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Sponsor/company:	**sanofi-aventis**	**ClinialTrials.gov Identifier:**	**NA**
		Study Code:	**HOE901_4019**
Generic drug name:	**Insulin glargine**	**Date:**	**06 March 2007**

Title of the study: Transfer of patients with type 1 diabetes mellitus from NPH to glargine as basal insulin: a multicenter, randomised, parallel group, open label study

Investigators: 21 principal investigators

Study centres: 21 centres, all in Italy

Publication (reference): None

Study period: First patient enrolled: 19/11/2001; Last patient completed: 13/10/2004

Phase of development: IIIb

Objectives:

The primary objective of the present study was to compare the activity of the two treatments (Lantus+Lys-pro and NPH+Lys-pro) in normalizing the fasting plasma glucose at the end of the treatment phase (last 4 weeks of treatment).

The secondary objectives were to compare glargine with NPH as basal insulin in intensified treatment of type 1 diabetes mellitus in terms of: self monitoring of blood glucose (SMBG) on a 7-point measurement (before and after breakfast, lunch and dinner, and at bedtime); stability of glycemic control in terms of daily Mean Blood Glucose and daily Mean Amplitude Glucose Excursion (MDBG and MAGE); changes of HbA_{1c} from baseline to the end of the treatment; changes of the total daily basal insulin dose; stability of body weight; quality of life; safety profile (adverse events, including hypoglycaemia, clinical and laboratory parameters).

Methodology:

This was a 30-week duration (4 run-in weeks + 24 treatment weeks + 2 safety weeks), randomised, parallel group, open label, clinical study. During the run-in period (4 weeks) the individual insulin therapy of patients was optimised. The pre-meal lys-pro or regular insulin dose was titrated to obtain optimal blood glucose levels 2 hours after meals (SMBG < 140 mg/dl), and the number of NPH injections might have been increased to obtain optimal fasting and pre-meal blood glucose. The increase in the number of daily NPH administrations was encouraged to obtain a pre-meal glycemic value at the target range (BG > 100 and < 140 mg/dl). Then patients were randomly allocated to one of the two treatment groups (Lantus+Lys-pro and NPH+Lys-pro).

The following visits were performed:

Phase	**Run-in (4 weeks)**	**Treatment period (24 weeks)**	**Safety**

Visit number Visit code	V1 V-1	V2 V0	V3 V0-i	V4 V1	V5 V1-i	V6 V2	V7 V2-i	V8 V3	V9 V4
Week	-4	0	4	8	12	16	20	24	26

Number of patients (total and in each arm):

	Randomised	ITT	Safety	Completed
Total	175	168	171	152
Lantus + Lyspro	85	84	85	78
NPH + Lyspro	90	84	86	74

Diagnosis and main criteria for inclusion:

Subjects aged 18-60 years with type 1 diabetes mellitus for more than 3 years; fasting plasma C-peptide level < 0.1 nmol/l; treatment with intensive insulin therapy with lys-pro or regular insulin injection at each meal and NPH insulin (twice or more/daily) for more than one year; HbA_{1c} > 7 and < 9 % at the randomisation visit; patients without demonstrable micro- and macro-angiopathic complications; body mass index 18-26 kg/m^2; female subjects postmenopausal or under adequate contraception, and with a negative serum pregnancy test during Visit 0 and a negative urine pregnancy tests on visits V1i and V3; written informed consent obtained.

Test product, dose and mode of administration : Lys-pro insulin at each meal and glargine insulin as basal insulin given as a single daily injection at the dinner time in conjunction with lys-pro injection. The starting glargine insulin dose was calculated as follow: if the patient used once-daily NPH insulin injection during the last 2 weeks before the randomisation, patients started with the same daily-dose. If the patient used twice or more daily NPH insulin injection during the last 2 weeks before the randomisation, the glargine daily-dose was to be calculated as 90 % of total daily requirement of NPH insulin. Lys-pro and glargine insulin were titrated according to a standard algorhythm.

Duration of treatment: 24 weeks.

Reference therapy, dose and mode of administration : lys-pro insulin + NPH insulin (either 1, 2 or 3 times daily as necessary) at each meal and NPH insulin at bedtime, titrated according to a standard algorhythm.

