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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00659477
		Study Code:	LANTU_L_02673
Generic drug name:	Insulin glargine	**Date:**	29 July 2010

Title of the study:	**Comparison safety and efficacy of basal insulin Lantus® (insulin glargine) vs NPH insulin in combination with OADs in subjects with DMT2, assessed by continuous glucose monitoring system (CGMS). Multicentre, prospective, open- label, single arm, comparative study in subjects switched from NPH insulin to insulin Lantus®.** **STUDY CODE: Lantu_ L_ 02673**
Investigator(s):	Coordinating investigator was Prof. MUDr. Milan Kvapil, CSc., MBA, FN Motol, V Úvalu 84, Praha 5, Czech Republic
Study center(s):	National study in Czech republic, 12 active centers
Publications (reference):	No preliminary publication was performed

Study period: Study Initiation Date (first subject enrolled): 31-Mar-2008 Study Completion Date (last subject completed): 03-Jun-2009	**Phase of development:** Phase IV

Objectives:	***The primary objective of the study*** **was** to compare blood glucose (BG) variability of the two treatments (insulin glargin as basal insulin vs insulin NPH) by the Continuous Glucose Monitoring System (CGMS®, Medtronic MiniMed, Inc.) by means of Area Under Curve (AUC) for blood glucose (BG): at the range (in mmol/L) of: (0, 3.3]; (0, 3.9]; (3.9, 7.5); [7.5, ∞); [10, ∞); [15, ∞) according to the mean change from baseline (insulin NPH treatment phase) to the endpoint of study (insulin glargine treatment phase) in patients with type 2 DM treated with basal insulin with OADs. ***The secondary efficacy objectives of the study were:*** To assess the difference between treatments in following parameters (derived from data recorded by CGMS measurement): time in percentage spent at the BG range (in mmol/L) of: (0, 3.3]; (0, 3.9]; (3.9, 7.5); [7.5, ∞); [10, ∞); [15, ∞), mean amplitude of glycemic excursion (MAGE), coefficient of variance (CV), M-value, standard deviation and mean of BG measured during whole day (24 hours), during day-time (07-22 hours), night-time (22-07hours) and occurrence of hypoglycaemia episodes detected by CGMS measurement (BG ≤ 3.3 mmol/L).

	Other main secondary objectives (not related to CGMS measurement) were to assess the difference between treatments in following parameters: glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG), variability (standard deviation) and intra individual variability of 6-point capillary blood glucose profile value measured by SMBG, overall incidence of hypoglycaemia (using following categories: all hypoglycaemia, all symptomatic hypoglycaemia, symptomatic hypoglycaemia confirmed by PG ≤ 3.3 mmol/L and symptomatic hypoglycaemia without confirmation, asymptomatic hypoglycaemia confirmed by PG ≤ 3.3 mmol/L), body weight, insulin total daily dose and insulin total daily dose per body weight. ***Safety objectives of the study*** Safety objectives included comparison of treatments in overall safety parameters including: incidence of adverse events, serious adverse events and severe hypoglycaemia, vital signs (systolic blood pressure, diastolic blood pressure and heart rate), safety laboratory parameters (alanine aminotransferase, aspartate aminotransferase and creatinine) and BMI.		
Methodology:	This was national, interventional, prospective, multicentre, open, single arm, clinical study in patients with Type 2 diabetes treated on basal insulin + stable dose of OADs. The study consisted of a 4 week NPH insulin treatment phase, followed by a 12 weeks insulin glargine treatment phase with active titration of basal insulin glargine to target FBG 5,5 mmol/L.		
Number of subjects:	Planned: 120 subjects	Randomized: NA Screened: 150 subjects Enrolled: 117 subjects	Treated: 116 subjects
Evaluated:	Efficacy: 116 subjects in the intent-to -treat (ITT) population 101 in the per-protocol (PP) population		Safety: 116 subjects
Diagnosis and criteria for inclusion:	***Inclusion criteria*** 1. Men or women, aged from 18 to 80 years inclusive 2. Diabetes type 2 3. Patients treated NPH insulin with stable dosage of OADs for at least 2 months prior to study start and OADs treatment with metformin at least 1,7 g /day in combination with sulfonylurea or glinides. 4. Patients must have a HbA1c range of ≥ 4,5% IFCC (6,2% DCCT) and ≤ 8% IFCC (9,4 % DCCT) 5. Ability and willingness to perform CGMS 6. Written informed consent obtained prior to enrollment in the study 7. Women are either not of childbearing potential (surgically sterile, or postmenopausal) or women of childbearing potential must not be pregnant and must use a reliable contraceptive measure for the duration of the study. Reliable contraceptive measures include the following: systemic contraceptive (oral, implant, injections), diaphragm with intravaginal spermicide, cervical cap, intrauterine device or condom with spermicide. ***Exclusion criteria*** Patients meeting any of the following criteria will not to be included in the study: 1. Fasting value C peptide ≤ 400 pmol/L 2. Active proliferative diabetic retinopathy, as defined by the application of photocoagulation or surgery, in the 6 months before study entry or any other unstable (rapidly progressing retinopathy that may require photocoagulation or surgery during the study. 3. Pregnant women or women planning gravidity during clinical study protocol 4. Breast-feeding 5. History of hypersensitivity to the study drugs or to drugs with similar chemical structure 6. Treatment with systemic corticosteroids in the 3 months prior to study entry and during study and other treatment that can significantly have impression to glycaemia.		

