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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00272090
		Study Code:	HOE901_3507
Generic drug name:	insulin glargine	**Date:**	28 August 2007

Title of the study: Italian experience trial for the implementation of the use of Lantus in basal-bolus regimen in T1 DM patients

Investigators: 47 principal investigators

Study centers: 47 centers, all in Italy

Publication (reference): None

Study period: First patient enrolled: 11/11/2002; Last patient completed: 22/12/2005	**Phase of development**: IIIb

Objectives:

The primary objective of the study was to show that the safety of new regimen (insulin glargine + regular insulin) was no worse than that of reference regimen (insulin glargine + LISPRO insulin) assessed by reducing the incidence of severe nocturnal hypoglycemia at the end point.

The secondary objectives of the study were to assess the following outcome measures: glycemic control (assessed by HbA_{1c}, MBG and MAGE index calculated using SMBG data); reproducibility of action assessed by frequency/patient/month of FBG at target value > 90 and < 120 mg/dl and of pre-meal BG at the target value > 100 and < 140 mg/dl; maintenance of body weight; safety (laboratory data, overall hypoglycemia, AE); health economics assessed by adjustment of total daily basal insulin dose; compliance to basal insulin algorithm, assessed by frequency of BG at the target values; Quality of Life (by self-patient WED questionnaire administration).

Methodology:

This was a national, multicenter, randomized, parallel group, open label, non-inferiority trial. The study duration was 28 weeks (2 run-in weeks + 8 qualification phase weeks + 16 treatment weeks + 2 follow-up weeks).
After the screening visit (V1), during the run-in period (2 weeks) the individual insulin therapy of patients was optimized and the patients were educated to the use of new glucometer. At the end of run-in period (inclusion visit, V2) the patients started the qualification phase in order to optimize the administration of the study treatment according to following criteria: a) the patients who were using once/daily NPH insulin injection during the run-in period were switched to the same daily dose of insulin glargine (at dinner time); b) the patients who were using twice or more daily NPH insulin injection during run-in period were switched to insulin glargine at a dose calculated as 90% of total daily requirement of NPH insulin; c) the patients who were using insulin glargine during the run-in period optimized the use of insulin glargine according to procedure described in protocol appendix G.

At the end of Qualification phase (baseline/randomization visit, V4), all patients were randomized to Treatment A or B:

- Treatment A (New regimen): Regular insulin at each meal + insulin glargine at dinner time.
- Treatment B (Reference regimen): LISPRO insulin at each meal + insulin glargine at dinner time.

The 16-weeks treatment period (V5-V8) was then followed by a 2 weeks safety follow up phase (V9).

Number of patients (total and in each arm):

	Randomized	ITT	PP	Safety	Completed
Total	395	395	392	395	373
Insulin glargine + regular (Regular)	202	202	200	202	192
Insulin glargine + LISPRO (LISPRO)	193	193	192	193	181

Diagnosis and main criteria for inclusion:

Subjects aged 18-60 years with type 1 diabetes mellitus for more than three years; subjects on multiple daily injection insulin therapy, basal-bolus scheme therapy; $HbA_{1c} \leq 9$ %; evidence of lack of the insulin secretion as show by one of the following: a) fasting C-peptide ≤ 0.1 nmol/l with FBG > 126 mg/dl at screening visit, or b) screening fasting C-peptide < 0.3 nmol/l in sample performed 6 minutes after administration of 1 mg i.v. of glucagone (Glucagone Stimulation Test), or c) diagnosis of type 1 diabetes for at least 3 years with fasting C-peptide ≤ 0.1 nmol/l and concurrent FBG > 126 mg/dl previously documented; Body Mass Index (BMI) < 30 kg/m^2 ; willingness to accept intensive insulin therapy; ability and willingness to perform SMBG using plasma glucose meter; female subjects had to be postmenopausal or under adequate contraception; written informed consent.

Test product, dose and mode of administration, batch no: insulin glargine, subcutaneously administered in the evening (at dinner time) + regular insulin (at each meal). Dose adjustments were done according to standard algorhythms.

Duration of treatment: 24 weeks.

