SYNOPSIS

Title of the study:

A randomized, cross-over, open euglycemic clamp study on the relative bioavailability and activity of 0.4 U/kg insulin glargine and 20 µg AVE0010, given as on-site mixes in 2 strengths compared to separate simultaneous injections in subjects with diabetes mellitus type 1 (BDR11038)

Investigator(s): [redacted]

Study center(s): 1 study center in Germany

Publications (reference): None

Study period:

Date first subject enrolled: 19 June 2009

Date last subject completed: 10 September 2009

Phase of development: I

Objectives:

Primary:

- To assess the relative bioavailability of insulin glargine and lixisenatide (AVE0010) given separately simultaneously versus given in 2 strengths of on-site mixes.

Secondary:

- To compare the activity of insulin glargine and lixisenatide given separately simultaneously versus given in 2 strengths of on-site mixes as subcutaneous single dosing;
- To asses the safety and tolerability of insulin glargine - lixisenatide given in 2 strengths of in-syringe mixes.

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

Number of subjects: Planned: 24; Randomized: 26; Treated: 26

Evaluated: Pharmacodynamic: 25; Safety: 26; Pharmacokinetics: 26

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 <1.2 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 A): injection of an on-site mix of insulin glargine (Lantus) U100 (0.4 U/kg) and 100 µg/mL unbuffered lixisenatide (20 µg) at one peri-umbilical site;
- Test 2 (T2; strength B): injection of an on-site mix of insulin glargine U300 (0.4 U/kg) and 100 µg/mL unbuffered lixisenatide (20 µg) and saline solution as needed at one peri-umbilical site.

Batch numbers: [redacted]

Duration of treatment: 3 treatment visits, 1 treatment per day, 3 treatments in total (in treatment periods [TP] 1, 2 and 3)

Duration of observation: Up to 72 h after injection

Reference therapy:

Reference (R): separate simultaneous injections of insulin glargine U100 (0.4 U/kg) and 100 µg/mL lixisenatide (20 µg) 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 body weight standardized glucose infusion rate (GIR) within 24 h (GIR-$AUC_{0\text{-}24h}$) and the time to 50% of the total GIR-AUC within 24 h ($T_{50\%}$-GIR-$AUC_{0\text{-}24h}$). Maximum GIR (GIR_{max}) and the time to GIR_{max}, GIR-t_{max} were also calculated.

Safety: Adverse events (AEs) reported by the subject or noted by the Investigator; standard hematology; biochemistry; serology; urinalysis; vital signs and electrocardiogram (ECG); anti-lixisenatide antibodies; injection-site tolerability.

Pharmacokinetics:

Lixisenatide: The area under the plasma lixisenatide concentration curve as AUC and AUC_{last}, 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 ($AUC_{0\text{-}24h}$), $T_{50\%}$-GIR-$AUC_{0\text{-}24h}$, C_{max} and t_{max} were calculated.

Pharmacokinetic sampling times and bioanalytical methods:

Blood was collected for the determination of plasma concentrations of lixisenatide 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 plasma concentrations of insulin glargine 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 compared both test treatments with the R treatment.

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

Safety

Safety analyses were based on a review of the individual values and descriptive statistics by treatment. For adverse events frequencies of treatment emergent adverse events (TEAEs) were reported by the subjects or noted by the Investigator, and classified by system organ class and preferred term. All AEs were listed. Frequencies of subjects with potentially clinically significant abnormalities 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 bioavailabilities of T1 and T2 and were assessed using a linear mixed effects model. Estimate and 90% CI for the ratio of geometric means between test and reference treatment were provided for AUC, AUC_{last} and C_{max}.

Insulin glargine: For log transformed $AUC_{0-24h,}$ the relative bioavailability between test and reference treatments were assessed using a linear mixed effects model. Estimate and 90% CI for the ratio of geometric means between test and reference treatments were provided for AUC_{0-24h}. The times to 50% of AUC_{0-24h} were compared non-parametrically between treatments.

Summary:

Pharmacodynamic results:

GIR-AUC_{0-24h} was not equivalent between T1 and R but was comparable between T2 and R. The point estimates of treatment differences for T1-R, T2-R, and T2-T1 for $T_{50\%}$-GIR AUC_{0-24h} did not indicate any difference.

Safety results:

Irrespective of the treatment given, the most frequent TEAE observed during the study was headache, with 7 cases in 4 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 7 subjects experienced 13 TEAEs which consisted of vomiting, and single cases of abdominal discomfort, heartburn and diarrhea.

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

Pharmacokinetic results:

Lixisenatide exposure for AUC_{last}, total AUC and C_{max}, was not equivalent with T1 and R. Test 1 produced lower lixisenatide exposure as compared to R. Lixisenatide exposure was equivalent with T2 and R. The point estimates for the ratio T2/R for AUC_{last} were 1.04 (90%CI: 0.95 to 1.14), for AUC 1.04 (90%CI: 0.95 to 1.14), and for C_{max} 0.91 (90%CI: 0.82 to 1.02).

Insulin glargine exposure for AUC_{0-24h} was not equivalent with T1 and R. Insulin glargine exposure was 26 % higher after T1 as compared to R. Insulin glargine exposure, AUC_{0-24h}, was equivalent with T2 and R. The point estimate for the ratio T2/R for AUC_{0-24h} was 1.02 (90% CI: 0.92 to 1.14). $T_{50\%}$-GIR AUC_{0-24h} was about 1 h shorter with T1 as compared to R and T2.

Conclusions: [redacted]

Date of report: 19-Jun-2012