Non Interventional Study Report

Study Number: LANTU_L_04761 **Date: July 15, 2011**

SYNOPSIS

Title of the study:	A non-interventional post authorization study to evaluate the efficacy and tolerability of Lantus® and Insuman® basal in approaching target values for fasting blood glucose according to guidelines during a basal-supported oral therapy (BOT) in patients with type 2 diabetes (EARLY).
Study centre(s):	787 centres in Germany (approx. 1,8 patients per participating centre)
Publications (reference):	Not applicable.
Documentation period:	October 2009 until June 2010
Objectives:	This study documented a) the change in fasting blood glucose (FBG) and HbA_{1c} during an observation period of 3 resp. 6 months (approx. 12 resp. 24 weeks) after initiation/adaptation of a basal-supported oral therapy (BOT) according to guidelines using insulin glargine Lantus® resp. Insuman® basal in patients with type 2 diabetes (T2DM) under conditions of everyday practice. b) therapy effects (tolerability, adverse events [AEs]) in association with the initiation of an additional administration of basal insulin to an established metformin monotherapy in early-stage T2DM patients over an observation period of 3 resp. 6 months under conditions of everyday practice in regard to metabolic control.
Methodology:	An open, non-controlled, non-interventional, multi-centre and prospective post authorization study in T2DM patients.
Number of patients for analysis:	In this study, a total of 1438 patients gave their informed consent to participate. 1389 (96.6%) were treated with Lantus® and were included in the analysis as target population. Data of the 49 (3.4%) patients treated with Insuman® basal were analyzed separately.
Diagnosis and criteria for inclusion:	• Insulin-naïve patients with T2DM • Metformin mono-therapy since at least 3 months • HbA_{1c} ≥7.5% • Age ≥18 years • Medical history without known malign disease • Ability to perform blood glucose self-monitoring • Informed consent.
Exclusion criteria:	• Contraindication of therapy with Lantus® or Insuman® basal • Known alcohol or drug abuse • Dementia or general inability to understand the study.
Duration of observation:	The duration of the survey was 6 months (approx. 24 weeks) per patient.

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Criteria for evaluation: Primary:	• Change in HbA_{1c} from start of insulin therapy with Lantus® resp. Insuman® basal in a BOT until end of study • Change in FBG from start of insulin therapy with Lantus® resp. Insuman® basal in a BOT until end of study • Number of patients who reached the glycaemic target for HbA_{1c} <6.5% until end of study • Number of patients who reached the glycaemic target for HbA_{1c} <7.0% until end of study • Number of patients who reached the glycaemic target for FBG <100 mg/dL (5.6 mmol/L) until end of study.
Secondary:	• Documentation of individual goal of therapy in regard to FBG • Change in daily insulin dose from start of insulin therapy until end of study • Change in daily insulin injections from start of insulin therapy until end of study • Change in metformin dose from start of insulin therapy until end of study • Change in weight from start of insulin therapy until end of study • Number of adaptations of insulin dose during the first 3 months after start of insulin therapy • Number of adaptations of insulin dose between 3 and 6 months after start of insulin therapy • Consumption of blood glucose test strips per day/month after 3 and 6 months • Consumption of insulin pen needles per month until end of study after 3 and 6 months
Safety and tolerability criteria:	• Incidence of confirmed symptomatic hypoglycaemias with blood glucose values ≤70 mg/dL (3.9 mmol/L) or severe hypoglycaemias with blood glucose values <56 mg/dL (3.1 mmol/L) during insulin therapy with Lantus® resp. Insuman® basal in a BOT. • Incidence of AEs during insulin therapy with Lantus® resp. Insuman® basal in a BOT.
Statistical methods:	Descriptive statistics were applied to all data obtained in this study. For continuous variables mean, standard deviation (SD), minimum, 1st percentile, 25th percentile, median, 75th percentile, 99th percentile and maximum were determined; for categorical variables absolute and relative frequencies were determined. All statistical analyses of the data were purely exploratory. Statistical tests were applied to demonstrate and quantify any differences. All tests were chosen according to the data, i.e. the scales of measurement and the distribution of the variables evaluated. Data with approximately normal distribution and metric scaling were assessed using paired Student's t-tests, while differences in non-normal distributed continuous data were explored using non-parametric tests (Friedman test). Frequencies of categorical variables were determined using Chi-square or Cochran's Q tests. Confidence intervals were also determined using methods appropriate for the measured data. All p-values and confidence intervals provided using the applied statistical methods were purely exploratory and are not to be interpreted as a measure of statistical significance.

