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Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	ClinicalTrials.gov Identifier:	NCT00488527
		Study Code:	LANTU_L_01890
Generic drug name:	Insulin glargine	Date:	10/Sep/2010

Title of the study:	Use of Optimal Method to Initiate and Maintain Lantus (insulin glargine) Therapy in Combination With Hypoglycemic Agents, Assessing the Resulting Metabolic Control and the Safety in Type 2 Diabetes Mellitus Patients. A multicenter, open-label clinical trial (DOMME) / LANTU_L_01890		
Investigator(s):	Dr. Fernando Javier Lavalle Gonzalez Universidad Autónoma de Nuevo Leon, Departamento de Endocrinologia, Monterrey, Nuevo León Phone (+52) 81 8123 1241 Fax: (+52) 81 8348 5351 Email: fjlavallegzz@hotmail.com		
Study center(s):	Country: Mexico Opened sites: 74 Active sites: 44		
Publications (reference):	No publications have been done up to date		
Study period: Date first patient/subject enrolled: 28-Apr-2007 Date last patient/subject completed: 09-Dec-2008		Phase of development: Phase IV	
Objectives:	PRIMARY: ▪ To evaluate the efficacy of Lantus combined with oral hypoglycaemic agents in terms of percentage of responders. The responder is defined as the subject achieving a value of HbA1c < 7% at study endpoint (final determination of value) and/or a relative reduction in HbA1c of ≥ 12% compared to the baseline HbA1c value (endpoint vs. baseline HbA1c). SECONDARY: ▪ To evaluate the glycemic (FBG) and body weight change according to responding and non-responding subjects, ▪ Adverse events ▪ To evaluate the incidence and severity of hypoglycemic events, during Lantus medication (symptomatic, diurnal, nocturnal, severe). ▪ To evaluate the intra-patient variability of blood glucose levels in the fasting state.		
Methodology:	This is a prospective, multicenter, open–label, non-randomized, longitudinal (duration of 26 weeks and 5 days follow-up) study in patients with type 2 Diabetes mellitus.		
Number of patients/subjects:	Planned: 350	Randomized: --	Treated: 365

Evaluated:	Efficacy: not evaluated due to a protocol violation.	Safety: 365	mPP: 282
Diagnosis and criteria for inclusion:	● Patients (male/female: not pregnant or breast feeding) ● Diagnosis of type 2 diabetes mellitus ● Treatment with oral hypoglycemic agents (1 or 2) for more than 6 months ● age 18 years or older ● HbA1c > 8.0% and < 10% ● BMI < 40 kg/m^2 ● no renal function disorder or acute or chronic metabolic acidosis, or liver disease, or surgical treatment for diabetic retinopathy ● Informed Consent		
Investigational product: Dose: Administration:	Insuline glargine (Lantus®) The initial dose of Lantus in insulin-naive patients must be 10 U/day at bed time with forced titration to reach a fasting blood glucose of <100 mg/dL (<6.0 mmol/L). The titration steps will consist in increasing of 2, 4, 6 or 8 U. The titration will be weekly during the following 12 weeks and will be reviewed at each visit (on site and telephone visits), the previously adjusted dose will be maintained during the rest of the treatment period (the last three months) Subcutaneous injection		
Duration of treatment: 26 weeks		Duration of observation: 5 days	
Criteria for evaluation:			
Efficacy:	PRIMARY ▪ Change in HbA1c (%) from baseline to endpoint SECONDARY ▪ Change in the fasting blood glucose values at each visit ▪ Change in body weight from baseline to endpoint		
Safety:	PRIMARY ▪ Number of severe hypoglycemia SECONDARY ▪ Incidence of symptomatic and asymptomatic nocturnal hypoglycemia ▪ Evaluation of safety with regards to the use of insulin glargine, recording the adverse events, excluding hypoglycemia ▪ Abnormal laboratory results		
Statistical methods:	The primary population (PP) of interest for this study is defined as all treated subjects who successfully completed the study. Due to a protocol violation (no titration in the dose performed) there is not a PP, the patients which complied with inclusion / exclusion criteria and full data availability were analyzed as a modified primary population (mPP). The intent to treat population (ITT), consisting of all patients treated with at least one dose of study medication, will be analyzed as well. All statistical tests will be done bilateral with error type I at 5% (α=0.05). Population characteristics (including demographics, medical history, nature, duration and severity of the disease, current treatment) will be summarized into mean, standard deviation, and minimum, maximum, median, 95% confidence interval of the mean for quantitative variables and frequencies and percentage with 95% confidence interval, of the population for categorical data; both for non-missing data. Demographic characteristics are summarized to evaluate baseline recruitment. Main analysis for efficacy will be by classifying patients as responders or non-responders as per definition of HbA1c <7% at endpoint. According to groups of		

