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:**	NCT00322075
		Study Code:	LANTU_L_00722
Generic drug name:	insulin glargine	**Date:**	4 March 2008

Title of the study:	LANTU_L_00722 A prospective, intervention, open-label, single arm national study in adult subjects with diabetes mellitus: Comparison of glycaemic fluctuations during 3 days subcutaneous continuous glucose monitoring in patients with basal substitution human insulin NPH versus basal substitution with insulin glargine (Lantus ®) once daily after 3 months therapy
Investigator(s):	Doc. MUDr. Milan Kvapil CSc, FN v Motole Praha 5, V Úvalu 84, Department of internal medicine
Study center(s):	National, one centre study
Publications (reference):	No preliminary publication was performed

Study period: **Date first patient enrolled:** 06-Apr-2006 Date last patient completed: 27-Nov-2006	**Phase of development:** **IV. phase**

Objectives:	The primary objective of the study was to confirm a reduction risk of hypoglycaemia and lower fluctuation of 24 hours blood glycaemia in patients with DMT1 and DMT2 treated by Intensive insulin therapy (IIT) after their switch from insulin NPH to insuline glargine The secondary objectives of the study were: To assess change of HbA1c between V1,V2 and V8 To assess change of FBG between V1 and V8 To assess change of BMI between V1 and V8 To assess change of total insulin dose and dose basal and prandial insulin V1 and V8 To compare satisfaction with treatment during NPH and insulin glargine therapy thought the use of visual – analog scale V2 and V8 Occurrence of adverse drug reaction (ADR) from V1 to V9 except hypoglycemia
Methodology:	National,intervention, open-label, single arm, clinical study assessed glycaemic control and occurrence of hypoglycemic events at patients with diabetes mellitus treated on IIT with NPH basal insulin, followed by 3 months treatment with insulin glargin in basal-bolus regime. Blood glucose variability was measured as a change of standard deviations: - by the Continuous Glucose Monitoring System (CGMS®, Medtronic MiniMed, Inc.). 72 hours CGMS registration was performed at the end of the NPH insulin (V2-baseline) and insulin glargine period (V8-endpoint). The Area Under Curve (AUC) for blood glucose, representing the extent patients were within, above or below defined blood glucose ranges < 3,3 mmol/l; ≥ 3,3 < 3,9 mmol/l; ≥ 3,9 < 7,5 mmol/l; ≥ 7,5 < 15 mmol/l; ≥ 15 mmol/l; ≥ 3,3 < 15 mmol/l detected by CGMS average to 24 hours (hr * mmol/l over 24hours), was calculated for targeted glucose ranges and percentage of time spent in defined blood glucose ranges from over all time during CGMS was calculated. Standard deviation (SD) of blood glucose and nocturnal blood glucose during CGMS was calculated and compare by Wilcoxon ranked-pair test. - by within subject variability of the six – point capillary blood glucose profile (SMBG). For statistic analysis within variability of values of six – point capillary blood glucose profile were calculated records from home blood glucose monitoring during NPH treatment phase, from V1 to V2 and during insulin glargine treatment phase during last 4 weeks before V8.The within subject variability of six – point capillary blood glucose profile were measured by intra individual standard deviation and is compared by paired t-test.

<table>
<tr><td>Number of patients/subjects:</td><td>Planned: 35</td><td>Randomized: NA</td><td>Treated: 35</td></tr>
<tr><td>Evaluated:</td><td colspan="3">29 Safety: 35

<table><tr><td>Planned</td><td>Included</td><td>Treated insulin glargine</td><td>Completed treatment</td><td>Evaluated</td></tr><tr><td>35</td><td>37</td><td>35</td><td>32</td><td>29</td></tr></table>2 patients dropped screening
From 35 treated:
1 patient discontinued the study prematurely on own request during treatment
1 patient – the contact was lost during treatment
1 patient was dropped from treatment due to non – compliance of the protocol
From 32 completed treatment:
2 patients were lost to technical problems with saving the CGMS data
1 patients was dropped additionally from evaluation due to non – compliance of the protocol</td></tr>
<tr><td>Diagnosis and criteria for inclusion:</td><td colspan="3">Diabetes mellitus treated by Intensive insulin therapy and basal substitution by NPH insulin.

Patients aged from 18 to 65 years inclusive
Patients with unsatisfactory compensation of diabetes, it means with HbA1c ≥ 6% (IFCC) before change of therapy to insulin glargine or often occurrence of hypoglycaemia, it means more than two hypoglycemia during last year confirmed by measurement FBG < 3,3 mmol/l
Patients with written informed consent obtained prior to enrollment in the study</td></tr>
<tr><td>Investigational product:
Dose:

Administration:</td><td colspan="3">Insulin glargine: Lantus (100 UI/ml) solution for injection, 3 ml cartridge system for OptiPen Pro1
The dose of insulin Lantus was initiated once daily (at any time but at the same time each day) no matter previous dose of NPH isulin.. Initial dosage of insulin glargine was in line with recommendation of SPC insulin Lantus chapter 4.2. Posology and method of administration. Adjustment of basal and prandial insulin at the discretion of the investigator according values of FBG and PPG.

subcutaneous (SC) injection, to the abdominal wall, to the deltoid muscle or to the thigh.</td></tr>
<tr><td colspan="2">Duration of treatment: 3 months</td><td colspan="2">Duration of observation: 4 months</td></tr>
</table>

Reference therapy: Dose: Administration:	NA NA NA
Criteria for evaluation:	
Efficacy primary objective:	Hypoglycaemic events Glycaemia levels during CGMS Six point capillary blood glucose profile – selfmonitoring of blood glucose (SMBG)
Safety:	Adverse events by the patient and noted by the investigator. Standard hematological and blood chemistry data
Statistical methods:	Continuous variables are described by mean and standard deviation. Discrete variables are described by absolute and relative frequencies. Comparison of V1 and V8 for continuous variables is done paired t-test. In case of skewed distributions the one sample Wilcoxon test is applied. Discrete variables are compared by Mc Nemar chi-square test. ANOVA with repeated measures is used to compare the glycaemic curves. All test are two-sided and significance level less than 5% is used.