	7. Likelihood of requiring treatment during the study period with drugs not permitted by the clinical study protocol 8. Clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major disease making implementation of the protocol or interpretation of the study results difficult 9. Impaired hepatic function as shown by Alamine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) greater than three times the upper limit of normal range at study entry 10. Impaired renal function as shown by serum creatinine >/= 133 μmol/L in men and >/= 124 μmol/L 1 in women at study entry 11. History of drug or alcohol abuse in the last year 12. Mental condition causing the patient unable to understand the nature, scope and possible consequences of the study 13. Patient unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits and unlikelihood of completing the study 14. Patient is the investigator or any sub-investigator, research assistant, study coordinator, other staff or relative there of directly involved in the conduct of the protocol 15. Use of insulin glargine outside the scope of the current SPC (Summary of Product Characteristics) 16. Patients included in other clinical studies
Investigational product:	Insulin glargine, trade name: LANTUS®, formulation: 100IU/ml inj sol 5x3ml cartridge for Opticlik
Dose:	The dose of insulin Lantus was initiated once daily in the evening (at the same time every day. The starting dose of insulin glargine was identified by investigator based on the actual dose of NPH insulin. A forced titration insulin glargine after its initiation was used to obtain FBG < 5.5. mmol/L.
Administration:	Subcutaneous (SC) injection, to the abdominal wall, to the deltoid muscle or to the thigh
Duration of treatment:: 3 months	**Duration of observation:** 4 months
Reference therapy:	unspecified NPH insulin
Administration:	routinely administered for at least 3 month, out of it 1 month within the study

Criteria for evaluation:	
Efficacy:	***The primary endpoint*** was a composite variable based on 72-hour registration of blood glucose (BG) recorded using the Continuous Glucose Monitoring System (CGMS®, Medtronic MiniMed, Inc.). The primary endpoint was the difference between treatments in area under the curve (AUC; expressed as hrs*mmol/L over 24 hours) for BG at the range (in mmol/L) of: (0, 3.3]; (0, 3.9]; (3.9, 7.5); [7.5, ∞); [10, ∞); [15, ∞) derived from CGMS measurements. Only complete records during the second day of measurement (0:00-24:00) were used for statistical analysis. ***The main secondary endpoints were as follows:*** ***Endpoints derived from CGMS measurements:*** The differences between treatments in following parameters derived from data recorded by CGMS measurement): time in percentage spent at the BG range (in mmol/L) of: (0, 3.3]; (0, 3.9]; (3.9, 7.5); [7.5, ∞); [10, ∞); [15, ∞), mean amplitude of glycemic excursion (MAGE), coefficient of variance (CV), M-value, standard deviation and mean of BG measured during whole day (24 hours), day-time (07-22 hours), night-time (22-07hours) and occurrence of hypoglycaemia episodes detected by CGMS measurement (BG ≤ 3.3 mmol/L). ***Other endpoints:*** Other main secondary endpoint (not related to CGMS measurement) were the differences between treatments in following parameters: glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG), variability (standard deviation) and intra individual variability of 6-point capillary blood glucose profile value from data from SMBG, overall incidence of hypoglycaemia (using following categories: all hypoglycaemia, all symptomatic hypoglycaemia, symptomatic hypoglycaemia confirmed by PG ≤ 3.3 mmol/L and symptomatic hypoglycaemia without confirmation, asymptomatic hypoglycemia confirmed by PG ≤ 3.3 mmol/L), body weight, insulin total daily dose and insulin total daily dose per body weight,
Safety:	***Safety endpoints*** Safety endpoints included difference between treatments in overall safety parameters including: incidence of adverse events, serious adverse events and severe hypoglycaemia, vital signs (systolic blood pressure, diastolic blood pressure and heart rate), safety laboratory parameters (alanine aminotransferase,aspartate aminotransferase and creatinine) and BMI.
Statistical methods:	***ANALYSIS POPULATIONS*** Three analysis populations were defined. Safety population (SP), Intent-To-Treat (ITT) Population and Per Protocol (PP) Population. The safety population consisted of all subjects who received at least one dose of insulin glargine. Analysis of the safety variables was performed on this population. The intent-to-treat population was arbitrarily defined as a subset of SP, including only the subjects who fulfilled the eligibility criteria. The per-protocol population was arbitrarily defined as a subset of the ITT population, excluding all subjects with (a) a major protocol violation AND/OR (b) missing data on the primary efficacy variable. ***GENERAL METHODOLOGY*** All collected efficacy and safety assessments were presented by means of descriptive statistics. All the parameters were tabulated according to the different types of data. Continuous variables (e.g. weight): arithmetic mean, standard deviation, median, minimum, maximum (and confidence interval if appropriate), categorical or discrete variables (e.g. classification of diabetes complications): absolute and relative frequencies, binary variables (e.g. sex): absolute and relative frequencies. The number of subjects included in the respective analysis (N) and number of missing values was presented in all tables. For all statistical tests the significance level was fixed at α = 0.05 and 95% confidence intervals were calculated. Normal distribution of all tested continuous variables was assessed by means of Shapiro-Wilks test. If variables were normally distributed, a parametric tests (paired t-test) were

