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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00405418
		Study Code:	LANTU_C_00579
Generic drug name:	Insulin Glargine	**Date:**	9 October 2009

Title of the study:	Target glycemic control and the incidence of documented symptomatic hypoglycemia in insulin naïve subjects with type 2 diabetes failing on oral hypoglycemic agent(s) and treated with Lantus® (insulin glargine) or Levemir® (insulin detemir): multicenter, multinational, randomized, open-label, comparative, parallel-group study.	
Coordinating Investigator(s):	Frits Holleman, MD, PhD, Department of Internal Medicine, AMC F4-260, Meibergdreef 9, P.O Box 22660, 1100 DD Amsterdam, The Netherlands.	
Study center(s):	122 centers in 20 countries in Asia, Australia, Brazil, Canada, Eastern and Western Europe.	
Publications (reference):	None.	
Study period: Date first patient enrolled: 14 Nov 2006 Date last patient completed: 12 Jun 2008		Phase of development: IV
Objectives:	Primary objective: To demonstrate the non-inferiority of insulin glargine in comparison to insulin detemir in terms of percentage of patients who reached the target of hemoglobin A1c (HbA1c) < 7% at the end of the treatment period and do not experience symptomatic hypoglycemia, confirmed by plasma glucose (PG) ≤ 56 mg/dL (3.1 mmol/L) Secondary objectives: • To compare between the 2 treatment groups, the percentage of patients who reached the target of HbA1c < 7% and < 6.5% at the end of the treatment period • To compare the changes in HbA1c and fasting plasma glucose (FPG) • To compare the evolution of plasma glucose profiles • To compare the day to day FPG variability, the insulin doses; • To determine in each treatment group the biochemical and patient-related predictors/determinants of failure to reach HbA1c targets • To compare the overall incidence and rate of symptomatic hypoglycemia and nocturnal symptomatic hypoglycemia confirmed by PG ≤ 56 mg/dL (3.1 mmol/L) • To compare over the treatment period, the overall incidence and rate of symptomatic hypoglycemia and symptomatic nocturnal hypoglycemia (PG ≤ 70 mg/dL [3.9 mmol/L]), symptomatic day-time hypoglycemia (with PG ≤ 70 mg/dL [3.9 mmol/L] and with PG ≤ 56 mg/dL [3.1 mmol/L].), of severe hypoglycemia and asymptomatic hypoglycemia with PG ≤ 56 mg/dL. The incidence and rate of hypoglycemia will also be computed for the following 2 intervals: from 1 to 12 weeks	

<table>
<tr><td></td><td>= from day 1 (date of 1st dose) to day 84 (12 weeks) included, and from 13 to 24 weeks = from 12 weeks to end of treatment period
• To compare the overall safety; incidence of AEs (including serious hypoglycemia and local tolerance at injection site), change in body weight, in waist circumference and in waist/hip ratio
• To assess the quality of life (QoL) and treatment satisfaction.</td></tr>
<tr><td>Methodology:</td><td>This was a multinational, multicenter, randomized (1:1), open label, parallel-group comparative study.
The study consisted of a 1 to 4-week screening phase, followed by a 24-week randomized treatment phase.
During the 1 to 4-week screening phase, the patients continued on current therapy including diet, exercise and stable doses of Oral Antidiabetic Drugs (OADs). They were trained to use the plasma glucose meter provided by the sponsor for the study.
At the end of the screening phase, the patients eligible for the study were randomized to either insulin glargine (once daily in the evening: at dinner or at bedtime) or insulin detemir (twice daily, at breakfast and before dinner) for the 24-week treatment phase.
At the time of the randomization the treatment with thiazolidinediones had to be stopped. Treatment with insulin secretagogues (sulfonylureas and glinides) was maintained in combination with insulin, or discontinued at the Investigator's discretion, taking into account country specific requirements.
During the randomization treatment phase, OADs that were continued (at least metformin) were kept at a stable dose throughout the study.
No add-on or increase in OADs were permitted during the randomization phase.</td></tr>
<tr><td>Number of Patients:</td><td><table>
<tr><th></th><th>Insulin glargine</th><th>Insulin detemir</th><th>Total</th></tr>
<tr><td>Planned</td><td></td><td></td><td>910</td></tr>
<tr><td>Randomized</td><td>486</td><td>487</td><td>973</td></tr>
<tr><td>Randomized and treated</td><td>478</td><td>486</td><td>964</td></tr>
<tr><td>miTT population (primary criterion)</td><td>473</td><td>472</td><td>945</td></tr>
<tr><td>PP population</td><td>436</td><td>439</td><td>875</td></tr>
<tr><td>Safety population</td><td>478</td><td>486</td><td>964</td></tr>
<tr><td>QoL population</td><td>451</td><td>460</td><td>911</td></tr>
</table></td></tr>
<tr><td>Diagnosis and criteria for inclusion:</td><td>Men and women from 40 to 75 years old with a body mass index (BMI) of < 40 kg/m^2 who were insulin naïve and had type 2 diabetes for at least one year, who were treated with stable doses of oral antidiabetic drugs (OADs) for at least 3 months prior to study start, including metformin (at least 1g/day), who were willing and able to perform plasma glucose monitoring and use a patient diary and who gave their written informed consent.</td></tr>
</table>