	responders and non-responders, secondary analysis will analyze fasting blood glucose, and weight change using repeated measurement analysis of variance. Secondary analysis will analyze intrasubject variability using repeated measurement analysis of variance. The frequency of hypoglycemia will be recorded incl. severe hypoglycemia according to DCCT definition, for the entire treatment period and follow-up treatment. All adverse events and serious adverse events will be listed overall and, if appropriate, frequency distributions by body system will be provided.
Summary:	A total of 365 patients were included from 74 sites, however titration algorithm was not followed by investigator / patient. As this fact was classified as a protocol violation, none of the patients were considered for efficacy analysis and therefore efficacy analysis was not performed as defined in the protocol. Of 365 patients included 282 of them were considered as mPP (modified Primary Population) and analysed. The percentage of responders (patients with HbA1c ≤7% and/or a relative reduction of ≥ 12% at endpoint compared to baseline value) was 53.19% (150 patients). In the overall mPP fasting blood glucose levels decreased significantly ($p<0.001$) from 169.53 ± 39.77 mg/dL at baseline visit to 123.60 ± 27.66 mg/dL at week 26 (endpoint). This significant decrease in FBG was observed similarly in responders and as well in non-responders (-50.1 mg/dL and -40.9 mg/dL from baseline to endpoint). There was no significant weight change in the responder group (+ 0.29 kg; $p=0.184$), whereas in the non-responder group a marginal increase in weight was observed (+ 0.97 kg; $p=0.001$). In the total group of 365 recruited patients, 88 patients (24.10%) presented at least one adverse event and 29 patients (7.95%) presented at least one event of hypoglycemia. Nocturnal hypoglycemia, was reported for 12 patients (3.29%), while 14 patients (3.84%) only presented diurnal hypoglycemia and 3 patients (0.8%) reported both types. ▪ From those 29 patients with hypoglycemia, in 6 patients it was classified as severe (1.64%). ▪ From those 29 patients with hypoglycemia, 5 patients did not present any symptoms (1.37%).

Efficacy results:

A total of 365 patients (ITT population) were collected from 74 sites, however titration algorithm was not followed by investigator / patient. Therefore, no PP population is considered for this analysis. An efficacy analysis is performed for mPP that was 282 patients which complied with inclusion / exclusion criteria and had a full set of data.

The baseline characteristics of the 365 patients are the following:

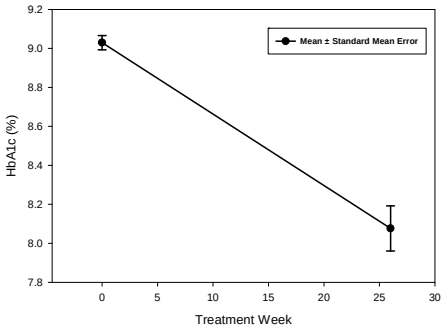
- Mean age was 55.8 ± 12 years
- 65%/35% were female/ male,
- Mean BMI was 28.94 ± 4.7 kg/m^2).
- Mean fasting blood glucose (FBG) at baseline was 170.88 ± 40.45 mg/dL
- Mean HbA1c at baseline was 9.08 ± 0.7%
- Mean duration of diabetes mellitus type 2 was 10.59 ± 7.1 years
- 335 patients (91.8%) received prior OAD treatment with Metformin (45.7%), Glibenclamide (35.8%),Glimepiride (7.3%) and others (11.2%).

An efficacy analysis was performed for mPP of 282 patients.

Patients responding to therapy were defined as those patients with HbA1c ≤ 7% at final evaluation (endpoint) and/or who had a relative reduction of ≥ 12% at endpoint compared to baseline value. A total of 150 patients (53.2%) presented one or both conditions (responders). From the 150 responders, 83 patients (30%) achieved a HbA1c value of ≤7.0 %.

