses.

The efficacy analyses in terms of HbA1c and FPG showed comparable results for the two dosing interval regimens.

Overall incidence of hypoglycemia (% of patients with at least one event) during the 3-month substudy period was similar in both regimens regardless of the category of hypoglycemia

HOE901-U300 adaptable dosing intervals and HOE901-U300 fixed dosing intervals were well tolerated during the 3-month comparative substudy period; no specific safety concerns were observed.

Taken together, according to the substudy results, no negative effects on main efficacy and safety endpoints were seen with occasional adaptations of injection intervals.

2 RESULTS

2.1 STUDY PATIENTS

2.1.1 Study disposition

Table 43 **- Patient disposition – Randomized sub-study population**

	HOE901-U300 Adaptable Dosing Intervals (N=56)	**HOE901-U300 Fixed Dosing Intervals (N=54)**
Randomized and treated	56 (100%)	54 (100%)
Completed 3-month comparative regimen period	55 (98.2%)	54 (100%)
Permanently discontinued the IMP during the 3-month comparative regimen period	1 (1.8%)	0
Subject's request for treatment discontinuation	1 (1.8%)	0
Reason for treatment discontinuation during the 3-month comparative regimen period		
Adverse event	0	0
Lack of efficacy	0	0
Poor compliance to protocol	0	0
Other reasons	1 (1.8%)	0
Status at last study contact of patients who permanently discontinued the treatment during the 3-month comparative regimen period		
Alive	1 (1.8%)	0
Dead	0	0

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

Table 44 **- Sub-study analysis populations**

	HOE901-U300 Adaptable Dosing Intervals	**HOE901-U300 Fixed Dosing Intervals**	**All**
Randomized sub-study population	56 (100%)	54 (100%)	110 (100%)
Efficacy sub-study populations			
Modified Intent-to-Treat (mITT)	55 (98.2%)	54 (100%)	109 (99.1%)
Sub-study completers	55 (98.2%)	54 (100%)	109 (99.1%)
Safety sub-study population	56	54	110

Note: patients are tabulated according to their randomized treatment.

2.1.2 Demographics and baseline characteristics

Table 45 **- Demographics and patient characteristics at baseline - Randomized sub-study population**

	HOE901-U300 Adaptable Dosing Intervals (N=56)	**HOE901-U300 Fixed Dosing Intervals (N=54)**	**All (N=110)**
Age (years)			
Number	56	54	110
Mean (SD)	61.0 (7.4)	58.9 (9.6)	60.0 (8.6)
Median	61.0	61.0	61.0
Min : Max	40 : 77	28 : 74	28 : 77
Age Group (years) [n(%)]			
Number	56	54	110
<65	36 (64.3%)	39 (72.2%)	75 (68.2%)
[65-75[	18 (32.1%)	15 (27.8%)	33 (30.0%)
≥ 75	2 (3.6%)	0	2 (1.8%)

	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)	All (N=110)
Gender [n (%)]			
Number	56	54	110
Male	24 (42.9%)	25 (46.3%)	49 (44.5%)
Female	32 (57.1%)	29 (53.7%)	61 (55.5%)
Race [n (%)]			
Number	56	54	110
Caucasian/White	51 (91.1%)	52 (96.3%)	103 (93.6%)
Black	5 (8.9%)	1 (1.9%)	6 (5.5%)
Asian/Oriental	0	1 (1.9%)	1 (0.9%)
Other	0	0	0
Ethnicity [n (%)]			
Number	56	54	110
Hispanic	4 (7.1%)	4 (7.4%)	8 (7.3%)
Not Hispanic	52 (92.9%)	50 (92.6%)	102 (92.7%)
World region [n (%)]			
Number	56	54	110
North America	20 (35.7%)	15 (27.8%)	35 (31.8%)
Western Europe	3 (5.4%)	3 (5.6%)	6 (5.5%)
Eastern Europe	29 (51.8%)	30 (55.6%)	59 (53.6%)
Rest of the world	4 (7.1%)	6 (11.1%)	10 (9.1%)

Age is assessed at main study baseline.

Table 46 **- Baseline (month 6) efficacy data related to injection time - Randomized sub-study population**

	HOE901-U300 Adaptable Dosing Intervals (N=56)	**HOE901-U300 Fixed Dosing Intervals (N=54)**	**All (N=110)**
Average injection time from previous injection (hours)			
Number	56	53	109
Mean (SD)	24.05 (0.49)	24.00 (0.10)	24.02 (0.35)
Median	24.00	24.00	24.00
Q1 : Q3	24.00 : 24.01	24.00 : 24.02	24.00 : 24.01
Min : Max	23.7 : 27.6	23.7 : 24.2	23.7 : 27.6
Average injection time from reference injection (hours)			
Number	56	53	109
Mean (SD)	24.03 (0.60)	24.20 (0.63)	24.11 (0.62)
Median	24.00	24.00	24.00
Q1 : Q3	23.93 : 24.25	23.95 : 24.68	23.94 : 24.44
Min : Max	21.5 : 26.3	22.2 : 25.6	21.5 : 26.3

Average: mean interval value over at least 3 times intervals during the last 7 days preceding month 6.

2.1.3 Measurement of treatment compliance

Table 47 **- Compliance – Dosing regimen compliance during the 3-month comparative regimen period – Percentage of injections (time from previous injection) by dosing interval category - Safety sub-study population**

% of injections by patient	**HOE901-U300 Adaptable Dosing Intervals (N=56)**	**HOE901-U300 Fixed Dosing Intervals (N=54)**

% of injections by patient	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
<21.5 hours or >26.5 hours		
Number	55	52
Mean (SD)	23.02 (26.62)	3.85 (10.97)
Median	16.67	0.00
Q1 : Q3	0.00 : 36.36	0.00 : 0.00
Min : Max	0.0 : 100.0	0.0 : 46.2
[23 – 25] hours		
Number	55	52
Mean (SD)	63.44 (26.60)	87.96 (22.01)
Median	66.67	100.00
Q1 : Q3	41.67 : 83.33	83.33 : 100.00
Min : Max	0.0 : 100.0	16.7 : 100.0
[21.5 – 23[hours or]25 – 26.5] hours		
Number	55	52
Mean (SD)	13.54 (15.23)	8.19 (16.11)
Median	8.33	0.00
Q1 : Q3	0.00 : 25.00	0.00 : 8.71
Min : Max	0.0 : 58.3	0.0 : 66.7

Note: Percentage of injections (time from previous injection) in each dosing interval category is calculated for each patient using all intervals obtained during the last 7 days values before Month 7.5 and Month 9 visits.

Note: Only patients with at least 3 time intervals during the last 7 days values before Month 7.5 or Month 9 visits are considered for this table.

Table 48 **- Compliance – Number of patients for whom less than 20% of injections are outside the 23 to 25-hour time window from the previous injection time - Safety sub-study population**

	HOE901-U300 Adaptable Dosing Intervals (N=56)	**HOE901-U300 Fixed Dosing Intervals (N=54)**
Patients for whom less than 20% of injections are outside the 23 to 25-hour time window from the previous injection time	19/55 (34.5%)	41/52 (78.8%)

Note: Percentage of injections (time from previous injection) is calculated using all intervals obtained during the last 7 days values before Month 7.5 and Month 9 visits.

Note: Only patients with at least 3 time intervals during the last 7 days values before Month 7.5 or Month 9 visits are considered for this table.

Table 49 **- Compliance – Dosing regimen compliance during the 3-month comparative regimen period – Percentage of injections (time from reference injection) by dosing interval category - Safety sub-study population**

% of injections by patient	**HOE901-U300 Adaptable Dosing Intervals (N=56)**	**HOE901-U300 Fixed Dosing Intervals (N=54)**
<21.5 hours or >26.5 hours		
Number	55	52
Mean (SD)	17.27 (19.25)	0.82 (3.05)
Median	14.29	0.00
Q1 : Q3	0.00 : 28.57	0.00 : 0.00
Min : Max	0.0 : 64.3	0.0 : 14.3

% of injections by patient	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
[23 – 25] hours		
Number	55	52
Mean (SD)	64.96 (25.45)	83.52 (25.22)
Median	71.43	100.00
Q1 : Q3	50.00 : 85.71	75.65 : 100.00
Min : Max	0.0 : 100.0	0.0 : 100.0
[21.5 – 23[hours or]25 – 26.5] hours		
Number	55	52
Mean (SD)	17.77 (19.40)	15.65 (24.67)
Median	14.29	0.00
Q1 : Q3	0.00 : 28.57	0.00 : 21.43
Min : Max	0.0 : 78.6	0.0 : 100.0

Note: Percentage of injections (time from reference injection chosen at the start of the main study) in each dosing interval category is calculated for each patient using all intervals obtained during the last 7 days values before Month 7.5 and Month 9 visits.

Note: Only patients with at least 3 time intervals during the last 7 days values before Month 7.5 or Month 9 visits are considered for this table.

2.2 EFFICACY EVALUATION

2.2.1 Primary efficacy endpoint

Table 50 **- Main efficacy analysis - Mean change in HbA1c (%) from baseline (month 6) to Month 9 endpoint using LOCF procedure - mITT sub-study population**

HbA1c (%)	HOE901-U300 Adaptable Dosing Intervals (N=55)	HOE901-U300 Fixed Dosing Intervals (N=54)

HbA1c (%)	HOE901-U300 Adaptable Dosing Intervals (N=55)	HOE901-U300 Fixed Dosing Intervals (N=54)
Baseline (month 6)		
Number	55	52
Mean (SD)	7.21 (0.91)	7.17 (0.88)
Median	7.10	7.00
Min : Max	5.7 : 10.6	5.7 : 9.4
Month 9 endpoint (LOCF)		
Number	55	52
Mean (SD)	7.25 (0.96)	7.12 (0.96)
Median	7.10	6.80
Min : Max	5.5 : 9.9	5.8 : 10.7
Change from baseline to Month 9 endpoint (LOCF)		
Number	55	52
Mean (SD)	0.03 (0.56)	-0.05 (0.72)
Median	0.00	0.00
Min : Max	-1.4 : 1.4	-2.8 : 1.8
LS Mean (SE) [a]	0.22 (0.111)	0.14 (0.121)
95% CI	(-0.006 to 0.436)	(-0.099 to 0.380)
LS Mean difference (SE) vs. HOE901-U300 Fixed Dosing Intervals [a]	0.07 (0.123)	
95% CI	(-0.169 to 0.318)	

LOCF = Last observation carried forward.

[a] Analysis of covariance (ANCOVA) model with treatment regimen and country as fixed effects and baseline HbA1c value as a covariate.

The mean HbA1c (%) by visit during the 3-month comparative regimen period - mITT sub-study population is described in Figure 9.