Reference therapy, dose and mode of administration, batch no: insulin glargine, subcutaneously administered in the evening (at dinner time) + LISPRO insulin (at each meal). Dose adjustments were done according to standard algorhythms.

Criteria for evaluation:

Primary variable: rate of severe nocturnal hypoglycemia (BG < 50 mg/dl).

Efficacy variables: change of HbA_{1c}; self monitoring of blood glucose (fasting blood glucose [FBG], mean daily blood glucose [MDBG], glycemic time course, MAGE; health economics outcomes (insulin dosage); improvement of the quality of life; stability of body weight.

Safety variables: adverse events (including hypoglycemia, nocturnal hypoglycemia and severe hypoglycemia), laboratory parameters (hematology, clinical chemistry, microalbuminuria) and clinical variables (physical examination with fundus oculi, ECG, vital signs with blood pressure and heart rate).

Statistical methods:

The non-inferiority in safety, of the new regimen (A) versus the reference regimen (B), was assessed by means of the CI approach. The non-inferiority in safety was stated if the upper limit of the one-sided 95% CI of the difference (A – B) in severe nocturnal hypoglycemia at end point was less than delta = 5%.

The analysis of efficacy variables was performed in the ITT population, defined as all randomized patients who took at least one dose of study drug and who had provided enough data to assess the primary variable. Descriptive summary statistics (number of patients, mean, standard deviation, minimum, maximum) was provided for quantitative variables, while frequency (absolute and relative) distributions were provided for categorical variables.

The parametric variables were analysed by using an analysis of variance (ANOVA) model, with multiple comparison within and between groups, when appropriate. The non-parametric variables were analysed by using the Mc Nemar test in the comparisons within group and the Chi-square test in the comparisons between groups. The results of the laboratory safety and of the physical examination parameters were analysed in terms of normal/abnormal findings.

Study population:

A total number of 395 patients were randomized to receive the assigned treatment; 202 (51.1% of randomized) were included in the insulin glargine + regular insulin (named regular hereinafter) and 193 (48.9%) were randomized to receive insulin glargine + LISPRO insulin (named LISPRO hereinafter). A total of 22 patients, 10 in the regular group and 12 in the LISPRO group, prematurely discontinued the study and 373 patients, 192 in the regular group and 181 in the LISPRO group, completed the total study period. Consent withdrawal was the main reason of early study discontinuation.

Extent of exposure and compliance:

The mean extent of exposure in the randomized population was 196.5 ± 25.5 days (range 77-297) in the regular group and 191.4 ± 36.3 days (range 54-318) in the LISPRO group. The compliance to study drug was not evaluated.

Results of hypoglycemia:

Primary variable: severe nocturnal hypoglycemia at visit 8

The number of patients with severe nocturnal hypoglycemia at visit 8 was 3 (1.55%) in the regular group and 2 (1.11%) in the LISPRO group. The analysis of non-inferiority showed that the difference between the adjusted means was equal to 0.44%. The upper 95% unilateral CI of the difference between groups was 2.21%, which was < than the pre-specified limit of 5%, thus showing that regular treatment was non-inferior to LISPRO treatment.

The number of patients with severe nocturnal hypoglycemia in the randomized treatment phase (i.e. between visit 5 and visit 8) was 8 (4.0%) in the regular group and 9 (4.8%) in the LISPRO group (p = 0.880 between groups). No differences between groups were also found in the assessment of the rate of patients and of the number of episodes/patient/month of severe nocturnal hypoglycemia at any time point.

Other assessments of hypoglycemia:

The number of patients with severe hypoglycemia in the randomized treatment phase was 19 (9.4%) in the regular group and 15 (8.0%) in the LISPRO group (p = 0.749 between groups). No differences between groups were also found in the assessment of the rate of patients and of the number of episodes/patient/month of severe hypoglycemia at any time point.

The number of patients with hypoglycemia of any degree in the randomized treatment phase was 152 (75.2%) in the regular group and 143 (76.1%) in the LISPRO group (p = 0.945 between groups). No differences between groups were also found in the assessment of the rate of patients and of the number of episodes/patient/month of hypoglycemia of any degree at any time point, except in the time between Visit 7 and Visit 8, due to a higher frequency in the LISPRO groups compared to the regular group (p = 0.035 between groups in rate and p = 0.049 in the number of episodes).