Investigational products: Dose: Administration:	Insulin glargine: Lantus® (100 U/ml), 3 ml cartridge system for OptiClik® Starting dose 0.2 U/kg body weight Subcutaneous injection, once daily in the evening
Dose: Administration:	Insulin detemir: Levemir® (100 U/ml), 3 ml cartridge system for Novopen®3 Starting dose 0.2 U/kg body weight Subcutaneous injection, twice a day (before breakfast and before dinner)
Duration of treatment: 24 weeks. Both insulins were titrated every 2 days, according to the FPG values (in order to reach FPG < 100 mg/dL)	Duration of observation: 28 weeks
Criteria for evaluation:	
Primary endpoints and main secondary endpoints:	The primary efficacy variable was the composite of last HbA1c measured during the treatment period, and the occurrence of symptomatic confirmed hypoglycemia (PG ≤ 56 mg/dL [3.1mmol/L]) during the treatment period. For the assesment of the primary and secondary endpoints, the following data were collected: • HbA1c recorded at baseline, Week 12 and Week 24 • Self-monitored FPG values at each visit • Self-monitored PG values from 8-point 24-hour profile (immediately before and 2 hours after breakfast, lunch and dinner, at bedtime and at 3:00 a.m.) recorded on 2 consecutive days within the week prior to randomization visit 2 (baseline) visit 12 (Week 12) and last visit (Week 24). In this study, bedtime should be at least 2 hours and 30 minutes after dinner • Episodes of hypoglycemia (symptomatic hypoglycemia:total and categorized as day-time/nocturnal, severe hypoglycemia, asymptomatic hypoglycemia) • Self monitored PG values whenever the patient experienced symptoms of hypoglycemia • Daily doses of insulin glargine or insulin detemir • Laboratory fasting plasma glucose at baseline, Week 12 and Week 24 • Lipid profile at baseline and Week 24 • Patient reported outcomes (quality of life (QoL) and treatment satisfaction) were assessed at baseline, Week 4, Week 12 and at the last visit, using: the Fear of hypoglycemia score (in the Netherlands, Germany, Australia and UK), the diabetes symptom checklist (DSC-R) and the WHO-Five Well-being index (WHO-5) (in selected countries), and the diabetes treatment satisfaction (DTSQ) questionnaires
	• Safety data: occurrence of AEs and weight were assessed at each visit. Waist and hip circumferences were measured at baseline, Week 12 and Week 24. Systolic and diastolic blood pressure was measured at study entry, baseline, Week 12 and Week 24. A physical examination was performed at study entry and at the last visit.
Statistical methods:	Primary efficacy analyses were performed on the modified ITT (mITT) population for primary criterion and confirmed in the PP population. The mITT for primary criterion