	applied and 95% confidence intervals for mean were calculated. If variables were not normally distributed, a nonparametric tests (Wilcoxon Signed Rank test) were applied and 95% confidence intervals for median were calculated. Stepdown Bonferroni (Holm's) sequential multiple test procedure was applied to adjust significance levels in primary variable analysis as well as analysis of percentage of time spent in defined blood glucose ranges. No interim analysis was planned. No imputation techniques for missing data were applied. ***EFFICACY ANALYSIS*** ***Primary efficacy analysis*** The primary endpoint was the difference between treatments in area under the curve (AUC; expressed as hrs*mmol/L over 24 hours) derived from CGMS measurements. Only complete records during the second day of measurement (0:00-24:00) were used for statistical analysis. The hypothesis of no difference between treatments in AUC for BG range (in mmol/L) of: (0, 3.3]; (0, 3.9]; (3.9, 7.5); [7.5, ∞); [10, ∞); [15, ∞) detected by complete 24 hours CGMS®, Medtronic MiniMed, Inc. was tested by Wilcoxon signed-rank test. To control the type I error rate the Holm's sequential multiple test procedure was applied to particular significance levels. ***Secondary efficacy analysis*** The hypotheses of no difference between treatments were tested for all secondary efficacy variables (except Self-monitored blood glucose values). Variables derived from CGMS measurement were secondary analysis variables. These variables were derived from 24 hours complete records from second day of CGMS measurement as well as primary efficacy variables. The hypothesis of no difference between treatments in mean time (in percentage) spent at the BG range (in mmol/L) of: (0, 3.3]; (0, 3.9]; (3.9, 7.5); [7.5, ∞); [10, ∞); [15, ∞) detected by complete 24 hours CGMS®, Medtronic MiniMed, Inc. was tested by Wilcoxon signed-rank test. To control the type I error rate the Holm's sequential multiple test procedure was applied to particular significance levels Self-monitored blood glucose values (measured during insulin Lantus treatment phase), whenever the patient experiences symptoms possibly related to hypoglycemia will be analysed descriptively. The hypotheses of no difference between treatments in following parameters were tested for all subjects, subjects with entry HbA1c ≤ 6% IFCC and subjects with entry HbA1c > 6 % IFCC: occurrence of hypoglycaemia detected by 24 hours CGMS measurements, HbA1c, number of hypoglycaemia during 4 weeks of NPH treatment phase and during last 4 weeks before CGMS of insuline glargin treatment phase (all hypoglycaemia, all symptomatic hypoglycaemia, symptomatic hypoglycaemia confirmed by BG ≤ 3.3 mmol/L, symptomatic hypoglycaemia without confirmation, further asymptomatic hypoglycaemia confirmed by BG ≤ 3.3 mmol/L). Additional analysis of subjects with at least one hypoglycaemia event was performed (for all defined categories of hypoglycaemia events). The hypotheses of no difference between treatments were tested by Mc'Nemars test (paired test of two proportions). One more category of hypoglycaemia was assessed: all hypoglycaemia confirmed by blood glucose ≤ 3.3 mmol/L (i.e. asymptomatic hypoglycaemia episodes and confirmed symptomatic hypoglycaemia episodes). Beside intra-individual variability of 6-point plasma glucose profiles evaluated by standard deviation, evaluation using M-value calculated by following formula was performed as more valid index of intra-individual variability of blood glucose. ***SAFETY ANALYSIS*** The hypotheses of no difference between treatments were tested for following safety variables: Vital signs, safety laboratory parameters including alanine aminotransferase, aspartate aminotransferase and creatinine and body mass index.