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Results: Demographic Summary:	The patients' age ranged from 14 (one patient) to 99 years with a mean of 65.6 years. The number of men and women was almost balanced (53 and 47%). At baseline, all patients weighed from 47 to 183 kg with a mean value of 89.3 kg. Individual BMI values ranged from 17.3 to 67.5 kg/m^2, which resulted in a mean of 30.82 kg/m^2.
Results: Primary target variables	Out of 1472 patients documented in Germany, 1438 patients were found eligible for this observational study with an investigative period of 6 months. The majority of the patients (1389, 96.6 %) was initially treated with Lantus®, only 49 (3,4 %) had Insuman® basal. There was a decrease in mean HbA_{1c} from 8.7% at baseline to 7.8% at approximately 3 months and a further decrease to 7.4% at approximately 6 months after initiation of the BOT with Lantus®. All p-values provided by an exploratory analysis for differences between visits were <0.01. There was also a decrease in mean FBG concentrations from 181.7 mg/dL at baseline to 143.9 mg/dL at approximately 3 months and a further decrease to 130.5 mg/dL at approximately 6 months after initiation of the BOT with Lantus®. All p-values provided by an exploratory analysis for differences between visits were <0.01. The frequency of patients who reached the glycaemic target HbA_{1c} <6.5% increased from 0.2% at baseline to 3.9% at approximately 3 months and to 9.4% at approximately 6 months after initiation of the BOT with Lantus® . An exploratory Cochran's Q test for differences between the visits provided a p-value of <0.01. The frequency of patients who reached the glycaemic target HbA_{1c} <7.0% increased from 1.4% at baseline to 16.5% at approximately 3 months and to 34.1% at approximately 6 months after initiation of the BOT with Lantus®. An exploratory Cochran's Q test for differences between the visits provided a p-value <0.01. The frequency of patients who reached the glycaemic target FBG concentration <100 mg/dL (5.6 mmol/L) increased from 2.6% at baseline to 7.2% at approximately 3 months and to 12.9% at approximately 6 months after initiation of the BOT with Lantus® basal. An exploratory Cochran's Q test for differences between the visits provided a p-value of <0.01. Remarkably, there were more patients reaching the above mentioned HbA_{1c} targets when stratifying for baseline HbA1c values. More patients with lower baseline HbA_{1c} values (≤7.5%) reached the targets at 3 and 6 months (14.2% and 21.8%) as compared to the patients with baseline HbA_{1c} >7.5% (3.0% and 8.3%). For reaching of the FBG target, no such difference was observed.
Results: Secondary target variables	The daily insulin dose was increased from a mean value of 14.2 Units/day at baseline to 19.4 Units/day at approximately 3 months and a further increase to 21.4 Units/day at approximately 6 months after initiation of the BOT with Lantus® basal. All p-values provided by an exploratory analysis for differences between visits were <0.01. The patients' mean weight showed considerable decreases from 89.3 kg at baseline to 88.8 kg at approximately 3 months and to 88.3 kg at approximately 6 months after initiation of the BOT with Lantus®. The exploratory analysis for differences between visits provided a p-value of <0.01 for for the mean rank between the documentation points After initiation of the BOT with Lantus®, 1 to 2 adaptations in insulin dose per month were performed during the whole observation period.

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Safety results:	Overall, the frequency of patients with non-severe hypoglycaemia was low at 3 (1.9%) and 6 months (2.5%) after initiation of the BOT with Lantus®. The frequency of nocturnal hypoglycaemia did not change notably between the documentation points (0.9% to 0.7%). Severe hypoglycaemia occurred in 2 patients during the first 3 months of observation and in another patient during the following 3 months. Another severe hypoglycaemia in 1 patient required outside help. Within the target population of 1389 patients treated with Lantus®, a total of 7 AEs were documented (4 AEs, 0.3%, after 3 months and 3 AEs; 0.2% after 6 months). Two of the 4 AEs at 12 weeks were SAEs, one of which resulted in death. One AE, a reversible vision disturbance at 4 days after initiation of the BOT with Lantus®, was suspected to be related to treatment by the investigator. No adverse events were reported in the 49 patients treated with Insuman® basal. Overall, the rate of 7 adverse events (0.5%) that occurred during the 24 weeks after initiation of the BOT with Lantus® describes a good safety profile in the population analysed.
Conclusions:	Overall, the findings of the EARLY study are supportive of improved glycaemic control within 3 and 6 months after initiation of a BOT with Lantus® basal in insufficiently controlled T2DM patients on metformin. After 6 months of a BOT with Lantus®, the patients showed a lower HbA_{1c} (mean values 7.4% versus 8.7% at baseline) and a lower FBG concentration (mean values 131 mg/dL versus 181 mg/dL at baseline) as well as a higher frequency of patients who reached objective glycaemic targets, such as HbA_{1c} <6.5% (mean values 9.4% versus 0.2% at baseline), HbA_{1c} <7.0% (mean values 34.1% versus 1.4% at baseline) and FBG <100 mg/dL (mean values 17.4% versus 4.7% at baseline). The probability of reaching the glycemic targets was markedly higher when initiating the insulin treatment with HbA1c values below 7.5%. In contrast to common experiences of insulin treatment, there was no increase in weight observed, in contrary, the mean weight slightly decreased from 89.3 kg to 88.3 kg over the course of observation.
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