SYNOPSIS

Title of the study:

A randomized, cross-over, open euglycaemic clamp study on the relative bioavailability and activity of two fixed ratio premixed formulations of insulin glargine (Lantus) and AVE0010 compared to separate simultaneous injections of Lantus and AVE0010 in subjects with diabetes mellitus type 1 (BDR10880)

Investigator(s): [redacted]

Study center(s): 1 study center in Germany

Publications (reference): None

Study period:

Date first subject enrolled: 11 May 2009

Date last subject completed: 19 August 2009

Phase of development: I

Objectives:

The primary objective of this study was to assess the relative bioavailability of insulin glargine and lixisenatide (AVE0010) given separately simultaneously versus fixed ratio premixed insulin glargine/lixisenatide formulations as subcutaneous single dosings.

The secondary objectives of this study were to compare the activity of insulin glargine and lixisenatide given separately simultaneously versus fixed ratio premixed insulin glargine/lixisenatide formulations as single subcutaneous dosings; and the safety and tolerability of fixed ratio premixed insulin glargine/lixisenatide formulations.

Methodology: A randomized, cross-over, open euglycemic clamp study

Number of subjects: Planned: 40; Randomized: 43; Treated: 42

Evaluated: Pharmacodynamics: 42; Safety: 42; Pharmacokinetics: 42

Diagnosis and criteria for inclusion: Male and female subjects between 18 and 65 years of age with diabetes mellitus type 1 for more than one year with an average total insulin dose of <1.0 U/kg/day; fasting negative serum C-peptide (<0.3 nmol/L); glycohemoglobin (HbA1c) ≤9%; stable insulin regimen for at least 2 months prior to study.

Investigational product:

Test 1 (T1, strength 1): injection of insulin glargine (Lantus) 0.4 U/kg and lixisenatide 0.264 µg/kg of a premixed formulation, containing insulin glargine 100 U/mL and lixisenatide 66 µg/mL, at one peri-umbilical site;
Test 2 (T2, strength 2): injection of insulin glargine 0.4 U/kg and lixisenatide 0.100 µg/kg of a premixed formulation, containing insulin glargine 100 U/mL and lixisenatide 25 µg/mL, at one peri-umbilical site.

Batch numbers: [redacted]

Duration of treatment: 2 treatment visits, 1 treatment per day, with a wash-out period of 5-18 days.

Duration of observation: Up to 72 h after injection.

Reference therapy:
Reference 1 (R1, strength 1): separate simultaneous injections of insulin glargine 0.4 U/kg and lixisenatide 0.264 µg/kg at opposite peri-umbilical sites;
Reference 2 (R2, strength 2): separate simultaneous injections of insulin glargine 0.4 U/kg and lixisenatide 0.100 µg/kg at opposite peri-umbilical sites.

Batch numbers: [redacted]

Criteria for evaluation:

Pharmacodynamic:

To assess the pharmacodynamics (PD) of insulin glargine and lixisenatide given separately simultaneously and given as premixed formulations, the blood glucose concentration and glucose infusion rate (GIR) were continuously recorded during the clamp procedure, and used to calculate the area under the curve (AUC) for GIR within 24 h (GIR-AUC_{0-24h}) and the time to 50% of the total GIR-AUC within 24 h ($T_{50\%}$-GIR-AUC_{0-24h}), both standardized according to body weight. Maximum GIR (GIR_{max}) and the time to GIR_{max}, GIR-t_{max} were also calculated.

Safety:
Adverse events (AEs); standard hematology and blood chemistry tests; urinalysis; vital signs and electrocardiogram (ECG); anti-lixisenatide antibodies; injection-site tolerability.

Pharmacokinetic:
Lixisenatide: The area under the plasma lixisenatide concentration curve as AUC_{last} and AUC, apparent clearance (CL/F), apparent volume of distribution (Vz/F), and terminal half life $t_{1/2\lambda z}$, peak concentration C_{max}, and time to C_{max} (t_{max}) were calculated.

Insulin glargine: The plasma insulin glargine AUC concentration up to 24 h (AUC_{0-24h}), $T_{50\%}$ of AUC_{0-24h}, C_{max} and t_{max} were calculated.

Pharmacokinetic sampling times and bioanalytical methods:

Blood was collected for the determination of plasma lixisenatide concentrations at time (T) 0 and T0.25, T0.5, T1, T1.5, T2, T2.5, T3, T4, T5, T6, T8, T12, and T24 h after injection of investigational product and for the determination of serum insulin glargine concentrations at T0 and T0.25, T0.5, T1, T1.5, T2, T4, T6, T8, T10, T12, T14, T16, T18, T20, T22, and T24 h after injection of investigational product.

Statistical methods:

Pharmacodynamics:

Statistical analyses were performed separately for T1 and T2.

