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Sponsor / Company: Sanofi **Drug substance(s):** Insulin Glargine (HOE901)	**Study Identifiers:** NCT00949442, EudraCT 2007-006640-22 **Study code**: LANTU_C_02762
Title of the study: Superiority of Insulin Glargine Lantus vs NPH: "Treat to Normoglycemia concept". Effect of Insulin Glargine in Comparison to Insulin NPH in Insulin-naïve People With Type 2 Diabetes Mellitus Treated With at Least One OAD and Not Adequately Controlled (LANCELOT)	
Study center(s): 74 active sites among 17 countries (Brazil, Czech Republic, France, Italy, Korea, Kuwait, Mexico, Netherlands, Poland, Romania, Russia, Slovakia, Sweden, Switzerland, Thailand, United Arab Emirates, and Egypt)	
Study period: Date first patient enrolled: 13 July 2009 Date last patient completed: 17 July 2012	
Phase of development: Phase 3b/4	

Objectives: Primary:

To demonstrate the superiority of insulin glargine over neutral protamine hagedorn (NPH) insulin on the change in glycosylated hemoglobin (HbA1c) from baseline to the end of the Treatment Period.

Main secondary:

To compare between treatment groups:

- Plasma glucose (PG) (fasting nocturnal) over time,
- Changes from baseline in HbA1c over time,
- Percentage of patients who reach the target of HbA1c <7% and <6.5% between the 2 treatment groups,
- Use of prandial insulin as rescue medication at Month 6 (Week 24),
- Incidence and rate of hypoglycemia (symptomatic diurnal and nocturnal, asymptomatic and severe),
- Daily dose of insulin in each treatment group,
- Changes in body weight from baseline,
- Evolution of 8-point PG profiles,
- Overall safety,
- Patient reported outcomes (treatment satisfaction).

Methodology: This was a multicenter, international, open-label, comparative, parallel-group, randomized (ratio 1:1) study. The study consisted of a 2-week Screening Period followed by a 2-week Run-in Period, a 9-month Treatment Period, and a 1-week Follow-up Period. During the Run-in Period, all sulfonylurea (SU) medications (except glimepiride), glinides, or alpha-glucosidase inhibitors were switched to glimepiride. The starting dose of glimepiride was 1 mg once daily for 1 week, which was increased to a maximum dose of 2 mg the following week. After randomization into the insulin glargine or the insulin NPH group, patients had tight insulin titration based on fasting plasma glucose (FPG) and nocturnal PG (NPG). The insulin dose initiation was a maximum dose of 0.2 units (U)/kg. From Baseline (Week 0) to Week 4 and from Week 13 to the end of the Treatment Period, patients titrated their insulin dose once a week. From Week 5 to the end of Week 12, patients titrated their insulin dose twice a week. To ensure that an appropriate titration regimen (following the titration algorithm) was implemented in both treatment groups, a Titration Committee reviewed glucose values and insulin doses. The goal was to achieve a FPG between 80 and 100 mg/dL (4.4 and 5.5 mmol/L).

Number of patients:	Planned: 670 patients (335 per treatment group) Randomized: 708 Treated: 704
Evaluated:	Efficacy Modified intent-to-treat (mITT) population: 701 patients (352 patients in the insulin glargine group and 349 patients in the insulin NPH group) Patients in the mITT population eligible for primary efficacy analysis: 691 patients (348 patients in the insulin glargine group and 343 patients in the insulin NPH group) Per-protocol (PP) population: 652 patients (329 patients in the insulin glargine group and 323 patients in the insulin NPH group) Safety Safety population: 704 patients (354 patients in the insulin glargine group and 350 patients in the insulin NPH group)

Diagnosis and criteria for inclusion:

- Aged from 30 to 70 years inclusively
- Insulin-naïve type 2 diabetes mellitus (T2DM)
- T2DM diagnosed for at least 1 year
- Treated with at least 1 oral antidiabetic (OAD) medication (Metformin [daily dose of at least 1000 mg], SU, glinides, or alpha-glucosidase inhibitor) at stable dose for at least 3 months
- HbA1c $\geq$7.0% and $\leq$10.5%
- Body mass index (BMI) <40 kg/m^2
- Ability and willingness to perform PG monitoring using the sponsor-provided glucose meter and patient diary at home
- Informed consent obtained in writing at enrollment into the study
- Willingness and ability to comply with the study protocol

Study treatments

Investigational medicinal products:

Lantus® (insulin glargine)

Formulation: 100 U/mL solution for injection in a prefilled SoloStar® pen (3 ml)

Route of administration: Subcutaneous (SC)

Dose regimen: Initial insulin dose was 0.2 U/kg administered between 8 and 10 PM; titration used the 3 last daily FPG values and the NPG value from the previous night; from baseline to the end of Week 4, and from Week 13 to the end of the Treatment Period: patients titrated their insulin dose once a week; from Week 5 to the end of Week 12: patients titrated their insulin dose twice a week.