No evidence of marked differences between groups was observed in the total number of hypoglycemic events in the time frame between visit 2 and visit 8, and the results of the percentages distribution of hypoglycemic events showed a satisfactory control in both groups throughout the entire 24-hour period.

Efficacy results:

- HbA_{1c}

A statistically significant and similar decrease of mean HbA_{1c} from the screening visit (visit 1) to baseline (visit 4) was observed in both groups. The analysis of the results in the treatment phase did not show changes from baseline in both groups: the mean changes in the regular group were -0.04 % at visit 6 and -0.04 % at visit 8, while the mean changes in the LISPRO group were 0.02 % at visit 6 and -0.09 % at visit 8 (p = 0.432 and p = 0.566 between groups, respectively, at visit 6 and visit 8). The analysis in terms of normal/abnormal results from randomization to endpoint (visit 8) showed a statistically significant difference (p = 0.016), due to a higher number of patients with normal values at baseline and abnormal values at the final visit in the LISPRO group, compared to the regular group.

- Fasting blood glucose

A statistically significant decrease from baseline (visit 4) to the last visit was observed in the regular group, compared to no substantial changes in the LISPRO group. The mean changes were -5.9 mg/dl (95% CI: -11.8 to -0.0) in the regular group and -0.9 mg/dl (95% CI: -7.0 to 5.3) in the LISPRO group. The comparison between groups did not show statistically significant differences (p = 0.246).

- Mean Daily Blood Glucose

No substantial changes from baseline (visit 4) to the last visit were observed in both groups: the mean changes were 0.8 mg/dl in the regular group and -0.1 mg/dl in the LISPRO group (p = 0.724 between groups).

- Glycemic time course

The results of measurements before breakfast showed small non-significant decreases from baseline (visit 4) to the last visit in both groups: the mean changes were -2.8 mg/dl in the regular group and -3.0 mg/dl in the LISPRO group (p = 0.982 between groups). The results of measurements after breakfast showed no substantial changes from baseline to the last visit in both groups: the mean changes were 0.3 mg/dl in the regular group and -0.2 mg/dl in the LISPRO group (p = 0.947 between groups). The results of measurements before lunch showed no substantial changes from baseline to the last visit in the regular group and a small non-significant increase in the LISPRO group: the mean changes were 1.1 mg/dl in the regular group and 6.8 mg/dl in the LISPRO group (p = 0.377 between groups). The results of measurements after lunch showed a non-significant increase from baseline to the last visit in the regular group and no substantial changes in the LISPRO group: the mean changes were 9.7 mg/dl in the regular group and -1.9 mg/dl in the LISPRO group (p = 0.105 between groups). The results of measurements before dinner showed a significant decrease from baseline to the last visit in the regular group and a non-significant increase in the LISPRO group: the mean changes were -11.8 mg/dl in the regular group (p = 0.020) and 9.7 mg/dl in the LISPRO group; the comparison between groups showed a statistically significant difference (p = 0.004). The results of measurements after dinner showed a non-significant increase from baseline to the last visit in the regular group and a significant decrease in the LISPRO group: the mean changes were 5.4 mg/dl in the regular group and -14.6 mg/dl in the LISPRO group (p = 0.027); the comparison between groups showed a statistically significant difference (p = 0.029). The results of measurements at bedtime showed small non-significant increases from baseline to the last visit in both groups: the mean changes were 2.8 mg/dl in the regular group and 4.8 mg/dl in the LISPRO group (p = 0.823 between groups).

- Mean Amplitude Glucose Excursion (MAGE)

No substantial changes from baseline (visit 4) to the last visit were observed in both groups: the mean changes were -1.90 mg/dl in the regular group and -4.02 mg/dl in the LISPRO group (p = 0.764 between groups).

- Insulin dosage

The results of the mean daily dose of prandial insulin did not show marked differences between groups at any time point, except in the period between visit 7 and visit 8, in which the dose was slightly higher in the LISPRO than in the regular group. The results of the mean dose of prandial insulin at breakfast, lunch and dinner showed that the total men dose was slightly higher in the LISPRO than in the regular group at any time of the day and at any visit.