2.2.2 Secondary endpoints

2.2.2.1 Fasting plasma glucose

Table 51 **- Mean change in FPG (mmol/L) from baseline (month 6) to Month 9 endpoint using LOCF procedure - mITT sub-study population**

FPG (mmol/L)	HOE901-U300 Adaptable Dosing Intervals (N=55)	HOE901-U300 Fixed Dosing Intervals (N=54)
Baseline (month 6)		
Number	54	51
Mean (SD)	7.33 (2.09)	6.78 (2.58)
Median	7.20	6.50
Min : Max	2.4 : 11.4	2.5 : 15.3
Month 9 endpoint (LOCF)		
Number	54	51
Mean (SD)	7.61 (2.38)	7.07 (3.06)
Median	7.25	6.60
Min : Max	3.7 : 14.0	3.0 : 20.6
Change from baseline to Month 9 endpoint (LOCF)		
Number	54	51
Mean (SD)	0.28 (2.46)	0.29 (2.31)
Median	0.45	0.20
Min : Max	-5.0 : 7.7	-5.8 : 9.1
LS Mean (SE) [a]	1.40 (0.391)	1.18 (0.419)
95% CI	(0.624 to 2.177)	(0.350 to 2.015)
LS Mean difference (SE) vs. HOE901-U300 Fixed Dosing Intervals [a]	0.22 (0.429)	

FPG (mmol/L)	HOE901-U300 Adaptable Dosing Intervals (N=55)	HOE901-U300 Fixed Dosing Intervals (N=54)
95% CI	(-0.634 to 1.070)	

FPG=Fasting Plasma Glucose.

LOCF = Last observation carried forward.

[a]Analysis of covariance (ANCOVA) model with treatment regimen and country as fixed effects and baseline FPG value as a covariate.

2.2.2.2 Basal and mealtime insulin dose

The average daily basal (glargine) and mealtime insulin dose (U) by visit during the 3-month comparative regimen period - mITT sub-study population is described in Figure 10.

2.3 SAFETY EVALUATION

2.3.1 Extent of exposure

Table 52 **- Exposure to investigational product during the 3-month comparative regimen period – Safety sub-study population**

	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
Cumulative exposure to the sub-study 3-month treatment (patient years)	13.82	13.38
Duration of the sub-study 3-month treatment (days)		
Number	55	53
Mean (SD)	91.8 (4.9)	92.2 (6.2)
Median	92.0	92.0
Min : Max	77 : 112	83 : 126

	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
Duration of the sub-study 3-month treatment by category [n(%)]		
Missing duration	1 (1.8%)	1 (1.9%)
up to 6 weeks	0	0
>6 to 12 weeks	2 (3.6%)	3 (5.6%)
>12 weeks	53 (94.6%)	50 (92.6%)
Cumulative duration of the sub-study 3-month treatment by category [n(%)]		
Missing duration	1 (1.8%)	1 (1.9%)
≥ 1 days	55 (98.2%)	53 (98.1%)
>6 weeks	55 (98.2%)	53 (98.1%)
>12 weeks	53 (94.6%)	50 (92.6%)

2.3.2 Hypoglycemia

Table 53 **- Number (%) of patients with at least one hypoglycemia event during the 3-month comparative regimen period - Safety sub-study population**

	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)	
Type of hypoglycemia event n(%)	**HOE901-U300 Adaptable Dosing Intervals (N=56)**	**HOE901-U300 Fixed Dosing Intervals (N=54)**	**HOE901-U300 Adaptable Dosing Intervals (N=56)**	**HOE901-U300 Fixed Dosing Intervals (N=54)**
Any hypoglycemia event	32 (57.1%)	36 (66.7%)	15 (26.8%)	13 (24.1%)
Severe hypoglycemia	0	1 (1.9%)	0	1 (1.9%)

	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)	
Type of hypoglycemia event n(%)	**HOE901-U300 Adaptable Dosing Intervals (N=56)**	**HOE901-U300 Fixed Dosing Intervals (N=54)**	**HOE901-U300 Adaptable Dosing Intervals (N=56)**	**HOE901-U300 Fixed Dosing Intervals (N=54)**
Documented symptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	18 (32.1%)	23 (42.6%)	11 (19.6%)	9 (16.7%)
< 3.0 mmol/L (54 mg/dL)	11 (19.6%)	12 (22.2%)	3 (5.4%)	6 (11.1%)
Asymptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	22 (39.3%)	24 (44.4%)	3 (5.4%)	6 (11.1%)
< 3.0 mmol/L (54 mg/dL)	2 (3.6%)	6 (11.1%)	1 (1.8%)	1 (1.9%)
Probable symptomatic hypoglycemia	1 (1.8%)	0	0	0
Relative hypoglycemia				
> 3.9 mmol/L (70 mg/dL)	3 (5.4%)	0	1 (1.8%)	0
Severe and/or confirmed[a] hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	31 (55.4%)	36 (66.7%)	14 (25.0%)	13 (24.1%)
< 3.0 mmol/L (54 mg/dL)	13 (23.2%)	16 (29.6%)	4 (7.1%)	8 (14.8%)

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

[a] Severe and/or confirmed hypoglycemia= severe and/or confirmed by plasma glucose<=3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL)).

Note: All hypoglycemia events with missing time are counted in the column "All hypoglycemia", but not classified as "nocturnal" or "daytime".)

2.3.3 Treatment-emergent adverse events

Table 54 **- Treatment emergent adverse events during the 3-month comparative regimen period - Safety sub-study population**

n (%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
Patients with any TEAE	15 (26.8%)	15 (27.8%)
Patients with any treatment emergent SAE	4 (7.1%)	5 (9.3%)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	0

TEAE: Treatment emergent adverse event, SAE: Serious Adverse Event.

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

Table 55 **- Number (%) of patients with TEAE(s) by primary SOC, HLGT, HLT and PT events during the 3-month comparative regimen period - Safety sub-study population**

PRIMARY SYSTEM ORGAN CLASS **HLGT: High Level Group Term** **HLT: High Level Term** **Preferred Term n(%)**	**HOE901-U300 Adaptable Dosing Intervals (N=56)**	**HOE901-U300 Fixed Dosing Intervals (N=54)**
Any class	15 (26.8%)	15 (27.8%)
INFECTIONS AND INFESTATIONS	7 (12.5%)	4 (7.4%)
HLGT: Bacterial infectious disorders	2 (3.6%)	0
HLT: Bacterial infections NEC	1 (1.8%)	0
Conjunctivitis bacterial	1 (1.8%)	0
HLT: Staphylococcal infections	1 (1.8%)	0
Staphylococcal infection	1 (1.8%)	0
HLGT: Infections - pathogen unspecified	6 (10.7%)	3 (5.6%)
HLT: Abdominal and gastrointestinal infections	0	1 (1.9%)
Gastroenteritis	0	1 (1.9%)
HLT: Bone and joint infections	1 (1.8%)	0
Osteomyelitis	1 (1.8%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
HLT: Infections NEC	2 (3.6%)	0
Localised infection	1 (1.8%)	0
Postoperative wound infection	1 (1.8%)	0
HLT: Lower respiratory tract and lung infections	1 (1.8%)	0
Bronchitis	1 (1.8%)	0
HLT: Upper respiratory tract infections	2 (3.6%)	2 (3.7%)
Nasopharyngitis	2 (3.6%)	1 (1.9%)
Upper respiratory tract infection	0	1 (1.9%)
HLGT: Viral infectious disorders	1 (1.8%)	1 (1.9%)
HLT: Influenza viral infections	1 (1.8%)	0
Influenza	1 (1.8%)	0
HLT: Viral infections NEC	0	1 (1.9%)
Gastroenteritis viral	0	1 (1.9%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (1.9%)
HLGT: Reproductive neoplasms female benign	0	1 (1.9%)
HLT: Uterine neoplasms benign	0	1 (1.9%)
Uterine leiomyoma	0	1 (1.9%)
HLGT: Reproductive neoplasms female malignant and unspecified	0	1 (1.9%)
HLT: Endometrial neoplasms malignant	0	1 (1.9%)
Endometrial cancer	0	1 (1.9%)
METABOLISM AND NUTRITION DISORDERS	1 (1.8%)	0
HLGT: Glucose metabolism disorders (incl diabetes mellitus)	1 (1.8%)	0
HLT: Hyperglycaemic conditions NEC	1 (1.8%)	0
Hyperglycaemia	1 (1.8%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
NERVOUS SYSTEM DISORDERS	1 (1.8%)	1 (1.9%)
HLGT: Headaches	1 (1.8%)	0
HLT: Headaches NEC	1 (1.8%)	0
Headache	1 (1.8%)	0
HLGT: Neurological disorders NEC	1 (1.8%)	1 (1.9%)
HLT: Nervous system disorders NEC	1 (1.8%)	0
Nervous system disorder	1 (1.8%)	0
HLT: Neurological signs and symptoms NEC	1 (1.8%)	1 (1.9%)
Dizziness	1 (1.8%)	1 (1.9%)
EYE DISORDERS	0	1 (1.9%)
HLGT: Ocular infections, irritations and inflammations	0	1 (1.9%)
HLT: Lid, lash and lacrimal infections, irritations and inflammations	0	1 (1.9%)
Eyelid cyst	0	1 (1.9%)
CARDIAC DISORDERS	2 (3.6%)	0
HLGT: Cardiac disorder signs and symptoms	1 (1.8%)	0
HLT: Cardiac signs and symptoms NEC	1 (1.8%)	0
Palpitations	1 (1.8%)	0
HLGT: Coronary artery disorders	2 (3.6%)	0
HLT: Coronary artery disorders NEC	1 (1.8%)	0
Coronary artery disease	1 (1.8%)	0
HLT: Ischaemic coronary artery disorders	1 (1.8%)	0
Angina pectoris	1 (1.8%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (5.4%)	2 (3.7%)
HLGT: Bronchial disorders (excl neoplasms)	0	1 (1.9%)
HLT: Bronchospasm and obstruction	0	1 (1.9%)
Asthma	0	1 (1.9%)
HLGT: Respiratory disorders NEC	3 (5.4%)	0
HLT: Breathing abnormalities	1 (1.8%)	0
Sleep apnoea syndrome	1 (1.8%)	0
HLT: Coughing and associated symptoms	2 (3.6%)	0
Cough	2 (3.6%)	0
HLT: Upper respiratory tract signs and symptoms	1 (1.8%)	0
Oropharyngeal pain	1 (1.8%)	0
HLGT: Upper respiratory tract disorders (excl infections)	0	1 (1.9%)
HLT: Nasal congestion and inflammations	0	1 (1.9%)
Nasal congestion	0	1 (1.9%)
GASTROINTESTINAL DISORDERS	3 (5.4%)	3 (5.6%)
HLGT: Benign neoplasms gastrointestinal	1 (1.8%)	0
HLT: Benign neoplasms gastrointestinal (excl oral cavity)	1 (1.8%)	0
Large intestine polyp	1 (1.8%)	0
HLGT: Gastrointestinal motility and defaecation conditions	0	3 (5.6%)
HLT: Diarrhoea (excl infective)	0	3 (5.6%)
Diarrhoea	0	3 (5.6%)
HLGT: Gastrointestinal signs and symptoms	2 (3.6%)	0
HLT: Nausea and vomiting symptoms	2 (3.6%)	0
Nausea	1 (1.8%)	0
Vomiting	1 (1.8%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
HEPATOBILIARY DISORDERS	0	1 (1.9%)
HLGT: Bile duct disorders	0	1 (1.9%)
HLT: Obstructive bile duct disorders (excl neoplasms)	0	1 (1.9%)
Bile duct stone	0	1 (1.9%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4 (7.1%)	3 (5.6%)
HLGT: Joint disorders	2 (3.6%)	1 (1.9%)
HLT: Osteoarthropathies	2 (3.6%)	0
Osteoarthritis	1 (1.8%)	0
Spinal osteoarthritis	1 (1.8%)	0
HLT: Spondyloarthropathies	0	1 (1.9%)
Spondylitis	0	1 (1.9%)
HLGT: Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)	0	1 (1.9%)
HLT: Intervertebral disc disorders NEC	0	1 (1.9%)
Intervertebral disc protrusion	0	1 (1.9%)
HLGT: Musculoskeletal and connective tissue disorders NEC	2 (3.6%)	0
HLT: Musculoskeletal and connective tissue pain and discomfort	2 (3.6%)	0
Musculoskeletal pain	1 (1.8%)	0
Pain in extremity	1 (1.8%)	0
HLGT: Synovial and bursal disorders	0	1 (1.9%)
HLT: Synovial disorders	0	1 (1.9%)
Synovial cyst	0	1 (1.9%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	1 (1.9%)
HLGT: Menopause and related conditions	0	1 (1.9%)
HLT: Menopausal effects on the genitourinary tract	0	1 (1.9%)
Postmenopausal haemorrhage	0	1 (1.9%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (1.8%)	0
HLGT: General system disorders NEC	1 (1.8%)	0
HLT: Oedema NEC	1 (1.8%)	0
Oedema peripheral	1 (1.8%)	0
INVESTIGATIONS	0	1 (1.9%)
HLGT: Renal and urinary tract investigations and urinalyses	0	1 (1.9%)
HLT: Renal function analyses	0	1 (1.9%)
Blood creatinine increased	0	1 (1.9%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (5.4%)	3 (5.6%)
HLGT: Bone and joint injuries	0	1 (1.9%)
HLT: Upper limb fractures and dislocations	0	1 (1.9%)
Humerus fracture	0	1 (1.9%)
HLGT: Exposures, chemical injuries and poisoning	0	1 (1.9%)
HLT: Poisoning and toxicity	0	1 (1.9%)
Toxicity to various agents	0	1 (1.9%)
HLGT: Injuries NEC	1 (1.8%)	0
HLT: Muscle, tendon and ligament injuries	1 (1.8%)	0
Ligament sprain	1 (1.8%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
HLGT: Procedural related injuries and complications NEC	2 (3.6%)	1 (1.9%)
HLT: Gastrointestinal and hepatobiliary procedural complications	0	1 (1.9%)
Abdominal wound dehiscence	0	1 (1.9%)
HLT: Non-site specific procedural complications	2 (3.6%)	0
Procedural pain	2 (3.6%)	0

