These results are supplied for informational purposes only. *Prescribing decisions should be made based on the approved package insert in the country of prescription*

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00174681
		Study Code:	HOE901_4042
Generic drug name:	insulin glargine	**Date:**	8 April 2008

Title of the study:	TESTING THE USEFULNESS OF LANTUS WHEN INITIATED PREMATURELY IN PATIENTS WITH TYPE 2	
Investigator(s):	Professor André Grimaldi, Hôpital de la Pitié, 47-83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France.	
Study center(s):	49 active centers in France (32 centers), Slovenia (5 centers), Romania (4 centers), Russia (4 centers), Czech Republic (3 centers) and Croatia (1 center).	
Publications (reference):	Not applicable	
Study period: Date first patient enrolled: 01 April 2003 Date last patient completed: 14 February 2007		**Phase of development:** Phase IV
Objectives:	The primary objective was to evaluate the efficacy of initiating insulin glargine (Lantus®) combined with oral antidiabetic drugs (OAD) versus oral antidiabetic treatment optimized by enhancing the diet and exercise measures in type 2 diabetic patients whose blood glucose control was acceptable but not optimal on maximum oral treatment, based on the number of patients achieving an HbA1c value < 7% at the end of treatment. The secondary objectives of this study were to compare between the two treatment groups: - The variation in HbA1c between baseline and end of study. - The frequency of episodes of symptomatic hypoglycemia (diurnal and nocturnal), severe hypoglycemia (diurnal and nocturnal) and asymptomatic hypoglycemia. - The mean blood glucose levels at different times of the day. - The variation in weight and lipid profile between baseline and end of study. - The incidence of adverse events.	

<table>
<tr><td>Methodology:</td><td>International, multicenter, comparative, open-label, randomized (1:1), study in parallel groups. The study consisted of a 2–week selection period followed by a 40-week treatment period.

The first treatment arm (Lantus® arm) consisted in one daily injection of insulin glargine (Lantus®), in combination with the patient's previous oral antidiabetic treatment.

The second treatment arm (Hygienic and dietary measures (HDM) arm) consisted in optimization of the diet and exercise measures, in combination with the patient's previous oral antidiabetic treatment.

12 visits were performed: 6 visits (V) at the investigational center (V1 [selection], V2 [inclusion], V6, V8, V10 and V12 [end of study] on week -2, 0, 4, 12, 26 and 40 ± 2 weeks, respectively) and 6 phone consultations (V3, V4, V5, V7, V9 and V11 on week 1, 2, 3, 8, 19 and 33 ± 1 week, respectively).</td></tr>
<tr><td>Number of patients planned and evaluated:</td><td>
<table>
<tr><th></th><th>Lantus® arm</th><th>HDM arm</th><th>Total</th></tr>
<tr><td>Planned</td><td>100</td><td>100</td><td>200</td></tr>
<tr><td>Randomized</td><td>106</td><td>109</td><td>215</td></tr>
<tr><td>Randomized and treated [Full Analysis Set (FAS)]</td><td>103</td><td>108</td><td>211</td></tr>
<tr><td>Randomized and treated without any major protocol violation [Per protocol (PP)]</td><td>88</td><td>90</td><td>178</td></tr>
<tr><td>Safety Population (all treated patients)</td><td>103</td><td>108</td><td>211</td></tr>
<tr><td>Completed</td><td>95</td><td>102</td><td>197</td></tr>
</table>
</td></tr>
<tr><td>Diagnosis and criteria for inclusion:</td><td>Men and women with type 2 diabetes, aged 40 to 75 years (inclusive), with a Body Mass Index (BMI) between 24 and 35 kg/m^2 (inclusive), being treated with oral antidiabetics for at least two years (with the exception of glinides and thiazolidinediones), with an HbA1c between 7% and 8% (inclusive), treated at inclusion with at least a sulphonylurea and metformin at the maximum tolerated dosages.</td></tr>
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Investigational product:	Insulin glargine (Lantus®)
Dose:	Initial dose: 0.1 unit/kg/day. Dose adjustment was to be performed every 2 days in order to obtain Capillary Fasting Blood Glucose (FBG) levels between 0.70 g/L (3.9 mmol/L) and 1 g/L (5.5 mmol/L).
Administration:	One subcutaneous (SC) injection, with an OptiPen® Pro 1 insulin pen, in the evening (either before dinner or at bedtime) at the same time everyday