The mean difference in HbA1c from baseline to endpoint was -0.95% ($p < 0.0001$) during 26 weeks of treatment, as it is shown in next figure:

HbA1c	Mean (%)	Standard Deviation
Week 0	9.0293	0.6044
Week 26	8.0764	1.9240



Analyses of fasting bloof glucose (FBG) levels and body weight change according

to responders (n=150) and non-responders (n=132).

Group of responders:

- FBG decreased significantly (p<0.001) from 166.9 ± 37.09 mg/dL at baseline visit to 116.8 ± 23.03 mg/dL at week 26.
- Body weight changed from 74.9 ± 15.26 kg at baseline to 75.19 ± 15.07 kg at week 26 (p=0.184).

Group of non-responders:

- FBG decreased significantly (p<0.001) from 172.63 ± 42.71 mg/dL at baseline visit to 131.7 ± 30.52 mg/dL at week 26.
- Body weight changed from 73.99 ± 14.88 kg at baseline to 74.96 ± 14.61 kg at week 26 which was statistically significant (p=0.001),
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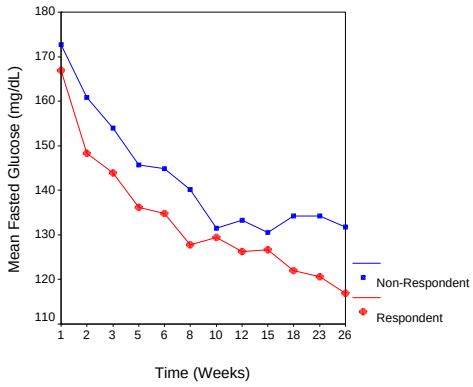
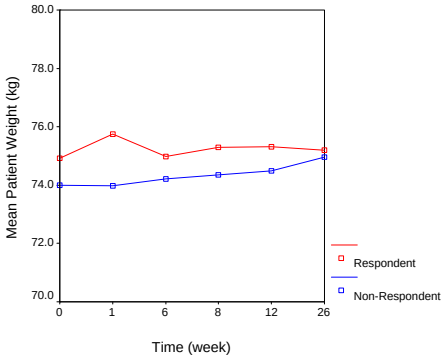
Next figure shows FBG changes during 26 weeks of treatment with Lantus for responder and non-responder groups. There was no difference between groups (p = 0.099).



Next figure shows changes in body weight during 26 weeks of treatment with Lantus for responder and non-responder groups. There was no difference between groups (p = 0.611).



Patient characteristics for the responder group (N= 150):

- The mean age was 55.9 ± 12 years, 66% of the included patients were females and 34% males
- Mean BMI was 29.26 ± 4.7 kg/m^2.

- Mean baseline FBG was 167 ± 37.1 mg/dL
- Mean duration of diabetes mellitus type 2 was 9.85 ± 7.2 years.

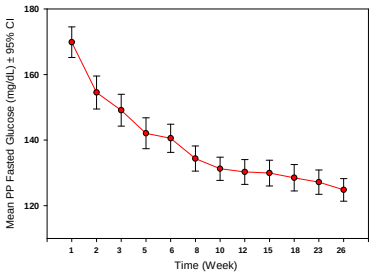
Patient characteristics for the non-responder group (N= 132):

- Mean age was 55.4 ± 13 years, 63% of the included patients were females and 37% males
- Mean BMI was 28.78 ± 4.6 kg/m^2
- Mean baseline FBG was 173 ± 42.7 mg/dL
- Mean duration of diabetes mellitus type 2 was 11.21 ± 7.5 years).

The patient characteristics between the two groups were very similar, so there was not an impact factor in the response per group.

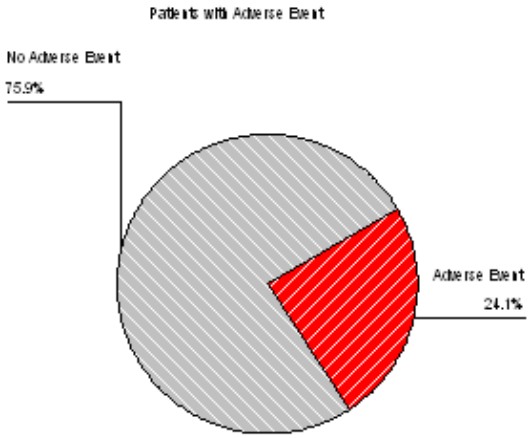
For mPP (N=282) FBG levels decreased significantly ($p<0.001$) from 169.53 ± 39.77 mg/dL at baseline visit to 123.60 ± 27.66 mg/dL at week 26.