	Screening laboratory parameters (cystatin C and fasting C peptid) were only summarized. Adverse events occurred on NPH treatment phase and insuline glargine treatment phase were tabulated by intensity, system organ, MedDRA preferred terms, intensity within system organ class and intensity within MedDRA Preferred Term. Adverse events and serious adverse events were tabulated by subjects. All adverse events with related details were listed. ***SAMPLE SIZE DETERMINATION*** Results of a pilot study (CGMS study, n=29) showed that within 24 hours following a switch from NPH insulin to insulin glargine, the BG AUC ≥ 15mmol/L decreased from 29.6 ± 44.77 hr*mmol/L to 14.6 ± 19.22 hr*mmol/L over 24hours. The expected change in AUC ≥ 15 mmol/L was 15.1 mmol/L with a SD of 41.27. For alpha (two-sided) risk of 1%, 92 evaluated subjects allow to reject the hypothesis of no change in favour of the alternative hypothesis of change with 80% power. Taking into account the non evaluated subjects (30%), 120 subjects in total had to be included. Therefore, a total of 120 subjects (equally distributed among 12 centres) were planned to be enrolled in the study, assuming that it would yield 92 evaluable subjects.
Summary:	A total of 150 subjects were screened for the study, 33 out of them did not meet eligibility criteria. In total, 117 subjects were enrolled, one subject prematurely terminated participation before the start of insulin glargine treatment. A total of 116 subjects (86.32% of enrolled subjects) were treated by insulin glargine and were included into both safety and ITT population. One subject prematurely terminated participation after the start of insulin glargine treatment (terminated treatment with glargin during hospitalization for anaemia). The total number of 115 subjects (98.29% of enrolled subjects) completed the study and 101 (99.15% of enrolled subjects) subjects were included into PP population. The analysis of primary variables and secondary variables derived from CGMS measurements were performed only on PP population, counting 101 patients. ***Demographic and summary characteristics of ITT Population after enrollment in the study*** Out of the 116 subjects in ITT population, 52% were males and 48% females. The mean (±SD) age at the time of enrolment was 61.78 ± 8.49 and mean (±SD) duration of diabetes was 12.33 ± 6.49 years.The mean (±SD) BMI was 31.65 ± 5.08 kg/m2, mean (±SD) FGK was 8.95 ± 2.47 mmol/L and mean (±SD) HbA1c was 6.47 ± 0,86 % IFCC. Subjects were treated with NPH insulin,in minimum duration 2 months, mean dose (±SD) 18.51±13.03 IU in combination with MET at least 1,7g per day (100%) and SU (94%) or glinides (6%). Frequency of the main diabetes complications were as follows: Macrovascular complication (24.1%), retinopathy (13.8%), nephropathy (7.8%) and neuropathy (19.8%).

Efficacy results:

Based on the primary criterion:

The CGMS data showed that AUCs of the lowest BG ranges (0, 3.3] mmol/L and (0, 3.9] mmol/L did not significantly change during insulin glargine treatment. On the other hand, the AUCs for high BG ranges (in mmol/L) of [7.5, ∞); [10, ∞) and [15, ∞) were significantly lower at the end of the insulin glargine treatment than at entry, i.e. at the end of the insulin NPH treatment (p<0.001, p<0.001 and p<0.001 respectively). Simultaneously, the AUC for normal BG range between 3,9 mmol/L and 7,5 mmol/L significantly increased during insulin glargine treatment (p<0.001). As a whole, the switch to insulin glargin normalized the periods characterized by abnormally high BG values, while low BG periods did not change significantly. Summary of efficacy results based on the primary criterion is presented in following table.

Strata defined by BG range [mmol/L]	N/Missing	Δ AUC (mean) [mmol/L*hr]	SD	P-value*
(0, 3.3]	101 / 0	1.26	7.70	0.2320
(0, 3.9]	101 / 0	1.62	10.14	0.2320
(3.9, 7.5)	101 / 0	15.48	41.21	0.0003
[7.5, ∞)	101 / 0	-43.88	89.27	<0.0001
[10, ∞)	101 / 0	-39.14	89.51	0.0003
[15, ∞)	101 / 0	-15.43	51.08	0.0003

* Stepdown Bonferroni (Holm's) correction of Wilcoxon Signed Rank Test p-value

Furthermore on the secondary criteria detected by CGMS:

1) Circadian fluctuation of BG measured by M-value (logarithmic transformation of the deviation from an arbitrary standard) shows a significant decrease of BG fluctuations on treatment with insulin glargine (p<0.003).