	consisted of all randomized subjects who had received study medication and had: - at least one post-baseline HbA1c measurement as well as information on symptomatic hypoglycemia, or - their last HbA1c measurement > 7% and no information on symptomatic hypoglycemia, or - no post-baseline HbA1c measurement but at least one symptomatic hypoglycemia with PG ≤ 56 mg/dL during the treatment period Secondary efficacy analyses were performed on the mITT population (defined as all randomized and treated subjects). QoL and treatment satisfaction analyses were performed on the QoL population (defined as all randomized and treated subjects who had at least 1 value for any of the QoL questionnaires). Safety analyses were performed in the safety population (defined as all treated patients). Subjects were analyzed according to the study medication they received. The primary efficacy analysis investigated the rate of patients with their last HbA1c value on treatment < 7% and no documented symptomatic hypoglycemia (assessed by PG ≤ 56 mg/dL) during the treatment period.The comparison was made using a 95% confidence interval (CI) of the difference in percentages (glargine-detemir).The conclusion of non-inferiority was reached if the lower limit of the confidence interval was higher than or equal to the non-inferiority margin, defined as ~30% of the rate that was measured wiih detemir. If non-inferiority was demonstrated then a test of superiority was to be performed using a Chi-squared test. For categorical secondary efficacy variables the difference between treatments was analyzed using a Chi-squared test (see objectives above). For continuous secondary efficacy variables HbA1c, FPG, PG profiles, the difference between treatment groups was analyzed using an analysis of covariance (ANCOVA). This analysis was based on change from baseline for all variables apart from variability for PG profile and FPG, which were based on ranked last on treatment values. Analysis of variance (ANOVA) was performed on total daily insulin dose, and the rate of hypoglycemia per patient-year was analyzed using a Wilcoxon rank-sum test. For the DTSQs questionnaire, the total treatment satisfaction score was to be analyzed as follows: the ranked variations measured between baseline and at the end of the study were to be compared between the treatment groups by an analysis of covariance (ANCOVA), with the variation as the dependent variable, the treatment as the fixed effect and the ranked value at baseline as the covariate. The analysis was also to be performed for each of the eight questions separately. For the DTSQc questionnaire, the total treatment satisfaction change score was to be analyzed as follows: the ranked values at the end of the study were to be compared between the treatment groups by an analysis of covariance (ANCOVA), with the ranked value at the end of the study as the dependent variable, the treatment as the fixed effect and the ranked value of DTSQs at baseline as the covariate. This analysis was also to be performed for each of the eight questions separately. For the DSC-R, WHO-5, a multiple analysis of variance (MANCOVA) of the scores measured at the 3 times (4, 12 and 24 weeks) adjusted for the initial score and for the treatment was to be performed; it was to be concluded that there was a difference

	between the treatment groups if the treatment effect was globally significant. For fear of hypoglycemia, the worry score was analyzed as the DTSQs total treatment satisfaction score. All statistical tests were two sided and performed at a significance level of alpha = 5%.
Summary:	A total of 1230 patients were screened and 973 patients were randomized, 964 (99.1%) were treated and of those, 893 completed the study. 22 (4.6%) patients from the insulin glargine group and 49 patients (10.1%) from the insulin detemir group were prematurely withdrawn The main reason for premature withdrawal (71 patients) were AE (7 patients [1.5%] in the insulin glargine group and 22 patients [4.5%] in the insulin detemir group) and patients not wishing to continue (4 patients [0.8%] in the insulin glargine group and 8 patients [1.6%] in the insulin detemir group. The study population was composed of 527 males and 437 females, with a mean age of 58.4 ± 8.3 years, a mean BMI of 30.1 ± 4.8 kg/m^2, a mean HbA1c of 8.7 ± 0.9 % and a mean duration of diabetes of 9.9 ± 5.8 years. All patients were being treated with metformin. Amongst 865 patients treated with insulinosecretagogues at study entry, 367 discontinued treatment at randomization. Thiazolidinediones were discontinued by the majority of the 163 patients who were taking them at study entry 22 patients did not discontinue thiazolidinediones at randomization but most discontinued before insulin started. No clinically relevant between-group differences were observed for demographic and baseline characteristics between the 2 treatment groups.
Efficacy results:	Main efficacy criterion: A total of 130 patients in the insulin glargine group (27.5 %) and 121 patients in the insulin detemir group (25.6%) reached HbA1c < 7% at endpoint with the absence of symptomatic hypoglycemia, confirmed by PG ≤ 56 mg/dL (≤ 3.1 mmol/L). The non-inferiority of insulin glargine versus insulin detemir was demonstrated since the lower limit of the confidence interval of the percentage difference (glargine – detemir) was higher than the non-inferiority margin (95% CI [-3.78%, 7.48%]; non-inferiority margin -7.7%). These results were confirmed in the PP population (95% CI [-3.66%, 8.15%]; non-inferiority margin -7.9%) with 28.4% of success in the insulin glargine group and 26.2% in the insulin detemir group. As non-inferiority was demonstrated, the superiority analysis was performed on mITT for primary criterion but the observed difference between the treatment groups was not significant (p = 0.520). Results were confirmed in the PP population (p = 0.456). Secondary criteria: At endpoint, 208 patients (44.1%) in the insulin glargine group and 225 patients (47.8%) in the insulin detemir group reached the target of HbA1c < 7 %, with no significant difference between groups (p = 0.254). A statistically significant (p = 0.017) greater number of patients with a HbA1c value of < 6.5% was seen for the insulin detemir group (107 patients [22.7%]) than for the insulin glargine group (78 patients [16.5%]). HbA1c values decreased from 8.7 ± 0.9% for the two treatment groups at baseline to 7.2