Insuman® Basal (human insulin [NPH])

Formulation: 100 IU/mL suspension for injection in a prefilled OptiSet® pen (3 mL)

Route of administration: SC

Dose regimen: Initial insulin dose was 0.2 U/kg administered between 8 and 10 PM; titration used the 3 last daily FPG values and the NPG value from the previous night; from baseline to end of Week 4, and from Week 13 to the end of the Treatment Period: patients titrated their insulin dose once a week; from Week 5 to the end of Week 12: patients titrated their insulin dose twice a week.

Non investigational medicinal product: Glimepiride

Formulation: Tablet 1 and 2 mg

Route(s) of administration: Oral

Dose regimen: Starting dose was 1 mg once daily for 1 week. If well tolerated the dose was increased by 1 mg the following week until the maximum dose of 2 mg.

Duration of treatment: 36 weeks

Duration of observation: 41 weeks (2-week Screening Period, 2-week Run-in Period, 36-week Treatment Period, and 1-week Follow-up Period)

Criteria for evaluation:

Efficacy: HbA1c, self-monitored FPG, 8-point PG profile, necessity of additional prandial insulin, daily doses of insulin

Safety: vital sign measurements, adverse events (AEs), lipid profile, episodes of hypoglycemia, body weight, and treatment satisfaction assessed by using the Diabetes Treatment Satisfaction Questionnaire – status (DTSQs) version and Diabetes Treatment Satisfaction Questionnaire – change (DTSQc) version

Statistical methods: Analysis populations included the randomized population (all patients who signed a consent form and who were successfully allocated a randomization number), mITT (randomized patients who received at least 1 dose of study medication and had 1 postbaseline primary or secondary efficacy assessment), PP population (a subset of the mITT population which excluded all patients who had a major protocol deviation), and safety population (all treated patients).

Sample size: It was planned to randomize 670 patients (335 per group). The aim of the study was to demonstrate the superiority of insulin glargine versus insulin NPH on change in HbA1c. The hypotheses to be tested was: H0: There was no difference between insulin glargine mean HbA1c change and insulin NPH mean HbA1c change (insulin glargine = insulin NPH); H1: There was a difference between insulin glargine mean HbA1c change and insulin NPH mean HbA1c change (insulin glargine $\neq$ insulin NPH). A total number of 564 evaluable patients was required on the basis of the following criteria:

- Estimated standard deviation (SD) of the change in HbA1c of 1.1%
- Expected mean difference to be detected of 0.3%
- Alpha risk of 5% (2-sided)
- Statistical power of 90%
- Equal sample size in each treatment group (1:1 randomization)

A total of 708 patients were randomized in the study.

Primary efficacy variable analysis: The primary efficacy variable was the HbA1c change from baseline to the last on-treatment measurement. This was analyzed with an analysis of covariance (ANCOVA) model, with treatment as a fixed effect and the corresponding baseline value as a covariate. Adjusted treatment means and the difference in adjusted treatment means were presented. The corresponding 95% confidence interval (CI) was calculated and presented for the difference in adjusted treatment means. The p value for the hypothesis of no difference was also presented.

Secondary efficacy variables and analysis:

HbA1c%: Variables included HbA1c and change from baseline at specified visits and HbA1c response rates (assessed as the percentage of patients who reached the targets of HbA1c <7% and HbA1c <6.5%). Change from baseline in HbA1c at specified visits was analyzed by using the same ANCOVA model used for the primary analysis. Comparison between treatments in HbA1c response rates at specified visits was performed by using Pearson's chi-square test. Two-sided CIs for the treatment difference (insulin glargine minus insulin NPH) were calculated by using the normal approximation to the binomial distribution.

FPG at specified visits: Variables included mean FPG, change from baseline in mean FPG, and within-patient FPG variability. Change from baseline in mean FPG was analyzed by using an ANCOVA model with a fixed effect for treatment as a covariate for baseline value. Within-patient FPG variability was analyzed by using a ranked ANCOVA where the covariate is the rank for baseline within-patient FPG variability.

PG Variables (8-point 24-hour profile): Variables included mean 8-point 24-hour PG profile at specified visits based on the 2 profiles captured during the preceding week. The NPG was included in the 8-point 24-hour profile. In addition, mean daily PG

and daily PG variability were calculated based on the 8 values across the 24-hour period. Change from baseline in mean 8-point PG profiles and mean daily PG at specified visits was analyzed by using an ANCOVA model with a fixed effect for treatment and a covariate for baseline value. Daily PG variability at specified visits was analyzed by using Rank ANCOVA, where the covariate was the rank for baseline daily PG variability.

