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Sponsor / Company: Sanofi **Drug substance(s):** Insulin Glargine	**Study Identifiers:** NCT00701831 **Study code:** LANTU_L_03502

Title of the study:

Assessment of "intensive insulin titration" to reach effective dosing for good glycemic control with Lantus treated insulin naïve Type 2 diabetes mellitus (DM) patients

Study center(s):

23 centers in Turkey

Study period:

Date first subject/patient enrolled: 30 May 2008

Date last subject/patient completed: 10 October 2010

Phase of development: Phase 4

Objectives:

Primary Objective:

- To observe the efficacy of "intensive insulin titration" with Lantus, for a duration of 6 months to reach good glycemic control defined as patients reaching HbA1c levels of ≤7%.

Secondary Objectives:

- Fasting blood glucose (FBG) levels
- Final basal insulin dose/day
- The number of dose adjustments during the intensive insulin treatment period
- The time taken to reach the final dose titration
- The safety of basal insulin treatment in insulin naïve patients treated with Lantus
- Weight gain

Methodology:

National, multi-center, open-label, single arm study.

Number of subjects/patients:

Planned: 240

Screened: 369

Treated: 241 (patients who received at least one dose of study medication)

Evaluated:

Efficacy/pharmacodynamic: 236 (5 patient were withdrawn)

Safety: 241

Diagnosis and criteria for inclusion:

Insulin naïve patients with Type-2 DM who received oral antidiabetic agents (OADs) for more than 3 months were included in the study. Subjects aged ≥ 18 years, with poor glycaemic control (7,5%<HbA1c>10 %) and a BMI<40 kg/m^2, who were considered for Lantus treatment were eligible for the study, if they wanted to participate and provided written informed consents.

Study treatments

Investigational medicinal product(s): Insulin glargine

Formulation: Lantus® SoloSTAR®

Route(s) of administration: Subcutaneous

Dose regimen: Initial dose was 10 IU/day. The dose was adjusted according to the patient's need varying between 2 and 100 IU once daily.

Duration of treatment and observation:

Six months

Criteria for evaluation:

Efficacy/pharmacodynamic: Proportion of patients that achieved HbA1c level ≤7%; FBG levels changes; final dose of basal insulin; number of dose adjustments; titration time to reaching target Fasting Blood Glucose (FBG) levels; DTSQ (Diabetes Treatment Satisfaction Questionnaire).

Safety: Hypoglycemia, nocturnal hypoglycaemia and adverse events noted by the Investigator; weight gain

Statistical methods:

The primary efficacy variable of this study was the HbA1c level achieved at the end of intensive insulin titration. This level has been defined as <7%. Assuming that the treatment success rate would be 70% (i.e. 70% of all participants would achieve targeted HbA1c level <7%), with an error rate of 10 %, α set at 0.05 and with a power (1-β) = 0.90, a minimum 220 patients were planned to be enrolled in the study. Lost to follow-up rate was estimated at around 10%, thus a total of 240 patients were planned to be enrolled.

Summary statistics for quantitative and ordinal variables were the number of observations (n), mean, standard deviation (SD), median, minimum (Min) and maximum (Max) for subjects with data. For qualitative variables per category the numbers and frequencies of subjects with non-missing data (n, %) were presented when appropriate. Treatment related comparisons were performed with Mann Whitney-U test and Wilcoxon Signed Rank test.

Statistical analyses of this study was performed on the following patient populations:

- **Intent To Treat (ITT) population**: This group indicates the population that received at least a single dose of IMP.
- **Per-Protocol (PP) Population**: Indicates the analysis population that matches overall conditions specified by the study protocol and that shows no protocol deviation.
- **Efficacy population:** Efficacy populations of this study are defined as the ITT (intent to treat) and Per-Protocol populations.
- **Safety population:** Safety population of this study is defined as the treated population, receiving at least one dosage of insulin glargine.

Summary:

Population characteristics:

Patients with inadequate control of HbA1c and FBG while on OAD treatment were invited to be enrolled to the study. All patients were asked to measure and record their FBG levels, three times weekly after enrollment, for the evaluation of their regular FBG levels. The main reason for these recordings was to evaluate FBG levels and according to this level, provide patients an insulin dose titration on a regular basis.

At 23 study sites, the number of screened patients was 359 and screen failures were 118. The number of patients who received at least one dose of study medication was 241. Five patients were withdrawn (AE/SAE:1; Protocol deviations:4). Thus, statistical analysis (efficacy analysis) was conducted on 236 evaluable patients.

The distribution of both genders was almost equal, females making a slight majority over males. The mean (±SD) age of the patients was 53.4 ± 9.47 years, with a minimum age of 31. The mean (±SD) age in males was slightly higher (males 54.2 ± 9.2 years; females 52.9 ± 9.7 years). Overall, 57.6% of patients had primary school level education and 39.8% was homemakers.

Baseline demographic data showed a mean (±SD) body weight of 81.4 + 13.4 kg, whereas mean (±SD) BMI was 29,9 + 4.27 kg/m2 and mean (±SD) waist circumference was 104.05 +11.73 cm for females and 101.91+12.34 cm for males at baseline. Duration (±SD) of diabetes was 9.02 + 5.52 years at baseline (median 7.5 years). Patients were only receiving OAD medication at baseline and a majority of patients were either treated with sulfonylurea (40.2%) or biguanides, mostly with metformin (38.3%). Nearly half of the patients were receiving two OAD's (49.6%) and 35 % were receiving three OAD's at baseline. Mean (±SD) FBG level at baseline was 186.28 + 52.45 mg/dL (median 178.0 mg/dL) and mean (±SD) HbA1c was 8.81 % + 0,62 % (median 8.8 %).