Criteria for evaluation:

Efficacy: The primary efficacy variable was the mean FBG over the last four weeks of treatment period.

The secondary efficacy variables were: fasting blood glucose over time; daily glycaemic profile in the SMBG; Mean Daily Blood Glucose (MDBG) and daily Mean Amplitude Glucose Excursion (MAGE); changes of % of HbA_{1c} from baseline to the end of the treatment; changes of the total daily basal insulin dose; body weight stability; changes of the quality of life measured using the Well-being Enquiry for Diabetics (WED) questionnaire.

Safety: Safety variables were: adverse events, including nocturnal hypoglycaemia/patient/week and overall number (diurnal and nocturnal) of the hypoglycaemia/patient/week episodes, laboratory parameters (haematology and blood chemistry) and physical examination.

Statistical methods:

The efficacy analysis was performed in the ITT population, defined as all randomised patients who took at least one dose of study drug and who attended at least one control visit other than the baseline visit.

The analysis of the parametric efficacy variables was performed on changes from baseline to the last available visit. Moreover, the analysis of the results of the glucose parameters measured at any visit (primary and secondary efficacy endpoints) were performed both in patients with all data and in patients with missing data. The analysis of the adverse events was performed in the safety population, defined as the all randomised patients with evidence of intake of at least one dose of study drug. The analysis of safety laboratory parameters was performed in patients having both the baseline and the final measurement.

Descriptive summary statistics (number of patients, mean, standard deviation, minimum, maximum) was provided for quantitative variables, while frequency (absolute and relative) distributions were provided for categorical variables.

The parametric variables were analysed by using an analysis of variance (ANOVA) model, with multiple comparison within and between groups, when appropriate. The non-parametric variables were analysed by using the Mc Nemar test in the comparisons within group and the Chi-square test in the comparisons between groups. The results of the

laboratory safety and of the physical examination parameters were analysed in terms of normal/abnormal findings.

Study population:

A total number of 175 patients were randomised: 85 (48.6% of randomised) were included in the Lantus+Lyspro group and 90 (51.4%) were randomised to receive NPH+Lyspro. A total of 23 patients, 7 in the Lantus+Lyspro group (8.2% of randomised) and 16 in the NPH+Lyspro group (17.8% of randomised), prematurely discontinued the study, while a total number of 152 patients, 78 in the Lantus+Lyspro group and 74 in the NPH+Lyspro group, completed the total study period. Consent withdrawal was the main reason of early study discontinuation.

Extent of exposure and compliance:

The mean extent of exposure to study drug was 170.6 ± 32.2 days (range 6-222) in the Lantus+Lyspro group and 158.9 ± 49.4 days (range 1-209) in the NPH+Lyspro group. The compliance to study drug was not evaluated.

Efficacy results:

Primary efficacy variable: fasting blood glucose (final visit vs. baseline visit)

A marked and statistically significant decrease from baseline of FBG was observed in both groups at the final visit. The extent of the decrease from baseline was higher in the Lantus+Lyspro group compared to the NPH+Lyspro group. The mean changes from baseline at the final visit were -28.0 mg/dl (95% CI: -37.3 to -18.7) in the Lantus+Lyspro group ($p < 0.01$) and -9.8 mg/dl (95% CI: -19.1 to -0.5) in the NPH+Lyspro group ($p = 0.037$). The difference between the Lantus+Lyspro and the NPH+Lyspro group of the mean changes from baseline was -18.2 mg/dl (95% CI: -31.3 to -5.2) and the comparison between groups showed a statistically significant difference ($p = 0.006$).

Secondary efficacy variables:

Fasting blood glucose over time:

In the analysis of patients with all data, a marked decrease from baseline of FBG was observed in both groups; the decrease was significant from visit 4 (week 8) onwards in the Lantus+Lyspro group and from visit 6 (week 16) onwards in the NPH+Lyspro group. The extent of the decreases from baseline was higher in the Lantus+Lyspro group compared to the NPH+Lyspro group at any time point. The mean changes from baseline at the final visit were -28.0 mg/dl in the Lantus+Lyspro group ($p < 0.01$). and -9.8 mg/dl in the NPH+Lyspro group ($p = 0.037$). The comparison between groups of the mean changes from baseline showed a statistically significant difference at visit 5 (week 12) ($p = 0.005$) and at visit 7 (week 20) ($p = 0.004$), due to greater FBG lowering effects in the in the Lantus+Lyspro group compared to NPH+Lyspro.