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

MedDRA 16.0.

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.

2.3.4 Serious treatment-emergent adverse events

Table 56 **- Number (%) of patients with treatment emergent SAE(s) by Primary SOC, HLGT, HLT and PT during the 3-month comparative regimen period - Safety sub-study population**

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
Any class	4 (7.1%)	5 (9.3%)
INFECTIONS AND INFESTATIONS	2 (3.6%)	0
HLGT: Infections - pathogen unspecified	2 (3.6%)	0
HLT: Bone and joint infections	1 (1.8%)	0
Osteomyelitis	1 (1.8%)	0
HLT: Infections NEC	1 (1.8%)	0
Postoperative wound infection	1 (1.8%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (1.9%)
HLGT: Reproductive neoplasms female benign	0	1 (1.9%)
HLT: Uterine neoplasms benign	0	1 (1.9%)
Uterine leiomyoma	0	1 (1.9%)
HLGT: Reproductive neoplasms female malignant and unspecified	0	1 (1.9%)
HLT: Endometrial neoplasms malignant	0	1 (1.9%)
Endometrial cancer	0	1 (1.9%)
CARDIAC DISORDERS	1 (1.8%)	0
HLGT: Coronary artery disorders	1 (1.8%)	0
HLT: Coronary artery disorders NEC	1 (1.8%)	0
Coronary artery disease	1 (1.8%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (1.9%)
HLGT: Bronchial disorders (excl neoplasms)	0	1 (1.9%)
HLT: Bronchospasm and obstruction	0	1 (1.9%)
Asthma	0	1 (1.9%)
HEPATOBILIARY DISORDERS	0	1 (1.9%)
HLGT: Bile duct disorders	0	1 (1.9%)
HLT: Obstructive bile duct disorders (excl neoplasms)	0	1 (1.9%)
Bile duct stone	0	1 (1.9%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	2 (3.7%)
HLGT: Joint disorders	0	1 (1.9%)
HLT: Spondyloarthropathies	0	1 (1.9%)
Spondylitis	0	1 (1.9%)
HLGT: Synovial and bursal disorders	0	1 (1.9%)
HLT: Synovial disorders	0	1 (1.9%)
Synovial cyst	0	1 (1.9%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	1 (1.9%)
HLGT: Menopause and related conditions	0	1 (1.9%)
HLT: Menopausal effects on the genitourinary tract	0	1 (1.9%)
Postmenopausal haemorrhage	0	1 (1.9%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.8%)	2 (3.7%)
HLGT: Bone and joint injuries	0	1 (1.9%)
HLT: Upper limb fractures and dislocations	0	1 (1.9%)
Humerus fracture	0	1 (1.9%)
HLGT: Procedural related injuries and complications NEC	1 (1.8%)	1 (1.9%)
HLT: Gastrointestinal and hepatobiliary procedural complications	0	1 (1.9%)
Abdominal wound dehiscence	0	1 (1.9%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
HLT: Non-site specific procedural complications	1 (1.8%)	0
Procedural pain	1 (1.8%)	0

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

MedDRA 16.0.

n (%) = number and percentage of patients with at least one treatment emergent SAE.

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

2.3.5 Treatment emergent adverse events leading to withdrawal

Table 57 **- Number (%) of patients with TEAE(s) leading to permanent treatment discontinuation by Primary SOC, HLGT, HLT and PT during the 3-month comparative regimen period - Safety sub-study population**

No data

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

MedDRA 16.0.

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 HLGT, HLT, PT by alphabetic order.

2.3.6 Other significant treatment emergent adverse events

2.3.6.1 Injection site reactions

Table 58 **- Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term - Injection site reactions during the 3-month comparative regimen period – Safety sub-study population**

No data

TEAE: Treatment emergent adverse event, PT: Preferred term.

MedDRA 16.0

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

Note: Table sorted by decreasing frequency of PT in HOE901-U300 adaptable dosing intervals regimen.

2.3.6.2 Hypersensitivity reactions

Table 59 **- Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term - Hypersensitivity reactions during the 3-month comparative regimen period – Safety sub-study population**

Preferred Term	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=54)
Any hypersensitivity reactions	0	1 (1.9%)
Asthma	0	1 (1.9%)

TEAE: Treatment emergent adverse event, PT: Preferred term.

MedDRA 16.0

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

Note: Table sorted by decreasing frequency of PT in HOE901-U300 adaptable dosing intervals regimen.

Example 4: 16-week, randomized, open-label, controlled study comparing the efficacy and safety of a new formulation of insulin glargine versus Lantus in patients with type 1 diabetes mellitus

Phase of development: 2

Objectives:

Primary objective: To compare the glucose control during treatment with a new formulation of insulin glargine (HOE901-U300) and Lantus in adult patients with type 1 diabetes mellitus.

Secondary objectives:

- To compare HOE901-U300 and Lantus given in the morning or in the evening regarding the continuous glucose monitoring (CGM) data: diurnal glucose exposure; diurnal glucose stability as measured by rate of change in median curve; diurnal glucose variability as measured by interquartile range (IQR); mean and variation in glucose profiles
- To compare HOE901-U300 and Lantus regarding glycated hemoglobin A1c (HbA1c), self-measured plasma glucose (fasting plasma glucose, prior to injection of study drug, 7-point profiles)
- To compare the incidence and frequency of hypoglycemic episodes classified as defined by ADA criteria, both symptomatic, confirmed by plasma glucose £70 mg/dL and CGM-detected
- To assess the safety and tolerability of HOE901-U300

Methodology: Multicenter, open-label, randomized, 4-arm parallel-group, comparative Phase 2 study comparing HOE901-U300 and Lantus in patients with type 1 diabetes mellitus. Patients were randomized to receive once daily basal insulin (HOE901-U300 or Lantus) and to the sequence of the injection time during study period A and study period B (morning then evening or evening then morning) with a ratio of 1:1:1:1. No formal sample size estimation was performed for this exploratory study.

Number of patients: planned 56, randomized 59, treated 59, Evaluated: efficacy 59, safety 59

Diagnosis and criteria for inclusion: Inclusion criteria: Patients with type 1 diabetes mellitus; signed written informed consent. Key exclusion criteria: Age <18 years and >70 years; HbA1c >9% at screening; less than 1 year on basal plus mealtime insulin; Patients receiving >0.5 U/kg body weight basal insulin and patients not on stable insulin dose (±20% total basal insulin dose) in the last 30 days prior to screening visit; Hospitalization for diabetic ketoacidosis or history of severe hypoglycemia (requiring 3rd party assistance) in the last 6 months prior to randomization.

Study treatments

Investigational medicinal products: Tested drug: HOE901-U300; Control drug: Lantus

Formulations: HOE901-U300 was supplied as 300 U/mL insulin glargine solution for subcutaneous (SC) injection in 3 mL cartridges. Lantus was supplied as insulin glargine solution for SC injection 100 U/mL in 10 mL vials.

Route of administration: SC injection

Injection of HOE901-U300 was through the commercially available BD Ultra-Fine™ Short Needle Insulin Syringe with half-unit-scale. Injection of Lantus was to be done using commercially available BD insulin syringes:

- for doses of 1–30 U insulin glargine: BD Ultra-Fine™ Short Needle Insulin Syringe with half-unit-scale [8 mm (5/16") x 31 G];
- for doses >30 U insulin glargine: BD Ultra-Fine™ Short Needle Insulin Syringe [8 mm (5/16") x 31 G] with whole unit scale.

Dose regimen: Once daily injection in the morning or evening for 8 weeks during Period A then in the evening or morning respectively for another 8 weeks during Period B according to randomization.