	± 0.9% for the insulin glargine group and 7.1 ± 0.9% for the insulin detemir group at last on treatment evaluation. The mean change from baseline was similar (p = 0.149) in both groups: -1.46 ± 1.09% for the insulin glargine group and -1.54 ± 1.11% for the insulin detemir group. Further analysis of secondary objectives showed a baseline to endpoint decrease in short term glycemic parameters (FPG, 8 -point PG profiles). The mean fasting plasma glucose decreased from 171.5 ± 41.5 mg/dL at baseline to 108.1 ± 23.9 mg/dL at endpoint for the insulin glargine group, and from 176.0 ±42.4 mg/dL to 118.8 ± 32.3 mg/dL in the insulin detemir group, resulting in a statistically significant greater change for the insulin glargine group (-63.5 ± 45.3 mg/dL) than the insulin detemir group (-57.7 ± 45.0 mg/dL) p < 0.001 (95% CI -13.64, -6.55). At baseline, the 8-point plasma glucose profiles were very similar in both groups and the mean daily plasma glucose was 192.4±43.3 mg/dL in the insulin glargine group and 191.8± 41.7 mg/dL in the insulin detemir group. A decrease from baseline to last measurement was observed in both groups and was statistically significantly greater for insulin detemir (52.4±43.2mg/dL) compared with insulin glargine (46.2±47.7 mg/dL) (p<0.001). The proportion of patients experiencing symptomatic hypoglycemia was 55.9% and 56.2% of patients in the insulin glargine and insulin detemir group respectively. In most cases, these patients experienced at least one symptomatic episode of hypoglycemia confirmed by a PG of ≤ 70 mg/dL (≤ 3.9 mmol/L). Symptomatic hypoglycemia confirmed by a PG ≤ 56 mg/dL (≤ 3.1 mmol/L) occurred in 29.9% of the patients in the insulin glargine group and 33.3% in the insulin detemir group. The difference between groups was not significant. Severe hypoglycemia was rare, affecting 26 patients (2.7%) in total, 14 patients (2.9%) in the insulin glargine group and 12 patients (2.5%) in the insulin detemir group. Day time severe hypoglycemia was experienced by 6 (1.3%) patients in the insulin glargine group and 8 (1.6%) patients in the insulin detemir group. Severe nocturnal hypoglycemia was experienced by 10 patients (2.1%) in the insulin glargine group and 6 patients (1.2%) in the insulin detemir group. The rate of symptomatic hypoglycemia per patient year was 7.50 ± 14.04 for the insulin glargine group and 8.87 ±18.40 for the insulin detemir group. The rate of daytime symptomatic hypoglycemia per patient year confirmed by a PG of ≤ 56 mg/dL was statistically lower for patients in the insulin glargine group (1.06 ± 3.13) than in the insulin detemir group (1.64 ± 5.42) (p = 0.046). The starting prescribed insulin dose was similar in both groups (16.4 ± 3.5 U in the insulin glargine group and 16.7 ± 4.0 U in the insulin detemir group). In each treatment group, the dose of insulin increased from baseline to the end of treatment; the increase was mainly marked during the first 12 weeks. At week 12, the mean daily dose of insulin glargine was 40.5 ±22.7 and the mean daily dose of insulin detemir was 64.7 ± 34.2. At the end of the treatment period, the mean insulin dose was statistically higher in the insulin detemir group (76.5 ± 50.5 U) compared to insulin glargine(43.5± 29.0 U) (p<0.001).