Next figure shows 95% confidence interval for FBG values from week 1 to week 26.



Safety results:

This analysis was done with the ITT population of 365 patients who have received at least one dose of insuline glargine: 88 patients (24.10%) presented at least one adverse event. Adverse event rate is shown in next figure.



The total number of adverse events in the 88 patients was 188.

- The intensity of the 188 AEs was:
  - Mild 80%
  - Moderate 19%
  - Severe 0.5%
  - In 0.5% the information was missing
- In 69.8% of the 188 AEs, the relation with the IP was excluded and in 30.2% it can not be excluded.
- 4 of these adverse events were classified as serious (2.1% of the AEs) and only in one of these the relation with the study medication can not be excluded.

The details for serious adverse events are shown in the following table:

CENTER	PAC	Diagnostic	Date	Reason for SAE	Relation to the study medication	Action with the study medication
38	9	Appendicitis	29-Feb-08	Require hospitalization	Exclude	None
9	20	Cholecystectomy	11-Jun-08	Require hospitalization	Exclude	None
71	7	Cerebral infarction	26-Nov-07	Persistent / significant disability	Exclude	None
58	9	Dizziness	06-Oct-07	Other medically important	Can not be excluded	None

In the ITT population (N=365) 29 patients (7.95%) presented at least one event of hypoglycemia, the total number of hypoglycemia events were 41. Hypoglycemia was evaluated as any blood glucose value that is less or equal than 72 mg/dL reported by the patient.

Hypoglycemia Event	Frequency	Percentage
Yes	29	7.9
No	336	92.1
Total	365	100.0

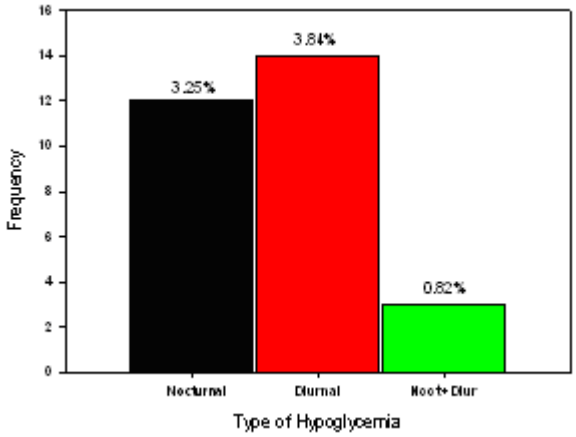
From those 29 patients with hypoglycemia, only 5 patients did not present any symptoms (1.37% from 365).

14 patients only presented diurnal hypoglycemia (3.84% from 365), the total number of events were 25.

Nocturnal hypoglycemia was defined as the hypoglycemia occuring while the patient is asleep, between the time of going to bed after the injection at night and before getting up in the morning, that is before the morning determination of the GA and before the morning injection, and is associated with a glucose level lower than 2.8 mmol/l (50 mg/dl), but without any kind of symptoms. These episodes will be identified when determining the available fasting glucose values.

- 12 patients had nocturnal hypoglycemia (3.29% from 365), the total number of events were 16.

3 patients had both nocturnal and diurnal hypoglycemia (0.82% from 365)



A severe hypoglycemic event was defined as an episode with symptoms of hypoglycemia during which the subject needed the help of someone else, associated with a level of hypoglycemia lower than 2.8 mmol/l (50 mg/dl); or having a prompt recovery after taking carbon hydrates orally or after the administration of glucose intravenously or glucagon subcutaneously, (as defined by the DCCT).

From those 29 patients with hypoglycemia, 6 patients (1.64% from 365) had a severe hypoglycemic episode. Severe hypoglycemia embraces all those episodes in which the neurological impairment was sufficiently severe so as to impede self-treatment, with the resulting risk of the subject harming him/herself or others.

The details of these events are shown in the following table:

Severe Hypoglycemia Event	Frequency	Glucose range
Diurnal	1	30
Nocturnal	5	37-51
Total	6	30-51

Date of report:	13-MAY-2010