2) The proportion of time (%) detected by CGMS, spent in the lowest BG ranges (0, 3.3] mmol/L and (0, 3.9] mmol/L did not change significantly during insulin glargine treatment period (p=0.230). The percentage of time the subjects spent in high BG ranges (in mmol/L) of [7.5, ∞); [10, ∞) and [15, ∞) was significantly lower at the insulin glargine treatment period than at the insulin NPH treatment period (Δ=-13.8 with p<0.001, Δ=-11.6 with p<0.001 and Δ=-3.7 with p<0.001 respectively). Simultaneously, the time the subject showed normal BG levels between 3.9 mmol/L and 7.5 mmol/L significantly increased during insulin glargine treatment period (an increment of 11.4 with p<0.001). As a whole, the change of treatment led to a significant reduction of time spent in high BG values and a simultaneous prolongation of time when glucose level was in normal range.

3) There was a significant decrease of mean BG detected by CGMS during whole day (Δ = -1.12 mmol/L; p <0.001), during night-time (22-07 hours, Δ = - 0.87 mmol/L; p=0.001) and during day-time (07-22 hours, Δ = -1.26 mmol/L; p <0.001) with insulin glargine.

5) No significant changes of hypoglycaemia detected by CGMS (glucose ≤3.3mmol/L) was detected between treatment phases.

4) The evaluation Standard Deviation (SD), Coefficient of Variance (CV) of BG during CGMS and The mean amplitude of glycemic excursion (MAGE) did not reveal any statistically significant difference.

Based on other main secondary criteria:

Results are presented in the IIT population (all were confirmed in the PP population)

1) There was a significant decrease of HbA1c % (IFCC) from 6.47 ± 0,86 at Visit 1 to 6.16± 1.07 at Visit 7 (difference Δ = - 0.30 %; p<0.001) and significant drop of FBG from 8.95 ± 2.47 at Visit 1 to 8.01 ± 2,82 mmol/L at Visit 7 (Δ = - 0.95 mmol/L; p=0.001).

2) There was a significant decrease of body weight from 92.52 ± 17.41 kg at Visit 1 to

	91.86±17.56 at Visit 7 (Δ = - 0.83 kg; p=0.001) 3) There was a significant decrease of all values BG measured at 6-point SMBG profile, and significant decrease of glucose fluctuations within the 6-point profile by means of analysis of two variability measures: Standard Deviation (SD) and M-value(Δ = - 0.35; p<0.0001 and Δ = - 13.07; p<0.001 during insulin glargine treatment period during insulin glargine treatment phase. 4) There were no statistical difference between treatment phase in frequency of asymptomatic hypoglycemia (SMBG) episodes per patient/year confirmed by PG ≤ 3.3 mmol/L (p=0.805). 5) There were no statistical difference between treatment phase in frequency of symptomatic hypoglycemia (SMBG) with confirmation value ≤ 3.3 mmol/L per patient/year (p=0.068) and symptomatic hypoglycemia (SMBG) without confirmation value ≤ 3.3 mmol/L per patient/year (p=0.625). Analysis of symptomatic hypoglycemic episodes revealed statistically significant increase during insulin glargine treatment phase in case of evaluation all clusters of symptomatic events (p=0.047) and entire hypoglycemic events (p=0.039) but there were no statistical difference between treatment phase in all hypoglycaemic events confirmed by BG value ≤ 3.3 mmol/L (i.e asymptomatic hypoglycaemia episodes and confirmed symptomatic hypoglycaemia episodes). There were no statistical difference between treatment phase in frequency of subjects with at least one hypoglycemia (SMBG); no statistical difference in any category of hypoglycemia. 6) The daily dose of basal insulin and daily dose of basal insulin per body weight significantly increased during study from 18.51 ± 10.88 U (0.2013 ± 0.1119 U/kg) with insulin NPH in V1 to 29.66 ± 15.51 U (0.3176 ±0.1446 U/kg) with insulin glargine in V7, i.e. by about 11.15 U (0.12 U/kg); p<0.001 for both daily dose of basal insulin and daily dose of basal insulin per body weight
Safety results:	No adverse events (except hypoglycemia), related to study treatment were reported. No severe hypoglycemia related to study treatment were reported No serious adverse events related to study treatment were reported. No clinically relevant abnormalities in laboratory values during study were detected.
Date:	28 July 2010