Starting dose: Patients on Lantus or on once daily NPH or once daily insulin detemir prior to the baseline visit: the daily dose (U) of HOE901-U300 or Lantus was equal to the daily basal insulin doses on the day prior to the baseline visit. Patients on more than once daily NPH or insulin detemir prior to the baseline visit: 80% of total daily NPH or

insulin detemir dose (= total daily dose reduced by 20%) on the day prior to the baseline visit.

Doses during the study: Dosing of insulin glargine given as HOE901-U300 or Lantus was done based on self-measured, fasting, pre breakfast plasma glucose levels (target range 80–130 mg/dL; 4.4–7.2 mmol/L), and taking into account also the presence of hypoglycemia. Minimum dose increments for the basal insulin were to be 1.5 U.

Batch number: HOE901 – U300: C1011129; Lantus: supplied by local pharmacies.

Non-investigational medicinal products: Short-acting mealtime (bolus) insulin analogue (glulisine, aspart or lispro).

Patients in both treatment groups were to continue with their mealtime insulin analogue during the study.

Mealtime insulin doses were to be adjusted based on SMPG data, including 2-hour postprandial plasma glucose results and the carbohydrate content of the meal to optimize glycemic control. The target range for 2-hour postprandial plasma glucose was <160 mg/dL (8.3 mmol/L). Bolus insulin doses could be reduced as basal insulin doses were increased.

Duration of treatment: Up to 16 weeks (8 weeks during Period A and 8 weeks during Period B)

Duration of observation:

- Up to 4-week screening (including a 2-week CGM training period);
- 2x8-week comparative efficacy and safety treatment period;
- 4 week post-treatment safety follow-up period after study completion or permanent discontinuation of study treatment.

In total the maximum study duration was up to 24 weeks per patient

Criteria for evaluation:

Efficacy

Primary efficacy endpoint: Percent (%) of time in glycemic range of 80-140 mg/dL (4.4-7.8 mmol/L) during week 7 and 8 within treatment period A and during week 15 and 16 in treatment period B based on CGM.

Secondary efficacy endpoints: Percent time above upper limit/below lower limit of glycemic range (%time in hyperglycemia/hypoglycemia).

The following secondary efficacy endpoints are not presented in this KRM: Diurnal glucose exposure; Diurnal glucose stability; Diurnal glucose variability; Mean and variation in glucose profiles; Average time within glycemic range in the last four hours of each dosing interval during 14 days of CGM usage in the last 2 weeks of the 8 weeks treatment period; Hyperglycemic AUC (Area below the CGM profile and above the upper limit of the glycemic range divided by total time period); and hypoglycemic AUC (Area above the CGM profile and below the lower limit of the glycemic range divided by total time period.

Further secondary efficacy endpoints: insulin dose; Not presented in this KRM: HbA_{1c}, fasting plasma glucose (FPG), pre-injection SMPG, 7-point SMPG.

Safety

Hypoglycemia, occurrence of adverse events particularly treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), injection site reactions and hypersensitivity reactions. Following information not presented in KRM: physical examination, other safety information including clinical laboratory data, vital signs and 12-lead ECG.

Statistical methods:

The primary endpoint was analyzed using a linear mixed model with treatment (HOE901-U300 or Lantus) and period (treatment period A or B) as fixed effects, and patient as random effect. Adjusted mean estimates for each treatment with standard errors, the adjusted estimate of treatment mean difference with standard error and a 95 % confidence interval for the treatment mean difference will be provided. The statistical test was two-sided tests at a nominal 5% significance level. The same model was used for secondary efficacy endpoints %time in hyperglycemia/hypoglycemia, diurnal glucose exposure, diurnal glucose stability and diurnal glucose variability. Other efficacy endpoints were descriptive. CGM related parameters were analyzed based on CGM population, non-CGM parameters were based on mITT population.

Safety analyses were descriptive, based on the safety population.

Summary:

Population characteristics:

A total of 59 patients with type 1 diabetes were randomized to 1 of 4 arms: HOE901-U300 morning injection in Period A followed by evening injection in Period B (n=15), HOE901-U300 evening then morning injection (n=15), Lantus morning then evening injection (n=15), or Lantus evening then morning injection (n=14). A total of 59 patients were exposed to IMP (safety population) and included in the mITT and CGM populations (efficacy populations). One patient (3.3%) in the HOE901-U300 group and 3 patients (10.3%) in the Lantus group discontinued the study treatment prematurely. Demographics and baseline characteristics were balanced between treatment groups. The mean age of the study population was 44.2 years, 2 patients were 65 years or older. All patients were Caucasian. The mean BMI at baseline was 27.3 kg/m^2. The mean duration of diabetes prior to study start was 22.1 years. The median dose of daily total insulin was 0.565 U/kg body weight. Mean HbA_{1c} at baseline was 7.46%.

Efficacy results:

Primary efficacy endpoint: During the last 2 weeks of each 8-week treatment period, when the basal insulin dose was to be kept as stable as possible, plasma glucose measured by CGM was observed within glycemic range in 31.75% (LS mean) of time in the HOE901-U300 group and in 30.99% (LS mean) of time in the Lantus group. The LS mean difference was 0.75% [95% CI:-3.614 to 5.124].

Secondary efficacy endpoints: During the last 2 weeks of each 8-week treatment period, percent time above the upper limit of glycemic range of 140 mg/dL (7.8 mmol/L) was comparable between treatment groups (58.24% in the HOE901-U300 group and 57.38% in the Lantus group in LS mean), so was the percent of time below the lower limit of 80 mg/dL (4.4 mmol/L) with 10.01% in the HOE901-U300 group and 11.64% in the Lantus group in LS mean.

Graphical presentation of average glucose based on CGM by hour of the day during the entire treatment period (Figure 11) suggests smaller excursions in the HOE901-U300 group than in the Lantus group. The profile appears flatter with HOE901-U300 than with Lantus even more during morning injection period (Figure 12) than during evening injection period (Figure 13).

Overall, in the HOE901-U300 and in the Lantus treatment groups, basal insulin was similarly increased mostly in the first 6 weeks of the study and remained relatively stable thereafter (at baseline, mean daily basal insulin dose was similar in both treatment groups: HOE901-U300: 24.9 units; Lantus: 25.0 units; at week 16, HOE901-U300: 30.11 units; Lantus: 28.22 units).

Mean mealtime insulin daily dose was higher at baseline in the HOE901-U300 group (29.92 units) than in the Lantus group (23.69 units), but was comparable at week 16 (HOE901-U300: 27.34 units; Lantus: 26.31 units).

Safety results:

During the on-treatment period, the percentages of patients experiencing hypoglycemia were generally comparable for overall and each category of hypoglycemia events (all hypoglycemia) in the HOE901-U300 group and the Lantus group. Consistently, similarity was observed in the hypoglycemia reporting between the following subgroups:

- the morning and evening injection groups within the HOE901-U300 group;
- the morning and evening injection groups within the Lantus group;
- the HOE901-U300 morning injection groups and the Lantus morning injection groups;
- the HOE901-U300 evening injection groups and the Lantus evening injection groups;

The percentages of patients experiencing nocturnal hypoglycemia were consistently lower in the HOE901-U300 group than in the Lantus group regardless of morning or evening injection time. The favorable numerical trends in the HOE901-U300 group have to be interpreted with caution because of the small number of patients.

The percentage of patients with any TEAEs was higher in the HOE901-U300 group (24/30 [80.0%]) than in the Lantus group (19/29 [65.5%]). In the HOE901-U300 group, one patient experienced serious intestinal obstruction (unrelated to IMP) and another patient discontinued treatment due to pregnancy. No death was reported during the study. TEAEs linked to injection site reactions were observed in 2/30 [6.7%] patients of the HOE901-U300 group, and in 1/29 [3.4%] patient of the Lantus group. There is no concern regardingTEAEs linked to hypersensitivity reaction which occurred in 4/40 patients of the HOE901-U300 group and in 1/30 patient of the Lantus group.

Conclusions:

Plasma glucose measured by CGM was observed within glycemic target range (80-140 mg/dL or 4.4-7.8 mmol/L) for a similar percentage of time during the last 2 weeks of each 8-week treatment period in the HOE901-U300 group and in the Lantus group. Notably, this target range was tighter as compared with the ADA recommendation of 70-180 mg/dL (3.9-10.0 mmol/L).

In both treatment groups, the percent time spent above upper limit of glycemic range was higher (57%-58%) than the percent time spent below lower limit of target range (10-11%).

Overall, the percentage of patients with at least one event regardless of the category of hypoglycemia, during study was comparable in both treatment groups (HOE901-U300, Lantus) and for both injection times (morning or evening). The numerical trends in favor of the HOE901-U300 group for nocturnal hypoglycemia have to be interpreted with caution because of the small number of patients.

HOE901-U300 and Lantus, administered either in the morning or in the evening, were well tolerated during the study period, and no specific safety concerns were observed.

Example 5: An investigational new insulin U300: glucose control and hypoglycemia in type 2 diabetes with basal insulin (EDITION II)

Aims: An investigational new insulin U300 with an even flatter and more prolonged PK/PD profile than insulin glargine 100 U/mL (U100) is in clinical development. The phase 3 EDITION II study compared the efficacy and safety of U300 versus U100 in people with T2DM using a basal-insulin regimen in combination with OAD.

Methods: In this multicenter, open-label, 6-month study, participants were randomized (1:1) to U300 or U100 once daily in the evening. Insulin dose was titrated to a target fasting plasma glucose (FPG) of 80-100 mg/dL. The primary endpoint was change in HbA_{1c} from baseline to 6 months and the 1st main secondary efficacy endpoint in a hierarchical analysis was the percentage of participants with ≥1 severe or confirmed (≤70 mg/dL) nocturnal (2400–0559 h) hypoglycemic event from week 9 to month 6.

Results: 811 participants were randomised [mean age 58.2 (SD 9.2) yr, duration of diabetes 12.6 (7.0) yr, BMI 34.8 (6.4) kg/m^2, basal insulin dose 0.67 (0.24) U/kg]. Baseline HbA_{1c} was comparable between groups; U300: 8.26 (0.86) % vs U100: 8.22 (0.77) %. U300 was non-inferior to U100 for change in HbA_{1c} [LS mean change -0.57 (SE: 0.09) % and -0.56 (SE: 0.09) %, respectively at 6 months; difference -0.01 (95% CI: -0.14 to +0.12) %]. No relevant differences were seen for FPG, 8-point self-monitored plasma glucose profiles and pre-injection plasma glucose. The percentage of participants with severe or confirmed nocturnal hypoglycemia was significantly lower with U300 vs U100 from week 9 to month 6 [21.6% vs 27.9%; relative risk (RR) 0.77 (95% CI: 0.61 to 0.99); p=0.038]. Over the 6-month treatment period, the incidence of

any nocturnal hypoglycemia (% of participants with ≥1 event) was lower with U300 vs U100 [30.5% vs 41.6%; RR 0.73 (95% CI: 0.60 to 0.89)] as was the incidence of any hypoglycemic event at any time of the day (24h) [U300 71.5%; U100 79.3%; RR 0.90 (95% CI: 0.84 to 0.97)]. Severe hypoglycemia at any time of day was reported by 1.0% of U300 and 1.5% of U100 participants. No between-treatment differences in serious adverse events were seen.