Safety results:	The number of patients who experienced at least one treatment-emergent adverse event (TEAE) is presented in the following table (see next page):

	Insulin glargine N = 478 n (%)	Insulin detemir N = 486 n (%)
Any TEAE	264 (55.2)	256 (52.7)
Any serious TEAE	21 (4.4)	18 (3.7)
Any serious TEAE resulting in death	1 (0.2)	0 (0.0)
Any TEAE resulting in permanent discontinuation of the study medication	7 (1.5)	22 (4.5)

A total of 520 patients (53.9%) experienced at least one TEAE in a similar proportion in the insulin glargine group (264 patients, 55.2%) and in the insulin detemir group (256 patients, 52.7%).

The most frequent TEAEs reported in the insulin glargine group were nasopharyngitis (40 patients, 8.4%), diarrhea (26 patients, 5.4%) and headache (19 patients, 4.0 %). The most frequent TEAEs reported in the insulin detemir group were nasopharyngitis (53 patients, 10.9%), headache (28 patients, 5.8%), upper respiratory tract infection (21 patients, 4.3%) and influenza (21 patients, 4.3%).

Serious TEAEs occurred in 21 patients (4.4%) of the insulin glargine group and 18 patients (3.7%) in the insulin detemir group. The investigator considered 4 of these events possibly related to study treatment: peripheral oedema and syncope in the insulin glargine group and hypoglycemia and drug hypersensitivity in the insulin detemir group. The case of drug hypersensitivity led to study drug discontinuation.

One serious TEAE (malignant lung neoplasm reported in insulin glargine group) resulted in death which occurred after the end of the study.

Seven patients (1.5%) in the insulin glargine group experienced a TEAE leading to discontinuation; one patient was prematurely withdrawn because of two possibly related TEAEs (rash and pruritis). A total of 22 patients (4.5%) in the insulin detemir group experienced a TEAE leading to discontinuation. For 20 of these patients, the TEAEs were considered to be possibly related to the study drug (drug hypersensitivity [6 patients], injection site hypersensitivity [4 patients], injection site reaction [3 patients], fibrosis [2 patients], injection site erythema [2 patients], hypersensitivity [2 patients], abdominal discomfort [1 patient]).

Body weight and BMI increased from baseline to last evaluation, in both treatment groups. The mean increase in body weight and BMI was higher in the insulin glargine group (1.4 ± 3.2 kg, BMI 0.5 ± 1.1 kg/m2) than in the insulin detemir group (0.6 ± 2.9 kg, BMI 0.2 ± 1.1 kg/m2) (: $p < 0.001$ [CI 0.38, 1.16]; BMI : $p < 0.001$ [CI 0.12, 0.41]).

	There was no significant difference in change from baseline between treatment groups in waist circumference The change from baseline was minimal in both groups no more than 1 cm in average.There was negligible change in the total waist/hip ratio for either group. There was no significant difference in the change from baseline in blood pressure (systolic or diastolic) between groups. There was no significant difference in the change from baseline between the treatment groups for total cholesterol, HDL, LDL or triglycerides.
Quality of life results:	Results from the DTSQs showed an improvement in total score for treatment satisfaction with a mean baseline to endpoint increase more pronounced for the insulin glargine group (from 25.9 ± 7.8. to 31.1 ± 5.8) compared to the insulin detemir group (from 25.3 ± 7.5 to 29.3 ± 7.0) ($p < 0.001$). Consistenly, the mean total treatment satisfaction scores from DTSQc were positive for both groups at the last measurement (14.3± 5.0 in the insulin glargine group and 12.1± 6.9 in the insulin detemir group)This increase in satisfaction was statistically significantly higher in the insulin glargine group($p < 0.001$). Both treatment groups showed an improvement in DSC-R total symptom score, indicating an improvement of symptom burden. The change from baseline to last measurement was -3.04 ± 10.51 for the insulin glargine group and -1.92 ± 11.82 for the insulin detemir group. There was no significant difference between the treatment groups. The mean change from baseline to last measurement in WHO-5 score was 6.13 ± 21.47 for the insulin glargine group and 7.54 ± 19.06 for the insulin detemir group. There was no significant difference between the groups. There was no significant difference between the groups regarding the worry score of the fear of hypoglycemia questionnaire
Date of report:	15 September 2009