The results of the mean daily dose of basal insulin glargine did not show marked differences between groups at any time point, except in the period between visit 7 and visit 8, in which the dose (expressed as IU/kg/die) was slightly higher in the LISPRO than in the regular group.

The results of the total daily dose of insulin showed that the mean doses (IU/die) were generally slightly higher in the LISPRO than in the regular group at any time point, and the difference resulted to be statistically significant in the time frame between visit 5 and visit 8, in which the mean doses were 38.3 ± 15.4 IU/die in the regular group and 42.3 ± 17.1 IU/die in the LISPRO group (p = 0.028). When the doses are expressed as IU/kg/die, the mean values also were generally slightly higher in the LISPRO than in the regular group at any time point, and the difference was statistically significant in the period between visit 7 and visit 8, in which the mean doses were 0.52 ± 0.22 IU/kg/die in the regular group and 0.64 ± 0.22 IU/kg/die in the LISPRO group (p = 0.044).

- Quality of life

A high amount of patients with missing data was found. No statistically significant changes from baseline to the final visit (visit 8) were observed for any domain (impact, satisfaction, general worries and diabetes-related worries) in both groups. The comparisons between groups of changes from baseline also did not show any statistically significant difference for any domain.

- Body weight

No substantial changes from baseline (visit 4) were observed in both treatment groups at any time-point. The mean changes from baseline in the regular group were -0.1 kg at visit 6 and 0.0 kg at visit 8, while the mean changes from baseline in the LISPRO group were 0.3 kg at visit 6 and 0.1 kg at visit 8 (p = 0.214 and p = 0.578 between groups, respectively, at visit 6 and visit 8).

Other safety results:

Adverse events:

A total number of 119 patients, 56 (27.7%) in the regular group, 59 (30.6%) in the LISPRO group and 4 (4.3%) among non-randomized patients, reported adverse events (p = 0.534 between groups). A total number of 6 patients, 2 (3.6%) in the regular group and 4 (6.8%) in the LISPRO group, reported drug-related adverse events (p = 0.724). The drug-related adverse events consisted of diabetic retinopathy in all patients in both groups.

Serious adverse events of any type were reported in less patients (4, 7.1%) in the regular group than in the LISPRO group (9, 15.3%); however, the comparison between groups did not show statistically significant differences (p = 0.281). When hypoglycemia is not taken into account, the rate of serious adverse events was also not significantly different between groups, with 2 patients (3.6%) in the regular group and 6 (10.2%) in the LISPRO group (p = 0.306 between groups). However, none of the serious adverse events (apart from 2 patients with hypoglycemia in the regular group and 3 in the LISPRO group) was also considered as being drug-related. One non drug-related serious adverse event among non-randomized patients was fatal. None of the adverse events caused early study discontinuation in any group. The most frequently reported individual adverse events were influenza (in 17 patients in the regular group and in 6 in the LISPRO group) or influenza-like illness (in 3 patients in both groups) and pyrexia (in 7 patients in the regular group and in 5 in the LISPRO group).

Laboratory parameters:

The results of safety laboratory parameters did not show evidence of clinically significant changes for any parameter. Statistically significant changes from baseline (visit 1) were found in lymphocytes count (increase in the LISPRO group), total cholesterol (decrease in the regular group), HDL-cholesterol (decrease in both groups), AST (increase in the LISPRO group), creatinine (decrease in both groups), sodium (decrease in the regular group) and potassium (decrease in the regular group). The comparison between groups showed a statistically significant difference for total cholesterol levels, due to the decrease in the regular group, which was the result of the effects on HDL cholesterol. These changes have no clinical relevance. An overall trend towards improvement of microalbuminuria was reported in both groups.

Vital signs, ECG and physical examination:

The results of vital signs (heart rate and blood pressure), ECG and physical examination of the main body districts did not show statistically or clinically significant changes from baseline (visit 1), apart from a small but significant decrease of heart rate at the final visit in both groups. The examination of fundus oculi showed that 12 patients in the regular group and 7 in the LISPRO group with normal finding at baseline had abnormalities at the final visit; 6 and 11 patients in the two groups, respectively, had their baseline abnormalities resolved at the final visit (p = 0.317 between groups).

Date of the report : 19 march 2007