Conclusion: In people with T2DM using a basal-insulin regimen with OAD, U300 was well tolerated and as effective as U100 in blood glucose control. U300 was associated with 23% reduction in severe or confirmed nocturnal hypoglycemia from week 9 to month 6 compared with U100 and with a lower incidence of any nocturnal hypoglycemia event and hypoglycemia at any time of the day (24h) over the entire 6-month study duration.

Example 6: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both in combination with oral antihyperglycemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period - Administration Sub-study Comparing Adaptable Dosing Intervals with Fixed dosing intervals

1 SYNOPSIS

Phase of development: Substudy to phase 3 main study

Objectives:

Primary Objective: To compare the efficacy of HOE901-U300 injected once daily every 24 hours and HOE901-U300 injected once daily at intervals of 24 ± 3 hours in terms of change of HbA1c from month 6 of the main study (=baseline of sub-study) to month 9 of the main study (=endpoint of sub-study) in patients with type 2 diabetes mellitus.

Main secondary Objectives: To compare the safety of the two injection regimens for HOE901-U300 in terms of occurrence of hypoglycemia.

Methodology:

Patients randomized on HOE901-U300 and having received HOE901-U300 in the 6-month main study period are randomized 1:1 to administer HOE901-U300 once daily either every 24 hours (fixed dosing intervals) or every 24 ± 3 hours (adaptable dosing intervals).

Patients on HOE901-U300 completing the 6-month main study period and meeting the eligibility criteria for the sub-study were eligible for the sub-study. No specific sample size was requested for the primary analysis that is descriptive.

Number of patients: Planned: up to 300 (150 pre treatment arm)
Randomized: 89
Treated: 87
Evaluated: Efficacy: 86 Safety: 87

Diagnosis and criteria for inclusion:

Inclusion criteria: Completion of the 6-month study period in main study (Visit 10), Randomized and treated with HOE901-U300 during the 6-month treatment period (Baseline – month 6), Signed written informed consent for sub-study obtained.

Key exclusion criteria: Patient not willing to use the adaptable injection intervals of 24 ± 3 hours on at least two days per week; In the investigator's opinion, not able to comply with an adaptable dosing schedule; Health condition which precludes further participation of the patient in the study.

Study treatments

Investigational medicinal product: Tested drug: HOE901-U300

Formulation: HOE901-U300 (insulin glargine 300 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution in a glass cartridge assembled in a pen-injector (prefilled, disposable pen).

Route of administration: subcutaneous injection

Tested regimen:

Adaptable dosing intervals: HOE901-U300 administered once daily every 24 ± 3 hours.

The injection time may have been adapted according to individual needs by up to 3 hours earlier or later than the daily reference injection time in the evening fixed at the start of the main study. The maximum intervals, ie, 3 hours earlier or 3 hours later than the fixed daily reference injection time was to be used on at least 2 days of the week at the patients' choice. The injection time fixed at start of the main study was to be maintained as reference time for the variation.

Control regimen:

Fixed dosing intervals: HOE901-U300, once daily injection every 24 hours.

Patients continued to inject HOE901-U300 once daily every 24 hours at the injection time fixed at start of the main study.

Dose:

The dose of HOE901-U300 was to be titrated as needed to achieve or maintain fasting plasma glucose in the target range of 80 to 100 mg/dL (4.4mmol/L to 5.6mmol/L) without hypoglycemia. Changes in the insulin dose were based on fasting self-monitored capillary plasma glucose (SMPG) measurements.

Non-investigational medicinal products:

Patients in both treatment regimens were to continue their oral antihyperglycemic background therapy during participation in the sub-study. Doses were to be kept stable throughout the study unless there was a specific safety issue related to these treatments. No other concomitant anti-diabetic treatments were to be used in this study.

Short term use (ie, 10 days at maximum) of short-acting insulin therapy (eg, due to acute illness or surgery) was not considered as rescue therapy. Rescue medication was considered as Non-investigational Medicinal Product.

Duration of treatment: The sub-study consisted of a 3 month comparative efficacy and safety treatment period starting at completion of the 6-month main study period and ending at completion of Month 9 of the main study.

After completion, patients on the adaptable dosing arm may have continued this regimen up to the end of the main study (Month 12). Patients injecting HOE901-U300 every 24 hours continued with their treatment regimen up to the end of the main study.

Duration of observation: The analysis period for efficacy and safety is the 3-month study period starting at Month 6 of the main study and ending at Month 9 of the main study. Results presented in the present KRM refer to this period.

Criteria for evaluation:

Primary efficacy endpoint: change in HbA_{1c} from baseline (Month 6) to endpoint (Month 9).

Secondary efficacy endpoints: change in FPG (central laboratory) and change in daily dose of basal insulin, from baseline (Month 6) to endpoint (Month 9).

Safety: Hypoglycemia (including nocturnal), occurrence of adverse events particularly treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), TEAEs leading to withdrawal, injection site reactions and hypersensitivity reactions. Following information not presented in KRM: other safety information including vital signs and overdose.

Statistical methods:

For this 3-month sub-study, Baseline is defined as Month 6 of the main study; the Endpoint is Month 9 of the main study using last observation carried forward (LOCF) procedure.

The primary efficacy endpoint (change in HbA_{1c} from baseline [Month 6] to endpoint [Month 9]) was analyzed using an analysis of covariance (ANCOVA) model with treatment regimen and country as fixed effects and using the HbA_{1c} baseline value as a covariate. Differences between HOE901-U300 adaptable dosing regimen and HOE901-U300 fixed dosing regimen and two-sided 95% confidence intervals were estimated within the framework of ANCOVA.

All continuous secondary efficacy variables were analyzed using an ANCOVA model with treatment regimen and country as fixed effects and using the corresponding baseline value as a covariate.

Safety analyses were descriptive, based on the safety population.

Summary

Population characteristics:

A total of 89 patients with type 2 diabetes mellitus were randomized to the sub-study: 45 patients to the HOE901-U300 adaptable dosing interval regimen and 44 patients to the HOE901-U300 fixed dosing interval regimen; 87 patients were exposed to IMP (safety population). The mITT sub-study population (efficacy population) included 86 patients.

A total of 40 (88.9%) patients randomized to HOE901-U300 adaptable dosing intervals and 38 (86.4%) randomized to HOE901-U300 fixed dosing intervals completed the 3-month comparative regimen period.1 patient (2.2%) randomized to HOE901-U300 adaptable dosing intervals and 2 patients (4.5%) randomized to HOE901-U300 fixed

dosing intervals discontinued the sub-study prematurely and also discontinued the extension period of the main study.

Demographics and patient characteristics at baseline (Month 6) were well-balanced between both regimen groups. The mean age of the sub-study population was 57.8 years; 16 of 89 (18.0%) patients were ≥ 65 years. 3 patients in the adaptable dosing interval regimen and 2 patients in the fixed dosing interval regimen were on insulin or insulin secretagogue started as rescue therapy during the main study period. No patient in either regimen group started rescue therapy during the 3-month comparative regimen period.

Compliance to dosing interval regimens:

Compliance to dosing interval regimen was assessed taking into account the time interval between 2 consecutive injections and the time interval between an injection and the reference injection time as scheduled at the main study baseline.

During the sub-study, on average 28.04% of the injections per patient in the adaptable dosing interval group were taken at the extreme intervals of <21.5 hours or >26.5 hours between 2 consecutive injections versus 2.41% of injections in patients in the fixed dosing interval group, while 88.77% of the injections per patient in the fixed dosing interval group versus 53.09% of the injections per patient in the adaptable dosing interval group were taken within a 23-25 hour interval between 2 consecutive injections.

Evaluation of the time intervals between the actual injection and the reference injection times showed a higher percentage of injections per patient within the 23–25 hour interval in the fixed dosing interval group (mean 65.07%) compared with the adaptable dosing interval group (56.38%). In the adaptable dosing interval group 21.69% injections per patient were taken at intervals of 21.5-23 hours or at intervals of 25-26.5 hours (25.51% in the fixed dosing interval group). These data suggest that the majority of injections were taken up to 3 hours before or after the reference injection time, which was to be fixed as per protocol in the evening.

Based on the documented injection times during the week preceding the visits at Month 7.5 and at Month 9, a total of 47.5% of patients in the adaptable dosing group had 4 or more of their injection intervals outside the 21.5-26.5 hours interval after previous injection and therefore were considered to be compliant with the adaptable dosing interval regimen versus 2.6% of patients in the fixed dosing interval regimen. In the fixed dosing interval group, in 61.5% of patients all consecutive injection intervals were within 23-25 hours and therefore patients can be considered to be compliant with the fixed dosing interval regimen.

Efficacy:

Primary efficacy endpoint (Month 9): The LS mean change in HbA_{1c} from baseline (Month 6) to endpoint (Month 9) was similar in the groups of adaptable dosing intervals (-0.12% [95% CI: -0.422 to 0.183]) and fixed dosing intervals (-0.25% [95 %CI: -0.574 to 0.072]) with the LS mean difference of 0.13% [95 % CI: -0.152 to 0.415].

Secondary efficacy endpoints (Month 9): The LS mean change in FPG from baseline (Month 6) to endpoint (Month 9) was similar in the groups of adaptable dosing intervals (-0.46 mmol/L [95% CI: -1.521 to 0.609]) and fixed dosing intervals (-0.25 mmol/L [95% CI: -1.378 to 0.881]) with the LS mean difference of -0.21 [95 % CI: -1.200 to 0.784].

In both dosing interval regimens, the average daily basal insulin dose remained stable during the 3-month comparative regimen period

Safety:

During the 3-month comparative substudy period, hypoglycemia events were reported in 16/44 (36.4%) of patients in the adaptable dosing interval regimen and 18/43 (41.9%) of patients in the fixed dosing interval regimen Each category of hypoglycemia event was reported by a comparable percentage of patients in both regimens. No event of severe hypoglycemia or severe nocturnal hypoglycemia occurred in either regimen.

The percentages of patients with any TEAE (adaptable dosing intervals 9/44 [20.5%]; fixed dosing intervals 11/43 [25.6%]) or with a serious TEAE (adaptable dosing intervals 2/44 [4.5%]; fixed dosing intervals 0/43) were comparable between the regimens.

No TEAEs leading to treatment discontinuationor to death, or linked to injection site reaction or to hypersensitivity reaction were observed in either dosing interval regimen during the 3-month substudy period.