Duration of treatment: 40 ± 2 weeks	**Duration of observation:** 42 ± 2 weeks

Diet and exercise measures:	Diet and exercise measures were reminded to all selected patients. Patients randomized in the HDM arm were instructed to enhance diet measures and to increase physical activity (i.e. 2-hour brisk walk or equivalent per week) in order to maintain a stable body weight if their baseline BMI was < 27 kg/m² but to loose 3 kg if their baseline BMI was ≥ 27 kg/m²
Oral antidiabetic treatment:	The previous OAD treatment including a sulphonylurea and metformin was to be continued at baseline dosage (maximum tolerated dosage) during the whole study, in both treatment arms. Sulphonylurea dosage could be adapted by the Investigator in case of hypoglycemia (except in case of fasting hypoglycemia, which required insulin dose adaptation, for patients randomized in the Lantus® arm).
Criteria for evaluation:	
Efficacy :	**Main efficacy criterion**: Percentage of patients achieving HbA1c <7% at the end of treatment. **Secondary efficacy criteria**: - Percentage of patients achieving HbA1c <6.5% at the end of treatment, - HbA1c value at each study visit (baseline, V8, V10, V12 [end of study visit], - Hypoglycemic episodes (i.e. asymptomatic, symptomatic, severe, and nocturnal episodes), - Values of 24-hour capillary blood glucose measurement (5-point profile: before and 2 hours after breakfast and lunch, before dinner) performed within the week prior to V2 (inclusion visit), V6, V8, V10, and V12 (end of study visit), - Fasting plasma glucose level at baseline and V12 (end of study visit), - Weight at each study visit, - Lipid profile at baseline and V12 (end of study visit), - Daily dose of insulin glargine (Lantus®) and daily dose per kilo.
Safety:	- Vital signs (Systolic Blood Pressure [SBP], Diastolic Blood Pressure [DBP]) recorded at each study visit, - Adverse events

Statistical methods:	Efficacy analyses were performed in the Full Analysis Set and in the PP populations. Safety analyses were performed in the Safety Population. In the HDM arm, a patient was considered as 'treated' if he/she had had at least one phone call from the investigator or the nurse during the course of the trial, reminding him/her of the dietary rules, weight target and physical activity. The association between the percentage of patients achieving HbA1c < 7% at endpoint and treatment groups was tested using a logistic regression model with the initial HbA1c value as a covariate; the 2-sided adjusted confidence interval for the difference in event rates was calculated. Between-groups comparisons of other variable changes (i.e. HbA1c, fasting plasma glucose and capillary blood glucose levels, weight, lipid profile) from baseline were performed using a covariance analysis (ANCOVA), with variable changes as the dependent variable, the treatment as the fixed effect and the initial value of the concerned variable as the covariate. The numbers of patients with hypoglycemic episodes were compared between groups using a Fisher's exact test and the number of episodes per year using an analysis of variance on rank.
Summary:	A total of 354 patients were screened and 215 patients randomized, 211 patients (98.1%) were treated, of those 197 (93.4%) completed the study. The main reasons for premature withdrawal (14 patients; 6.6%) were adverse events (4 patients; 1.9%) and patient's decision (4 patients; 1.9%), There were no between-group differences. The study population was composed of 52.6% of men and 47.4% of women, aged on average of 60.65 ± 7.89 years (1.4% of patients >75 years), with a mean BMI of 29.90 ± 3.48 kg/m², a mean HbA1c of 7.6 ± 0.4% and a duration of diabetes of 10.01± 6.53 years. No statistically significant or clinically relevant between-group differences were observed for demographic and baseline characteristics between the 2 treatments groups.

Efficacy results:	**Main efficacy criterion:** The percentage of patients achieving HbA1c <7% at endpoint (responders) was statistically significantly higher in the Lantus® arm (68 patients; 66.0%) than in the HDM arm (41 patients; 38.0%) (absolute difference 29.8%, 95%CI [16.1% ; 42.3%], p<0.0001). This result was confirmed in the PP population with 68.2% of responders in the Lantus® arm (60 patients) and 41.1% of responders in the HDM group (37 patients) ; p = 0.0002. **Secondary criteria:** The percentage of patients achieving HbA1c < 6.5% at endpoint was statistically significantly (p = 0.0001) higher in the Lantus® group (35 patients; 34.0%) than in the HDM group (12 patients; 11.1%). The HbA1c level decreased on average from 7.6 ± 0.3% at baseline to 6.8 ± 0.7% at endpoint in the Lantus® group and from 7.5 ± 0.4% to 7.3 ± 0.9% in the HDM group, resulting in a mean change statistically different in favor of the Lantus® arm (-0.8 ± 0.7% versus -0.2 ± 0.9%, p<0.0001). These results were confirmed in the PP population. The mean fasting plasma glucose decreased from 1.70 ± 0.34 g/L at baseline to 1.22 ± 0.33 g/L at endpoint in the Lantus® arm and from 1.67 ± 0.27 g/L to 1.61 ± 0.41 g/L in the HDM arm, resulting in a mean change of -0.50 ± 0.47 g/L versus - 0.05 ± 0.39 g/L, p <0.0001. Differences in mean daily capillary blood glucose (BG) values calculated from a 5-point blood glucose profile were observed between the 2 treatment groups with a change of -0.29 ± 0.33 g/L in the Lantus® arm and -0.11 ± 0.33 g/L in the HDM arm (p<0.0001). The proportion of patients having experienced hypoglycemia was statistically significantly more important in the Lantus® arm than in the HDM arm; the number of episodes extrapolated to one year was as follows: - Asymptomatic hypoglycemia: 4.36 ± 8.14 versus 1.65 ±4.50 (p<0.0001) - Symptomatic hypoglycemia: 4.20 ± 6.60 versus 1.99 ± 7.84,(p <0.0001); - Symptomatic hypoglycemia with blood glucose value <0.70 g/L: 3.49 ± 5.90 versus 1.68 ± 6.39, (p <0.0001); - Nocturnal symptomatic hypoglycemia: 0.73 ± 2.07 versus 0.28 ± 2.11, (p = 0.0011); - Nocturnal symptomatic hypoglycemia with blood glucose value <0.70 g/L: 0.61 ± 1.90 versus 0.19 ± 1.39,(p = 0.0019). Only 2 severe hypoglycemic episodes were reported, in the Lantus® arm, versus none in the HDM arm. No patient experienced severe nocturnal hypoglycemia in both treatment groups.