Insulin Dose: Variables included daily insulin dose prescribed, reported at each visit from Week 4 to Week 36, last dose taken and change between last dose and first dose, and daily insulin dose per kg body weight. Variables were summarized descriptively using summary statistics.

Prandial Insulin: Variables included percentage of patients who took prandial insulin as rescue medication at Month 6 (Week 24). Comparison between treatments was performed by using the Fisher's exact test. A 95% 2-sided CI for the treatment difference (insulin glargine minus insulin NPH) was also calculated by using the normal approximation to the binomial distribution.

Safety variables and analysis: Variables include AEs, incidence and rate of hypoglycemia, laboratory parameters (including lipid profile), body weight, vital sign measurements, and treatment satisfaction variables (DTSQs and DTSQc). Safety variables were summarized descriptively. In addition, change from baseline in body weight at the end of treatment was analyzed by using an ANCOVA model with a fixed effect for treatment and baseline value as a covariate.

Summary:

Population characteristics: A total of 1102 patients were screened (signed informed consent). There were 708 patients randomly assigned to one of the 2 treatment groups, 355 patients in the insulin glargine group and 353 patients in the insulin NPH group. Of the patients who were randomized, 704 (99.4%) were exposed to study drug and 335 patients (94.4%) in the insulin glargine group and 328 patients (92.9%) in the insulin NPH group completed the study.

Patient demographic and baseline characteristics were well balanced between the 2 treatment groups according to age, gender, weight, height, and BMI. The median age was 58.0 years, median weight before randomization was 82.00 kg, median height was 165.0 cm, and median body mass index before randomization was 29.59 kg/m^2. More females (393 patients [56.1%]) than males (308 patients [43.9%]) were enrolled in the study.

The mean duration (years) with T2DM was similar for both treatment groups, 9.1 years for patients in the insulin glargine group and 9.4 years for patients in the insulin NPH group. Patients in the insulin NPH group had been on OAD treatments longer (8.9 years) than patients in the insulin glargine group (8.2 years). The mean baseline HbA1c value was 8.21% for patients in the insulin glargine group and 8.16% for patients in the insulin NPH group.

Efficacy results:

- Based on the primary analysis, the study failed to show the superiority of insulin glargine compared with insulin NPH in terms of the mean HbA1c change from baseline. The adjusted mean HbA1c change from baseline for the insulin glargine group was –1.07 % and –0.97% for the insulin NPH group. The treatment effect was 0.10 in favor of insulin glargine and the p value was 0.142.
- Results of the comparison of the mean HbA1c change from baseline between the 2 treatment groups in the mITT population at Week 12, Week 24, and Week 36 were similar to those of the primary analysis. At Weeks 12, 24, and 36, the mean HbA1c change from baseline for the insulin glargine group was –0.97%, –1.14%, and –1.07%, respectively and –0.92%, –1.02%, and –0.98%, respectively for the insulin NPH group. Although the mean decrease from baseline was greater in the insulin glargine group at each visit, the difference was not significant.
- The proportion of patients achieving a targeted HbA1c response of <7% at the end of treatment was 6% in favor of the insulin glargine group (50.3% of the patients in the insulin glargine group and 44.3% of the patients in the insulin NPH group). The proportion of patients achieving a targeted response of <6.5% was similar between the 2 treatment groups with 22.1% of the patients in the insulin glargine group and 23.3% of the patients in the insulin NPH group.
- The FPG baseline mean for the insulin glargine group was 9.13 mmol/L and 8.91 mmol/L for the insulin NPH group. At Week 36, the adjusted mean FPG change from baseline for the insulin glargine group was –2.88 mmol/L and -2.65 mmol/L for the insulin NPH group. The treatment effect was 0.23 mmol/L in favor of insulin glargine and the p value was 0.009.