Conclusions:

The evaluation of the duration of the injection intervals and the % patients with shorter or longer injection intervals than the regular 24-hour period suggests that the majority of patients in both dosing interval regimen groups followed the injection schedule as randomized and used either adaptable dosing intervals (HOE901-U300 once daily every 24 hours $\pm$ 3 hours on at least 2 days a week) or fixed dosing intervals (HOE901-U300 once daily every 24 hours). This allows a comparison of the two dosing interval regimens for efficacy and safety analyses.

The efficacy analyses in terms of HbA1c and FPG change from baseline (Month 6) to endpoint (Month 9) showed comparable results for the two dosing interval regimens.

Overall incidence of hypoglycemia (% of patients with at least one event) during the 3-month substudy period was comparable in both regimens regardless of the category of hypoglycemia.

HOE901-U300 given at either adaptable or fixed dosing intervals was well tolerated during the 3-month comparative substudy period; no specific safety concerns were observed.

Taken together, the substudy results suggest that occasional adaptation of the injection intervals by up to 3 hours earlier or later than the reference time for the once daily injection for HOE901-U300 had no effects on main efficacy (HbA1c) and safety endpoints, particularly hypoglycemia events, as compared with once daily injections at 24-hour intervals.

2 RESULTS

2.1 STUDY PATIENTS

2.1.1 Study disposition

Table 60 *- Patient disposition – Randomized sub-study population*

	HOE901-U300 Adaptable Dosing Intervals (N=45)	**HOE901-U300 Fixed Dosing Intervals (N=44)**
Randomized and treated	44 (97.8%)	43 (97.7%)
Completed 3-month comparative regimen period	40 (88.9%)	38 (86.4%)
Rescue intake during the 3-month comparative regimen period [a]	3 (6.7%)	2 (4.5%)
Permanently discontinued the IMP during the 3-month comparative regimen period	1 (2.2%)	2 (4.5%)
Subject's request for treatment discontinuation	1 (2.2%)	1 (2.3%)
Reason for treatment discontinuation during the 3-month comparative regimen period		
Adverse event	0	0
Lack of efficacy	0	0
Poor compliance to protocol	0	1 (2.3%)
Other reasons	1 (2.2%)	1 (2.3%)

	HOE901-U300 Adaptable Dosing Intervals (N=45)	HOE901-U300 Fixed Dosing Intervals (N=44)
Status at last study contact of patients who permanently discontinued the treatment during the 3-month comparative regimen period		
Alive	1 (2.2%)	2 (4.5%)
Dead	0	0

Note: percentages are calculated using the number of patients randomized as denominator.
[a] Includes patients who started rescue therapy during the main 6-month period and continued during the 3-month comparative regimen period.

Table 61 *- Sub-study analysis populations*

	HOE901-U300 Adaptable Dosing Intervals	HOE901-U300 Fixed Dosing Intervals	All
Randomized sub-study population	45 (100%)	44 (100%)	89 (100%)
Efficacy sub-study populations			
Modified Intent-to-Treat (mITT)	44 (97.8%)	42 (95.5%)	86 (96.6%)
Sub-study completers	40 (88.9%)	38 (86.4%)	78 (87.6%)
Safety sub-study population	44	43	87

Note: patients are tabulated according to their randomized treatment.

2.1.2 Demographics and baseline characteristics

Table 62 *- Demographics and patient characteristics at baseline - Randomized sub-study population*

	HOE901-U300 Adaptable Dosing Intervals (N=45)	HOE901-U300 Fixed Dosing Intervals (N=44)	All (N=89)
Age (years)			
Number	45	44	89
Mean (SD)	58.4 (8.2)	57.2 (10.0)	57.8 (9.1)
Median	59.0	57.0	58.0
Min : Max	27 : 72	33 : 84	27 : 84
Age Group (years) [n(%)]			
Number	45	44	89
<65	36 (80.0%)	37 (84.1%)	73 (82.0%)
[65-75[	9 (20.0%)	6 (13.6%)	15 (16.9%)
≥ 75	0	1 (2.3%)	1 (1.1%)

	HOE901-U300 Adaptable Dosing Intervals (N=45)	HOE901-U300 Fixed Dosing Intervals (N=44)	All (N=89)
Gender [n (%)]			
Number	45	44	89
Male	22 (48.9%)	22 (50.0%)	44 (49.4%)
Female	23 (51.1%)	22 (50.0%)	45 (50.6%)
Race [n (%)]			
Number	45	44	89
Caucasian/White	42 (93.3%)	40 (90.9%)	82 (92.1%)
Black	3 (6.7%)	3 (6.8%)	6 (6.7%)
Asian/Oriental	0	0	0
Other	0	1 (2.3%)	1 (1.1%)
Ethnicity [n (%)]			
Number	45	44	89
Hispanic	5 (11.1%)	7 (15.9%)	12 (13.5%)
Not Hispanic	40 (88.9%)	37 (84.1%)	77 (86.5%)
World region [n (%)]			
Number	45	44	89
North America	22 (48.9%)	29 (65.9%)	51 (57.3%)
Western Europe	3 (6.7%)	1 (2.3%)	4 (4.5%)
Eastern Europe	20 (44.4%)	13 (29.5%)	33 (37.1%)
Rest of the world	0	1 (2.3%)	1 (1.1%)

Age is assessed at main study baseline.

Table 63 *- Baseline (Month 6) efficacy data related to dosing interval - Randomized sub-study population*

	HOE901-U300 Adaptable Dosing Intervals (N=45)	HOE901-U300 Fixed Dosing Intervals (N=44)	All (N=89)
Average injection time between 2 consecutive injections (hours)			
Number	41	40	81
Mean (SD)	23.98 (0.13)	23.99 (0.12)	23.99 (0.13)
Median	24.00	24.00	24.00
Q1 : Q3	24.00 : 24.00	24.00 : 24.02	24.00 : 24.01
Min : Max	23.2 : 24.1	23.3 : 24.2	23.2 : 24.2

	HOE901-U300 Adaptable Dosing Intervals (N=45)	HOE901-U300 Fixed Dosing Intervals (N=44)	All (N=89)
Average injection time from reference injection (hours)			
Number	42	41	83
Mean (SD)	24.13 (0.58)	24.20 (1.32)	24.16 (1.01)
Median	24.00	24.00	24.00
Q1 : Q3	24.00 : 24.50	23.98 : 24.38	24.00 : 24.49
Min : Max	22.6 : 25.6	20.2 : 28.7	20.2 : 28.7

Average: mean interval value over at least 3 times intervals during the last 7 days preceding month 6.

2.1.3 Compliance to dosing interval regimen

Table 64 *- Compliance – Dosing interval regimen compliance during the 3-month comparative regimen period – Percentage of injections per patient by dosing interval category (time between 2 consecutive injections) - Safety sub-study population*

% of injections by patient	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
<21.5 hours or >26.5 hours		
Number	40	38
Mean (SD)	28.04 (24.38)	2.41 (8.86)
Median	28.64	0.00
Q1 : Q3	0.00 : 52.27	0.00 : 0.00
Min : Max	0.0 : 75.0	0.0 : 50.0
[23 – 25] hours		
Number	40	38
Mean (SD)	53.09 (27.19)	88.77 (20.54)
Median	47.73	100.00
Q1 : Q3	33.33 : 75.00	83.33 : 100.00
Min : Max	8.3 : 100.0	16.7 : 100.0
[21.5 – 23[hours or]25 – 26.5] hours		
Number	40	38
Mean (SD)	18.86 (20.88)	8.81 (17.13)
Median	9.09	0.00
Q1 : Q3	0.00 : 33.33	0.00 : 8.33
Min : Max	0.0 : 66.7	0.0 : 80.0

Note: Percentage of injections (time between 2 consecutive injections) in each dosing interval category is calculated for each patient using all injection intervals obtained during the last 7 days values before Month 7.5 and Month 9 visits.
Note: Only patients with at least 3 time intervals during the last 7 days values before Month 7.5 or Month 9 visits are considered for this table.

Table 65 *- Compliance – Dosing interval regimen compliance during the 3-month comparative regimen period – Number (%) patients by injection interval between 2 consecutive injections - Safety sub-study population*

Number (%) of patients with	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
≥ 12 injection intervals in the range of [23-25] hours	4/40 (10.0%)	17/39 (43.6%)
100% of injection intervals in the range of [23-25] hours	6/40 (15.0%)	24/39 (61.5%)
≥ 4 injection intervals > 25 hours or <23 hours	27/40 (67.5%)	5/39 (12.8%)
≥ 4 injection intervals > 25 hours	18/40 (45.0%)	1/39 (2.6%)
≥ 4 injection intervals <23 hours	13/40 (32.5%)	1/39 (2.6%)
≥ 4 injection intervals > 26.5 hours or <21.5 hours	19/40 (47.5%)	1/39 (2.6%)
≥ 4 injection intervals >26.5 hours	7/40 (17.5%)	0/39
≥ 4 injection intervals <21.5 hours	3/40 (7.5%)	1/39 (2.6%)

Note: Number of injections (time between 2 consecutive injections) is calculated using all injection intervals (maximum 12) obtained during the last 7 days values before Month 7.5 and Month 9 visits.

Table 66 *- Compliance – Dosing interval regimen compliance during the 3-month comparative regimen period – Percentage of injections (time from reference injection) by dosing interval category - Safety sub-study population*

% of injections by patient	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
<21.5 hours or >26.5 hours		
Number	40	39
Mean (SD)	21.93 (21.45)	9.42 (26.43)
Median	28.57	0.00
Q1 : Q3	0.00 : 28.57	0.00 : 0.00
Min : Max	0.0 : 100.0	0.0 : 100.0
[23 – 25] hours		
Number	40	39
Mean (SD)	56.38 (28.41)	65.07 (39.62)
Median	64.29	85.71
Q1 : Q3	40.66 : 71.43	28.57 : 100.00
Min : Max	0.0 : 100.0	0.0 : 100.0

% of injections by patient	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
[21.5 – 23[hours or]25 – 26.5] hours		
Number	40	39
Mean (SD)	21.69 (23.29)	25.51 (34.30)
Median	14.84	7.14
Q1 : Q3	0.00 : 35.71	0.00 : 50.00
Min : Max	0.0 : 100.0	0.0 : 100.0

Note: Percentage of injections (time from reference injection chosen at the start of the main study) in each dosing interval category is calculated for each patient using all injection intervals obtained during the last 7 days values before Month 7.5 and Month 9 visits.
Note: Only patients with at least 3 time intervals during the last 7 days values before Month 7.5 or Month 9 visits are considered for this table.