	The mean body weight increased from 85.00 ± 12.46 kg at baseline to 86.00 ± 13.40 kg at the endpoint in the Lantus® arm and decreased from 83.98 ± 13.69 kg to 81.48 ± 13.50 kg in the HDM arm, resulting in a mean change of +0.91 ± 2.94 kg and -2.47 ± 3.19 kg respectively, p <0.0001. This mean decrease of about 2.5 kg in the HDM arm suggests good compliance to diet and exercise measures in this arm.
Compliance:	In the Lantus® arm, exposure time to insulin glargine ranged from 98 to 323 days with a median exposure of 277 days, (mean: 270.05 ± 40.67 days). The mean daily dose of insulin glargine per kg increased progressively from week 1 (0.12 ± 0.05 unit/kg/day) to end of treatment (0.27 ± 0.15 unit/kg/day). No relevant differences in the proportion of patients with good titration (defined as capillary FBG levels < 1 g/L) was observed between responders and non-responders, either at week 12 (44.8% versus 45.5%) or at end of treatment (56.9% versus 58.1%). In the HDM group, 95.1% of the responders and 89.6% of the non-responders have been considered compliant with exercise and diet recommendations. At the end of study, 79 patients of the Lantus® arm (77.5%) continued insulin glargine at the mean dose of 24.59 ± 14.28 units, 4 patients (3.9%) switched to another insulin and 19 patients (18.6%) discontinued insulin; 97.1% patients continued OAD. In the HDM arm, 14 patients (13.2%) started insulin and most of them continued oral treatment.

<table>
<tr>
<td>Safety results:</td>
<td>The number of patients who experienced at least one treatment-emergent adverse event (TEAE) is presented in the following table:

<table>
<tr><th></th><th>Lantus® arm
(N=103)</th><th>HDM arm
(N=108)</th></tr>
<tr><td>Any TEAE</td><td>45 (43.7%)</td><td>49 (45.4%)</td></tr>
<tr><td>Any Serious TEAE</td><td>10 (9.7%)</td><td>6 (5.6%)</td></tr>
<tr><td>Death</td><td>1 (1.0%)</td><td>0 (0.0%)</td></tr>
<tr><td>TEAE resulting in permanent discontinuation of study medication</td><td>3 (2.9%)</td><td>Not applicable</td></tr>
</table>

A total of 94 patients (44.5%) experienced at least one TEAE in a similar proportion in the Lantus® group (45 patients, 43.7%) and in the HDM group (49 patients, 45.4%).

The most frequent TEAEs reported are in the Lantus® arm, Bronchitis (4 patients, 3.9%), Hypertension (4 patients; 3.9%) and Paresthesia (3 patients; 2.9%), and in the HDM arm, Influenza (7 patients; 6.5%), Headache (3 patients; 2.8%), Chest pain (3 patients, 2.8%), Viral infection (3 patients, 2.8%) and Nasopharyngitis (3 patients; 2.8%).

A total of 10 patients (9.7%) in the Lantus® arm and 6 patients (5.6%) in the HDM arm experienced at least one serious TEAE. The investigators considered 2 of these events possibly related to study treatment in the Lantus® arm (one hypoglycemia completely recovered without sequelae and one occurrence of arterial hypertension still ongoing at the end of study).

One serious TEAE, in the Lantus® arm (Gastric cancer, not considered possibly related to study treatment) led to death.

Study medication was discontinued in 3 patients of the Lantus® arm (2.9%) due to adverse events. All these events were serious but none was considered possibly treatment related: they consisted in one severe and lethal gastric cancer, one severe hyperthyroidism ongoing at the end of the study and one moderate hyperglycemia which completely recovered without sequelae.

No relevant changes from baseline were observed for vital signs and no relevant differences were observed between groups.</td>
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<tr>
<td>Date of report:</td>
<td>14 January 2008</td>
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