- Analysis of within-patient FPG variability at Week 24, Week 36, and end of treatment showed there was no difference between the 2 treatment groups.
- At the end of treatment, a decrease in the mean 8-point 24-hour PG profile was observed at each of the time points for both treatment groups. At Week 24, with the exception of the 2-hour postbreakfast and nocturnal time points, patients in the insulin glargine group experienced a greater decrease in PG than did patients in the insulin NPH group. At Week 36, the decrease in PG at each time point was significantly greater for the insulin glargine group prebreakfast, 2 hours postbreakfast, predinner, and 2 hours postdinner; At the end of treatment, decreases in PG were significantly greater for the insulin glargine group prebreakfast, 2 hours postbreakfast, prelunch, 2 hours postlunch, and 2 hours postdinner; The daily mean decrease in PG was significantly higher in the insulin glargine group compared with the insulin NPH group.
- Analysis of daily PG variability at Week 24, Week 36, and end of treatment showed there was no difference between the 2 treatment groups.
- No patients in the insulin glargine group required prandial insulin at Month 6 and 4 patients (1.2%) in the insulin NPH group required prandial insulin rescue medication at Month 6. The p value for the difference in the percentages of patients taking prandial insulin as rescue medications was 0.059.
- During the Treatment Period, tight insulin titration was implemented based on the patient's FPG and NPG values. The mean insulin starting daily dose was 0.19 U/kg for both treatment groups. The mean insulin daily dose at Week 36 for the insulin glargine group was 0.39 U/kg and 0.37 U/kg for the insulin NPH group.

Safety results:

- The proportion of patients with any treatment-emergent adverse event (TEAE) was similar between the 2 treatment groups, 113 patients (30.9%) in the insulin glargine group and 107 patients (30.6%) in the insulin NPH group.
- The proportion of patients with any TEAE leading to death was slightly higher in the insulin glargine group (5 patients [1.4%]) than in the insulin NPH group (2 patients [0.6%]). None of the deaths were considered related to study drug.
- The proportion of patients with any treatment-emergent serious adverse event (SAE) was low and similar between the 2 treatment groups: 12 patients (3.4%) in the insulin glargine group and 11 patients (3.1%) in the insulin NPH group. No serious hypoglycemia events were reported during the study.
- The incidence of TEAEs that led to permanent treatment discontinuation was low and slightly higher in the insulin glargine group than in the insulin NPH group (6 patients [1.7%] in the insulin glargine group and 4 patients [1.1%] in the insulin NPH group).
- Results of the lipid panel over time were similar between the 2 treatment groups.
- With the exception of the all daytime hypoglycemia events, there was not a statistically significant difference in the number of patients in the insulin glargine group and insulin NPH group who reported at least 1 episode of each type of hypoglycemia (all, all with PG value ≤70 mg/dL, all with a PG value ≤56 mg/dL, all asymptomatic, all symptomatic, symptomatic with a document PG value ≤70 mg/dL, symptomatic with a documented PG value ≤56 mg/dL, severe symptomatic, all nocturnal, all nocturnal asymptomatic, all nocturnal asymptomatic, nocturnal symptomatic documented with PG value ≤70 mg/dL, severe nocturnal symptomatic, all daytime asymptomatic, all daytime symptomatic, daytime symptomatic documented with PG value ≤70 mg/dL, daytime symptomatic documented with PG value ≤56 mg/dL, and severe daytime symptomatic) during the Treatment Period. In the all daytime type of hypoglycemia events, there was a higher percentage of patients in the insulin glargine group (63.8%) than in the insulin NPH group (55.7%) ($p = 0.028$). Severe hypoglycemia events were reported in few patients in both treatment groups.

- The number of hypoglycemia events per patient-year for all of the nocturnal hypoglycemia event categories (except severe nocturnal symptomatic), daytime symptomatic documented with a PG ≤56 mg/dL, all with a PG ≤56 mg/dL, all asymptomatic, and symptomatic documented with a PG ≤56 mg/dL hypoglycemic events categories were lower in the insulin glargine group.
- The estimated event rates of hypoglycemia per patient-year modeled with a binomial negative distribution, was significantly lower in the insulin glargine group for all nocturnal (p value 0.035), all nocturnal asymptomatic (p value 0.032), and nocturnal symptomatic documented hypoglycemia with PG ≤56 mg/dL (3.1 mmol/L) (p value 0.023).
- Mean change from baseline in systolic and diastolic blood pressure and heart rate were similar for the 2 treatment groups.
- No significant differences were observed between the 2 treatment groups in changes of body weight.
- The change from baseline at the end of treatment adjusted mean scores for the DTSQs questionnaire total satisfaction score and items 1, 4, 5, 6, 7, and 8 scores were slightly higher for the insulin glargine group than the insulin NPH group. The change from baseline at the end of treatment adjusted mean score for item 2 was negative for both treatment groups and was slightly lower for the insulin glargine group, reflecting a greater shift to a more positive health state than the insulin NPH group. The change from baseline at the end of treatment adjusted mean score for item 3 was positive for both treatment arms reflecting a shift towards a worse health state for both treatment groups. These changes were small and not different between groups. The insulin glargine group showed a slightly lower increase than for the insulin NPH group.
- Analysis results of the DTSQc questionnaire for total satisfaction score were slightly better for the insulin glargine group and were similar between the 2 treatment groups for each of the 8 items in the questionnaire at the end of treatment.

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