Efficacy/pharmacodynamic results:

After the initiation of insulin glargine, each patient started to record daily blood glucose (BG) levels in a patient diary. Study nurses initiated their calls for the enrolled patients, and according to LANMET titration scheme, enrolled patients were instructed to adjust (titration) their daily basal insulin doses. After 90 days of follow-up by study nurses, patients were recalled for a visit on site and HbA1c levels were evaluated.

Mean (±SD) HbA1c was 7.40% ± 0.86% at Day 90 visit. The percent of patients that achieved HbA1c levels ≤ 7% was 36.9% after 90 days of intensive follow-up of blood glucose levels and titration of insulin glargine daily dose. On Day 180, however, only a slight increase occurred in the number of patients achieving HbA1c levels ≤ 7% (from 36.9 % to 38.2%, p=0,4590). Mean (±SD) HbA1c was 7.28% ± 0.92% at the last visit (Day 180 visit). FBG levels below 100 mg/dL and HbA1c levels ≤ 7% were achieved by 25.7% of the enrolled patients. The percentage of patients with FBG levels below 100 mg/dL and HbA1c levels ≤ 7% slightly decreased to 25.3% at the last visit. Mean (±SD) FBG levels significantly decreased to 111.51 ± 36.64 mg/dL from baseline to Day 90 visit and to 114.11± 34.81 mg/dL (p<0,001) on Day 180.

This study is the first study in Turkey which intended to intensify insulin titration in Type 2 DM patients. The results of this study indicated a successful outcome, since HbA1c levels ≤7% were achieved in approximately 40% of the patients, which is currently a difficult goal to target in Turkey. The baseline mean HbA1c level (8.81%), decreased to the level of 7.40% in 3 months and further decreased to 7.30% with intensified insulin treatment of 6 months duration. During this treatment period FBG levels decreased considerably as well. It is of note that laboratory FBG levels at visit days were slightly higher when compared to patient measurements (patient diary data), however, mean FBG laboratory measurements decreased to 111.5 mg/dL in 6 months from a baseline value of 186.3 mg/dL. Mean FBG levels recorded by patients were slightly lower, with median levels of 98 and 95 mg/dL at 3 and 6 months time points, respectively.

The insulin titration data indicated a rather quick increase in the mean (±SD) dose of basal insulin, from the initial 10 IU/day to 22.04 ± 6.71 IU/day in 25 days. This increase was slowed at 60 days, reaching a mean (±SD) of 29.64 ± 12.52 IU/day and mean FBG levels recorded by patients reached the level of 100 mg/dL in 60 days. Mean (±SD) insulin dose reached 32.67 ± 15.46 IU/day at Day 90 and remained constant thereafter. The mean (±SD) insulin dose was 36.83 ± 19.35 IU/day on Day 180. The mean number of titrations was 12 during the first 90 days of the treatment period, then decreased to 6 titrations during the second period of treatment.

The level of treatment satisfaction was also tested by means of Diabetes Treatment Satisfaction Questionnaire. Baseline results indicated that patients were not very happy with their current anti-diabetic treatment. Overall mean (±SD) DTSQ score was 20.28 ± 7.68 at baseline and mean (±SD) DTSQc was 13.29 ± 5.05 at the Day 180 (p<0.001). The highest score was found in perception of hyperglycemia at baseline (4.20 ± 1.44). After a treatment period of 6 months, only the scores regarding treatment flexibility was significantly higher in patients who achieved treatment goals, and perception of hyperglycemia and hypoglycemia were significantly low.

Safety results:

A total of 147 adverse events occurred throughout the study, nearly half of them {73 cases (49.7%)} were hypoglycemia. The second most frequent adverse event was weight gain (9.5%) followed by hypertension in only 2.7% of all cases. In three cases, coronary arterial disease (CAD) was reported (2.0%).

Body weight and BMI increased slightly, but did not reach significant levels. Mean body weight (±SD) was 82.19 ± 12.73 kg at Day 90 visit and 82.86 ± 13.27 kg at Day 180 visit. Mean (±SD) BMI was 30.66 ± 4.30 kg/m^2 and 30.87 ± 4.41 kg/m^2 at Day 90 and Day 180, respectively.

All of the observed hypoglycemia events were reported as related to study medication. There were additional12 cases of adverse events, reported as related to study medication, weight gain being the most frequent.

For hypoglycemia, the evaluation was made based on the following classification: if blood glucose levels were recorded below or equal to 52 mg/dL, this was rated as severe hypoglycemia, whereas overall hypoglycemia was rated as blood glucose level below or equal to 65 mg/dL. Patient diary review showed that 11.2% of all patients had severe hypoglycemia during the first three months of intensive insulin treatment and this level increased to 13.3% between Day 90 and Day 180. Hypoglycemia occurred more frequently at levels of 45% to 50% as evaluated at two visit points. During the first 90 days of treatment, almost 90% of the patients had 1 or 2 severe hypoglycemia events, but this pattern changed during the second period of observation. The proportion of patients who had one severe hypoglycemia event dropped to 34% during the second period of treatment, whereas the proportion of patients who had 3 severe hypoglycemia events increased to 24% (6 fold increase).

During this study a total of 17 cases of Serious Adverse Events (SAE) were reported. These 17 SAEs occurred in 14 patients at 7 study sites, with 3 SAEs occurring in one patient, and two SAEs occurring in another. Review of SAE reports showed that none of these SAEs were reported as related to study drugs and were mostly caused by concomitant morbidities, which resulted in hospitalizations either for treatment or interventions.

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