A linear mixed effects model to compare both treatments ((T1/T2 versus R1/R2)) for log transformed GIR-AUC_{0-24h} was used and the estimates and 90% CI for the ratio of geometric means were provided. Times to 50% of GIR-AUC_{0-24h} were compared non-parametrically between treatments.

Safety:

Safety analyses were based on a review of the individual values and descriptive statistics by treatment. Frequencies of treatment emergent adverse events (TEAEs) were reported by the subjects or noted by the Investigator. Frequencies of subjects with potentially clinically significant abnormalities (PCSAs) were summarized by treatment, for laboratory data, and vital signs and ECG data.

Pharmacokinetics:

Pharmacokinetic parameters were summarized by treatment using descriptive statistics.

Lixisenatide: For log transformed AUC, AUC_{last} and C_{max} the relative bioavailability of the treatments (T1/T2 and R1/R2) was assessed using a linear mixed effects model. Estimate and 90% confidence intervals (CI) for the ratio of geometric means of the 2 treatments (premix versus separate) were provided for AUC, AUC_{last} and C_{max}.

Insulin glargine: For log transformed AUC_{0-24h} the relative bioavailability of the respective test treatment was assessed using a linear mixed effects model. Estimate and 90% CI for the ratio of geometric of the 2 treatments (T1/T2 and R1/R2) were provided for AUC_{0-24h}. The times to 50% of AUC_{0-24h} were compared non-parametrically between treatments.

Summary:

Pharmacodynamic results:

As assessed by the results of GIR- AUC_{0-24h}, the PD activity of the premixed T1 were comparable with the effects observed with the reference treatment R1 (T1/R1: 0.95; 90% CI: 0.76 to 1.18), and comparable for T2 and R2, acknowledging that the lower limit of the CI of the treatment ratio was 0.61 (T2/R2: 0.83; 90% CI: 0.61 to 1.12). The $T_{50\%}$-GIR AUC_{0-24h} varied by approximately 1 h between treatments.

Safety results:

Irrespective of the treatment given, the most frequent TEAE observed during the study was headache, with 13 cases in 10 subjects. Headache is a known side-effect associated with the clamp procedure.

The most common TEAEs reported for lixisenatide were gastrointestinal symptoms. A total of 9 subjects experienced 10 TEAEs which consisted of nausea, vomiting diarrhea, dyspepsia, and abdominal upper pain. Only 9 PCSAs in vital signs were observed during the study and these were not considered to be clinically relevant. There were no individually clinically relevant abnormalities in ECG parameters. Two (2) subjects developed injection site reactions, one of which was hardly perceptible and the other was mild in nature. A total of 6 subjects were positive for anti-lixisenatide antibodies.

Otherwise, all treatments, R1, R2, T1 and T2 were well tolerated and judged safe for the study population.

Pharmacokinetic results:

Lixisenatide: For AUC_{last} and AUC, the point estimates for treatment ratios (T/R) were between 0.82 and 0.97, with only the latter calculated to be within formal equivalence limits.

Total lixisenatide exposure (AUC), when given as a premixed insulin glargine/lixisenatide combination, almost met the equivalence criteria for strength 1 (point estimate [PE] 0.92; 90% CI: 0.78 to 1.08), and did meet the equivalence criteria for strength 2 (PE 0.97; 90% CI: 0.83 to 1.13), as compared to the exposure of lixisenatide administered separately.

Following administration of either of the premix formulations (T1 or T2), the C_{max} observed for lixisenatide was lower than that observed after the separate administration of lixisenatide (R1 or R2), not meeting the equivalence criteria (80%-125%). C_{max} was 66% and 78% of the separate administrations (R1 and R2, respectively) and t_{max} was achieved 1 h later at T1 and 0.75 h later at T2 as compared to R1 and R2, respectively. Dose proportionality of lixisenatide exposure was indicated, both when given separately simultaneously with insulin glargine and when given in the premixed formulations. C_{max} did not increase in proportion to the dose.

Additional information from analysis across strengths (1 and 2) showed dose-proportionality of lixisenatide exposure, both for test (T1/T2) and reference treatments (R1/R2).C_{max} was shown to increase in a manner less than proportional with dose.

Insulin glargine: For AUC_{0-24h} the point estimates were 0.86 (90% CI: 0.77 to 0.96) and 0.88 (90% CI: 0.79 to 0.98) for the treatment ratios T1/R1 and T2/R2, respectively, indicating no formal equivalence of insulin glargine exposure, as the lower CI of the ratios T1/R1 and T2/R2 were below 0.8000. The time to 50% of AUC_{0-24h} following administration of R1 and T1, and R2 and T2, was not different.

Additional information from analysis across strengths (1 and 2) showed insulin glargine exposure to not differ between T1 and T2 or between R1 and R2.

Conclusions: [redacted]

Date of report: 19-Jun-2012