2.2 EFFICACY EVALUATION

2.2.1 Primary efficacy endpoint

Table 67 *- Main efficacy analysis - Mean change in HbA1c (%) from baseline (month 6) to Month 9 endpoint using LOCF procedure - mITT sub-study population*

HbA1c (%)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=42)
Baseline (month 6)		
Number	40	37
Mean (SD)	7.41 (0.96)	7.47 (1.05)
Median	7.35	7.30
Min : Max	5.8 : 9.1	5.9 : 10.3
Month 9 endpoint (LOCF)		
Number	40	37
Mean (SD)	7.47 (0.87)	7.49 (1.11)
Median	7.35	7.30
Min : Max	6.0 : 9.1	5.8 : 10.0
Change from baseline to Month 9 endpoint (LOCF)		
Number	40	37
Mean (SD)	0.06 (0.64)	0.02 (0.63)
Median	0.00	-0.10
Min : Max	-1.3 : 1.7	-1.3 : 1.5
LS Mean (SE) [a]	-0.12 (0.151)	-0.25 (0.162)
95% CI	(-0.422 to 0.183)	(-0.574 to 0.072)

HbA1c (%)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=42)
LS Mean difference (SE) vs. HOE901-U300 Fixed Dosing Intervals [a]	0.13 (0.142)	
95% CI	(-0.152 to 0.415)	

LOCF = Last observation carried forward.
[a] Analysis of covariance (ANCOVA) model with treatment regimen and country as fixed effects and baseline HbA1c value as a covariate.
Note: For all patients rescued during the 3-month comparative regimen period, the last postbaseline HbA1c measurement before rescue and during sub-study 3-month on-treatment period will be used as the HbA1c endpoint.

Figure 14 describes the mean HbA1c (%) by visit during the 3-month comparative regimen period - mITT sub-study population.

2.2.2 Secondary endpoints

2.2.2.1 Fasting plasma glucose

Table 68 *- Mean change in FPG (mmol/L) from baseline (month 6) to Month 9 endpoint using LOCF procedure - mITT sub-study population*

FPG (mmol/L)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=42)
Baseline (month 6)		
Number	39	38
Mean (SD)	7.08 (1.83)	7.13 (2.71)
Median	7.00	6.45
Min : Max	3.7 : 9.9	3.3 : 13.8
Month 9 endpoint (LOCF)		
Number	39	38
Mean (SD)	7.38 (2.30)	7.44 (2.16)
Median	7.10	7.25
Min : Max	3.3 : 11.7	4.1 : 12.5
Change from baseline to Month 9 endpoint (LOCF)		
Number	39	38
Mean (SD)	0.30 (2.44)	0.31 (2.62)
Median	0.10	0.30
Min : Max	-3.7 : 5.9	-6.7 : 5.5
LS Mean (SE) [a]	-0.46 (0.534)	-0.25 (0.566)
95% CI	(-1.521 to 0.609)	(-1.378 to 0.881)
LS Mean difference (SE) vs. HOE901-U300 Fixed Dosing Intervals [a]	-0.21 (0.497)	

FPG (mmol/L)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=42)
95% CI	(-1.200 to 0.784)	

FPG=Fasting Plasma Glucose.
LOCF = Last observation carried forward.
[a]Analysis of covariance (ANCOVA) model with treatment regimen and country as fixed effects and baseline FPG value as a covariate.
Note: For all patients rescued during the 3-month comparative regimen period, the last postbaseline FPG measurement before rescue and during sub-study 3-month on-treatment period will be used as the FPG endpoint.

2.2.2.2 Basal insulin dose

Figure 15 describes the average daily basal (glargine) insulin dose (U) by visit during the 3-month comparative regimen period - mITT sub-study population.

2.3 SAFETY EVALUATION

2.3.1 Extent of exposure

Table 69 *- Exposure to investigational product during the 3-month comparative regimen period – Safety sub-study population*

	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
Cumulative exposure to the sub-study 3-month treatment (patient years)	10.98	10.40
Duration of the sub-study 3-month treatment (days)		
Number	44	42
Mean (SD)	91.2 (4.8)	90.4 (10.7)
Median	92.0	92.0
Min : Max	76 : 104	42 : 117
Duration of the sub-study 3-month treatment by category [n(%)]		
Missing duration	0	1 (2.3%)
up to 6 weeks	0	1 (2.3%)
>6 to 12 weeks	3 (6.8%)	3 (7.0%)
>12 weeks	41 (93.2%)	38 (88.4%)

	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
Cumulative duration of the sub-study 3-month treatment by category [n(%)]		
Missing duration	0	1 (2.3%)
≥ 1 days	44 (100%)	42 (97.7%)
>6 weeks	44 (100%)	41 (95.3%)
>12 weeks	41 (93.2%)	38 (88.4%)

2.3.2 Hypoglycemia

Table 70 *- Number (%) of patients with at least one hypoglycemia event during the 3-month comparative regimen period - Safety sub-study population*

	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)	
Type of hypoglycemia event n(%)	**HOE901-U300 Adaptable Dosing Intervals (N=44)**	**HOE901-U300 Fixed Dosing Intervals (N=43)**	**HOE901-U300 Adaptable Dosing Intervals (N=44)**	**HOE901-U300 Fixed Dosing Intervals (N=43)**
Any hypoglycemia event	16 (36.4%)	18 (41.9%)	7 (15.9%)	10 (23.3%)
Severe hypoglycemia	0	0	0	0
Documented symptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	10 (22.7%)	14 (32.6%)	5 (11.4%)	7 (16.3%)
< 3.0 mmol/L (54 mg/dL)	4 (9.1%)	5 (11.6%)	4 (9.1%)	2 (4.7%)
Asymptomatic hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	11 (25.0%)	9 (20.9%)	3 (6.8%)	4 (9.3%)
< 3.0 mmol/L (54 mg/dL)	1 (2.3%)	0	0	0
Probable symptomatic hypoglycemia	1 (2.3%)	2 (4.7%)	0	0
Relative hypoglycemia				
> 3.9 mmol/L (70 mg/dL)	0	2 (4.7%)	0	0
Severe and/or confirmed[a] hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	16 (36.4%)	18 (41.9%)	7 (15.9%)	10 (23.3%)
< 3.0 mmol/L (54 mg/dL)	4 (9.1%)	5 (11.6%)	4 (9.1%)	2 (4.7%)

n (%) = number and percentage of patients with at least one hypoglycemia event.
[a] Severe and/or confirmed hypoglycemia= severe and/or confirmed by plasma glucose≤ 3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL)).
Note: All hypoglycemia events with missing time are counted in the column "All hypoglycemia", but not classified as "nocturnal" or "daytime".

2.3.3 Treatment-emergent adverse events

Table 71 *- Treatment emergent adverse events during the 3-month comparative regimen period - Safety sub-study population*

n (%)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
Patients with any TEAE	9 (20.5%)	11 (25.6%)
Patients with any treatment emergent SAE	2 (4.5%)	0
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	0

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

Table 72 *- Number (%) of patients with TEAE(s) by primary SOC, HLGT, HLT and PT events during the 3-month comparative regimen period - Safety sub-study population*

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
Any class	9 (20.5%)	11 (25.6%)
INFECTIONS AND INFESTATIONS	3 (6.8%)	4 (9.3%)
HLGT: Infections - pathogen unspecified	2 (4.5%)	4 (9.3%)
HLT: Female reproductive tract infections	0	1 (2.3%)
Vaginal infection	0	1 (2.3%)
Vulvovaginitis	0	1 (2.3%)
HLT: Lower respiratory tract and lung infections	0	2 (4.7%)
Bronchitis	0	2 (4.7%)
HLT: Upper respiratory tract infections	1 (2.3%)	1 (2.3%)
Nasopharyngitis	1 (2.3%)	1 (2.3%)
HLT: Urinary tract infections	1 (2.3%)	0
Urinary tract infection	1 (2.3%)	0
HLGT: Viral infectious disorders	1 (2.3%)	0
HLT: Influenza viral infections	1 (2.3%)	0
Influenza	1 (2.3%)	0
METABOLISM AND NUTRITION DISORDERS	0	1 (2.3%)
HLGT: Electrolyte and fluid balance conditions	0	1 (2.3%)
HLT: Total fluid volume decreased	0	1 (2.3%)
Dehydration	0	1 (2.3%)
NERVOUS SYSTEM DISORDERS	0	3 (7.0%)
HLGT: Headaches	0	2 (4.7%)
HLT: Headaches NEC	0	2 (4.7%)
Headache	0	2 (4.7%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
Sinus headache	0	1 (2.3%)
HLGT: Structural brain disorders	0	1 (2.3%)
HLT: Structural brain disorders NEC	0	1 (2.3%)
Cerebral atrophy	0	1 (2.3%)
EAR AND LABYRINTH DISORDERS	0	2 (4.7%)
HLGT: Inner ear and VIIIth cranial nerve disorders	0	2 (4.7%)
HLT: Inner ear signs and symptoms	0	2 (4.7%)
Vertigo	0	2 (4.7%)
CARDIAC DISORDERS	0	1 (2.3%)
HLGT: Cardiac neoplasms	0	1 (2.3%)
HLT: Cardiac neoplasms NEC	0	1 (2.3%)
Pericardial cyst	0	1 (2.3%)
HLGT: Coronary artery disorders	0	1 (2.3%)
HLT: Coronary artery disorders NEC	0	1 (2.3%)
Coronary artery disease	0	1 (2.3%)
HLGT: Heart failures	0	1 (2.3%)
HLT: Heart failures NEC	0	1 (2.3%)
Cardiac failure congestive	0	1 (2.3%)
HLGT: Myocardial disorders	0	1 (2.3%)
HLT: Cardiomyopathies	0	1 (2.3%)
Congestive cardiomyopathy	0	1 (2.3%)
VASCULAR DISORDERS	0	2 (4.7%)
HLGT: Arteriosclerosis, stenosis, vascular insufficiency and necrosis	0	1 (2.3%)
HLT: Non-site specific necrosis and vascular insufficiency NEC	0	1 (2.3%)
Venous stenosis	0	1 (2.3%)
HLGT: Vascular hypertensive disorders	0	1 (2.3%)
HLT: Vascular hypertensive disorders NEC	0	1 (2.3%)
Hypertension	0	1 (2.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	3 (7.0%)
HLGT: Respiratory disorders NEC	0	1 (2.3%)
HLT: Breathing abnormalities	0	1 (2.3%)
Dyspnoea	0	1 (2.3%)
HLGT: Upper respiratory tract disorders (excl infections)	0	2 (4.7%)
HLT: Nasal congestion and inflammations	0	1 (2.3%)
Nasal congestion	0	1 (2.3%)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
HLT: Paranasal sinus disorders (excl infections and neoplasms)	0	1 (2.3%)
Sinus congestion	0	1 (2.3%)
GASTROINTESTINAL DISORDERS	0	1 (2.3%)
HLGT: Gastrointestinal signs and symptoms	0	1 (2.3%)
HLT: Nausea and vomiting symptoms	0	1 (2.3%)
Nausea	0	1 (2.3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (2.3%)	1 (2.3%)
HLGT: Epidermal and dermal conditions	0	1 (2.3%)
HLT: Papulosquamous conditions	0	1 (2.3%)
Lichen sclerosus	0	1 (2.3%)
HLGT: Skin and subcutaneous tissue disorders NEC	1 (2.3%)	0
HLT: Skin and subcutaneous tissue ulcerations	1 (2.3%)	0
Skin ulcer	1 (2.3%)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (6.8%)	1 (2.3%)
HLGT: Joint disorders	1 (2.3%)	0
HLT: Osteoarthropathies	1 (2.3%)	0
Spinal osteoarthritis	1 (2.3%)	0
HLGT: Musculoskeletal and connective tissue disorders NEC	1 (2.3%)	0
HLT: Musculoskeletal and connective tissue pain and discomfort	1 (2.3%)	0
Pain in extremity	1 (2.3%)	0
HLGT: Tendon, ligament and cartilage disorders	1 (2.3%)	1 (2.3%)
HLT: Cartilage disorders	1 (2.3%)	1 (2.3%)
Osteochondrosis	1 (2.3%)	1 (2.3%)
RENAL AND URINARY DISORDERS	1 (2.3%)	0
HLGT: Urolithiases	1 (2.3%)	0
HLT: Renal lithiasis	1 (2.3%)	0
Nephrolithiasis	1 (2.3%)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (2.3%)	0
HLGT: Vulvovaginal disorders (excl infections and inflammations)	1 (2.3%)	0
HLT: Vulvovaginal disorders NEC	1 (2.3%)	0
Vaginal haemorrhage	1 (2.3%)	0