Summary:

Summary 37 patients were included in the study, in agreement of the calculated sample size (n=35). The primary and secondary objectives were assessed in finally population n=29, due to drop out. Safety of insulin glargine, except hypoglycaemia was assessed on safety population, it means in the patients who receive at least 1 dose of insulin glargine (n=35).

Demographic and baseline characteristic finally population:

Patients (n)	29
Male/female (%)	52/48
Type of diabetes DMT1/DMT2 (%)	31/69
Age (years)	56 ± 11,2
Duration of diabetes (years)	17 ± 12,0
Retinopathia (%)	24
Nephropathia (%)	28
Neuropathia (%)	52
HbA1c (%IFCC)	7,6 ± 1,9
FBG (mmol/l)	12,4 ± 3,9
BMI (kg/m2)	27,7 ± 5,1

Data mean ± SD

Efficacy results:	Based on the primary criterion: 1) Decreased risk of hypoglycaemia after switching insulin NPH to insulin glargine. The rate of total number of hypoglycemia, expressed as number of episodes per patient month, decrease after switching to insulin glargine from 2,0 ± 3,2 to 1,2 ± 2,4 (p = 0,087) and risk of total number of all hypoglycaemia decreased by 40%. The decrease is not statistically significant (probably due to small sample size), but there is downward tendency. 2) Lower fluctuation of 24 hours blood glycaemia in patients after their switch from insulin NPH to insuline glargine though CGMS assessment, according to an analysis change of median standard deviation (SD) BG. Glargine treated patients showed significant reduction in blood glucose variability and nocturnal blood glucose variability expressed as reduction of median SD blood glucose and nocturnal blood glucose during CGMS.(p = 0,02 ; p = 0,04). 3) Changes of AUC (mean AUC ± SD hr * mmol/l over 24hours) and time (%) spent in target ranges < 3,3 mmol/l; ≥ 3,3 < 3,9 mmol/l; ≥ 3,9 < 7,5 mmol/l; ≥ 7,5 < 15 mmol/l; ≥ 15 mmol/l; ≥ 3,3 < 15 mmol/l after patients switch from insulin NPH to insuline glargine were not statistically different (probably due to small sample size and together possibility diversity of finally population –different stage of compensation DM).The most expressive changes were observed in decrease mean AUC in target ranges ≥ 15 mmol/l an increase mean AUC in target range ≥ 3,9 < 7,5 mmol/l. 4) Reduction of within subject variability of fasting blood glucose (p=0.005) and blood glucose after lunch (p=0,047) was confirmed to an analysis of mean standard deviation (SD) assessment of the six – point capillary blood glucose profile after switch to insulin glargine. Based on secondary criterions: 1) Change of HbA1c from 7,6 ± 1,9% at Visit 1 to 6,9 ± 1,5 at Visit 8 (Difference between V8 – V1 Δ = - 0,7%; p <0,054 is on limit of significance.) 2) Significantly dropped FBG from 12,4 ± 3,9 at Visit 1 to 8,9 ± 2,5 mmol/l at Visit 8 (Δ = - 3,5 mmol/l; p <0,001). 3) Significantly decrease BMI from 27,7 ± 5,1 at Visit 1 to 27,0 ± 4,3 kg/m2 at Visit 8 (Δ = - 0,7 kg/m2; p=0,035). 4) There were no statistic change in dose of total daily dose of insulin between V1 and V8 (44,5 ± 13,8 and 42,0 ± 15,8 IU ± SD; p=0,148) . There were no statistic change in dose of basal insulin between V1 and V8 (12,8 ± 5,7 and 13,9 ± 5,6 IU ± SD; p=0,287) Daily dose of prandial insulin at V8 (endpoint) significantly decreased from 31,7 ± 12,2 at Visit 1 to 28,2 ± 11,6 IU at Visit 8 (Δ = - 3,5 IU; p = 0,039). 5) The insulin therapy with insulin glargine was associated with significant improvement (p <0,001) the patient's satisfaction measured through to visual analogue scale in V1 and V8 . (Questions: 1. How are you satisfied with your current therapy? 2.How often, in last time, you are feeling the risk of hypoglyceamia? 3.How is your current therapy suitable for you? 4.Would you have satisfied if you could continue your current therapy?) The values in cm are described by mean and standard deviation and compared by paired t-test.

Safety results:	No adverse events (except hypoglycaemia – primary objective), related to study treatment was reported. No serious adverse events related to study treatment was reported. No adverse event leading to withdrawal of study treatment was identified. No clinically relevant abnormalities in laboratory values during study were detected
Date of report:	3 December 2007