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (4.5%)	1 (2.3%)
HLGT: General system disorders NEC	2 (4.5%)	1 (2.3%)
HLT: Asthenic conditions	0	1 (2.3%)
Fatigue	0	1 (2.3%)
HLT: Oedema NEC	1 (2.3%)	0
Oedema peripheral	1 (2.3%)	0
HLT: Pain and discomfort NEC	2 (4.5%)	0
Chest pain	1 (2.3%)	0
Non-cardiac chest pain	1 (2.3%)	0
INVESTIGATIONS	0	2 (4.7%)
HLGT: Cardiac and vascular investigations (excl enzyme tests)	0	1 (2.3%)
HLT: Vascular tests NEC (incl blood pressure)	0	1 (2.3%)
Blood pressure increased	0	1 (2.3%)
HLGT: Physical examination and organ system status topics	0	1 (2.3%)
HLT: Physical examination procedures and organ system status	0	1 (2.3%)
Weight increased	0	1 (2.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (2.3%)	0
HLGT: Medication errors	1 (2.3%)	0
HLT: Overdoses	1 (2.3%)	0
Accidental overdose	1 (2.3%)	0
SURGICAL AND MEDICAL PROCEDURES	0	1 (2.3%)
HLGT: Head and neck therapeutic procedures	0	1 (2.3%)
HLT: Paranasal therapeutic procedures	0	1 (2.3%)
Sinus operation	0	1 (2.3%)

TEAE: Treatment emergent adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term.
MedDRA 16.0.
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.

2.3.4 Serious treatment-emergent adverse events

Table 73 *- Number (%) of patients with treatment emergent SAE(s) by Primary SOC, HLGT, HLT and PT during the 3-month comparative regimen period - Safety sub-study population*

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
Any class	2 (4.5%)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (2.3%)	0
HLGT: Joint disorders	1 (2.3%)	0
HLT: Osteoarthropathies	1 (2.3%)	0
Spinal osteoarthritis	1 (2.3%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (2.3%)	0
HLGT: General system disorders NEC	1 (2.3%)	0
HLT: Pain and discomfort NEC	1 (2.3%)	0
Chest pain	1 (2.3%)	0

TEAE: Treatment emergent adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term.
MedDRA 16.0.
n (%) = number and percentage of patients with at least one treatment emergent SAE.
Note: Table sorted by SOC internationally agreed order and HLGT, HLT, PT by alphabetic order.

2.3.5 Treatment emergent adverse events leading to withdrawal

Table 74 *- Number (%) of patients with TEAE(s) leading to permanent treatment discontinuation by Primary SOC, HLGT, HLT and PT during the 3-month comparative regimen period - Safety sub-study population*

No data

TEAE: Treatment emergent adverse event, SOC: System organ class, HLGT: High level group term, HLT: High level term, PT: Preferred term.
MedDRA 16.0.
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 HLGT, HLT, PT by alphabetic order.

2.3.6 Other significant treatment emergent adverse events

2.3.6.1 Injection site reactions

Table 75 *- Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term - Injection site reactions during the 3-month comparative regimen period – Safety sub-study population*

No data

TEAE: Treatment emergent adverse event, PT: Preferred term.
MedDRA 16.0
n (%) = number and percentage of patients with at least one injection site reactions TEAE.
Note: Table sorted by decreasing frequency of PT in HOE901-U300 adaptable dosing intervals regimen.

2.3.6.2 Hypersensitivity reactions

Table 76 *- Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term - Hypersensitivity reactions during the 3-month comparative regimen period – Safety sub-study population*

No data

TEAE: Treatment emergent adverse event, PT: Preferred term.
MedDRA 16.0
n (%) = number and percentage of patients with at least one hypersensitivity reactions TEAE.
Note: Table sorted by decreasing frequency of PT in HOE901-U300 adaptable dosing intervals regimen.

Claims

1. Use of an aqueous pharmaceutical formulation comprising 200 - 1000 U/mL [equimolar to 200 - 1000 IU human insulin] of insulin glargine, with the proviso that the concentration of said formulation is not 684 U/mL of insulin glargine in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in Type I or Type II Diabetes Mellitus, wherein the time interval from the previous administration is in the range of 24.5 hours to 28 hours or in the range of 20 hours to 23.5 hours on at least two days per week and wherein the average time interval from the previous administration is 24 hours.
2. The use of claim 1 comprising 200 U/ml to 650 U/mL of insulin glargine.
3. The use of claim 1 comprising 700 U/ml to 1000 U/mL of insulin glargine.
4. The use of claim 2 comprising 270 - 330 U/mL of insulin glargine [equimolar to 270 - 330 IU human insulin].
5. The use of claim 4 comprising 300 U/mL of insulin glargine [equimolar to 300 IU human insulin].
6. The use of any of the foregoing claims, wherein the nocturnal hypoglycemia is selected from symptomatic hypoglycemia, severe symptomatic hypoglycemia, documented symptomatic hypoglycemia, probable symptomatic hypoglycemia, relative symptomatic hypoglycemia, and asymptomatic hypoglycemia.
7. The use of any of the foregoing claims, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient having a HbA1 c value of at least 8% at the onset of treatment.

8. The use of any of the foregoing claims, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient having an age of at least 60 years at the onset of treatment.
9. The use of any of the foregoing claims, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient having a BMI of at least 30 kg/m^2 at the onset of treatment.
10. The use of any of the foregoing claims, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient receiving a basal insulin directly prior to the treatment.
11. The use of any of the foregoing claims, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient receiving a mealtime short-acting insulin directly prior to the treatment.
12. The use of claim 10 or 11, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient having SMPG of at least 9 mmol/L at the onset of treatment.
13. The use of claim 10 or 11, wherein the use of the formulation of claim 1 in the manufacture of a medicament for the treatment reducing the risk of nocturnal hypoglycemia in the patient having a fasting plasma glucose concentration of at least 8 mmol/L at the onset of treatment.
14. The use of any of the foregoing claims, wherein the patient additionally receives a mealtime short-acting insulin.
15. The use of any of the foregoing claims further comprising an analogue of exendin-4.
16. The use of claim 15, wherein the analogue of exendin-4 is selected from a group comprising lixisentatide, exenatide and liraglutide.
17. The use of claim 16 comprising 0.1 g to 10 g lixisenatide per U insulin glargine.

18. The use of claim 17 comprising 0.2 to 1 g lixisenatide per U insulin glargine.
19. The use of claim 18 comprising 0.25g to 0.7g lixisenatide per U insulin glargine.
20. The use of any of the foregoing claims comprising one or more excipients selected from a group comprising zinc, m-cresol, glycerol, polysorbate 20 and sodium.
21. The use of claim 20 comprising 90 µg/mL zinc, 2.7mg/mL m-cresol and 20 mg/ml glycerol 85%.
22. The use of claim 21 comprising 90 µg/mL zinc, 2.7mg/mL m-cresol, 20 µg/mL polysorbate 20 and 20 mg/mL glycerol 85%.
23. The use of any of the foregoing claims, wherein the pH is between 3.4 and 4.6.
24. The use of claim 23, wherein the pH is 4.
25. The use of claim 24, wherein the pH is 4.5.
26. The use of any one of the claims 1 to 25, wherein the Diabetes Mellitus is Type II Diabetes Mellitus.
27. The use of claim 26, wherein the Diabetes Mellitus Type II is not adequately controlled with at least one oral antihyperglycemic alone.
28. The use of claim 27, wherein the at least one oral antihyperglycemic is metformin.
29. The use of claim 28, wherein a treatment with at least 1.5 g/day of metformin does not adequately control the Diabetes Mellitus.
30. The use of any of the claims 26 to 29, wherein the medicament is to be administered in combination with at least one oral antihyperglycemic agent.
31. The use of claim 30, wherein the at least one antihyperglycemic agent is metformin.
32. The use of claim 1 wherein the time interval of claim 1 is at least three days per week.
33. The use of claim 32 wherein the time interval of claim 1 is at least four days per week.
34. The use of any one of the claims 32 to 33, wherein the time interval from the previous administration is in the range of 25 h to 28 h or in the range of 20 h to 23 h.

35. The use of any one of the claims 32 to 34, wherein the time interval from the previous administration is in the range of 25 h to 27 h or in the range of 21 h to 23 h.

36. The use of any one of the claims 32 to 35, wherein the time interval from the previous administration is in the range of 25 h to 26.5 h or in the range of 21 .5 h to 23 h.

37. The use of any one of the claims 32 to 36, comprising insulin glargine in an amount as defined in any one of the claims 2 to 5.

38. The use of any one of the claims 32 to 37, wherein the patient is defined as in any one of the claims 7 to 14.

39. The use of any one of the claims 32 to 38, further comprising an analogue of exendin-4, as defined in any one of the claims 15 to 19.

40. The use of any one of the claims 32 to 39, further comprising one or more excipients as defined in any one of the claims 20 to 22.

41. The use of any one of the claims 32 to 40, having a pH as defined in any one of the claims 23 to 25.

42. The use of claim 41, wherein the nocturnal hypoglycemia is selected from symptomatic hypoglycemia, severe symptomatic hypoglycemia, documented symptomatic hypoglycemia, probable symptomatic hypoglycemia, relative symptomatic hypoglycemia, and asymptomatic hypoglycemia.

43. The use of any one of the claims 32 to 42, wherein the Diabetes Mellitus is Type II Diabetes Mellitus.

44. The use of claim 43, wherein the Diabetes Mellitus type II is not adequately controlled with a least one oral antihyperglycemic agent alone, as defined in any one of the claims 28 to 32.