Mean Daily Blood Glucose (MDBG) (inclusive of patients with less than 7 glycaemic points/day):

A marked and statistically significant decrease from baseline of MDBG was observed in the Lantus+Lyspro group, compared to a small non-significant decrease in the NPH+Lyspro group. The mean changes from baseline at the last visit were -11.9 mg/dl in the Lantus+Lyspro group ($p < 0.01$). and -4.2 mg/dl in the NPH+Lyspro group ($p = 0.156$). The comparison between groups of changes at the last visit did not show statistically significant differences ($p = 0.069$).

Mean Daily Blood Glucose (MDBG) (in patients with at least 7 glycaemic points/day):

A marked and statistically significant decrease from baseline of mean daily glucose was observed in the Lantus+Lyspro group, compared to a small non-significant decrease in the NPH+Lyspro group. The mean changes from baseline at the last visit were -10.1 mg/dl in the Lantus+Lyspro group ($p = 0.013$) and -4.6 mg/dl in the NPH+Lyspro group ($p = 0.310$). The comparison between groups of changes at the last visit did not show statistically significant differences ($p = 0.358$).

Mean Amplitude Glucose Excursion:

A marked and statistically significant decrease from baseline of MAGE was observed in the Lantus+Lyspro group, compared to a small non-significant decrease in the NPH+Lyspro group. The mean changes from baseline at the last visit were -20.2 mg/dl in the Lantus+Lyspro group ($p = 0.006$) and -3.8 mg/dl in the NPH+Lyspro group ($p = 0.642$). The comparison between groups of changes at the last visit did not show statistically significant differences ($p = 0.133$).

HbA_{1c}:

A statistically significant and similar decrease from baseline of mean HbA_{1c} was observed in both groups. The mean changes from baseline at the last visit were -0.56 % in the Lantus+Lyspro group ($p < 0.01$) and -0.56 % in the NPH+Lyspro group ($p < 0.01$). The comparison between groups of changes at the last visit did not show statistically significant differences ($p = 0.984$).

SMBG (in patients with at least 3 times blood glucose monitoring during the last 2 weeks before the scheduled visit):

The results showed a similar significant decrease from baseline in the two groups on measurements performed before and after breakfast. The measurements performed before lunch did not show substantial changes from baseline in both groups, while a decrease from baseline in mean values measured after lunch was observed only in the Lantus+Lyspro group. The measurements performed before dinner showed a marked but non-significant increase in the Lantus+Lyspro group only, while the decrease in mean values measured after dinner, although not significant, was more marked in the NPH+Lyspro group compared to the Lantus+Lyspro group. The measurements at bedtime showed a significant decrease in the Lantus+Lyspro group, compared to a smaller and non-significant decrease in the NPH+Lyspro group.

Hypoglycaemia:

The results of hypoglycaemia showed no substantial changes in both groups of the number of episodes/patient/week in both groups. A small increase of the number of diurnal hypoglycaemia was observed in both groups, while the evaluation during the night showed a small decrease from baseline in the Lantus+Lyspro group over the entire study period, compared to a small increase in the NPH+Lyspro group. The analysis of the severity of hypoglycaemia showed a decrease of the number of severe hypoglycaemia in both groups. However, this decrease of time with severe hypoglycaemia led to an increase of the number of mild intensity in the Lantus+Lyspro group and to an increase of the number of moderate intensity in the NPH+Lyspro group. The decrease from baseline of the number of episodes/patient/month with serious nocturnal hypoglycaemia was significant only in the Lantus+Lyspro group.

Insulin dosing:

A small increase of daily dose of long-acting analogue or intermediate insulin was observed in both groups. The mean daily dose in the Lantus+Lyspro group was 16.1 ± 7.4 IU at baseline and 19.1 ± 5.7 IU at the final visit; the corresponding mean daily doses in the NPH+Lyspro group were 20.1 ± 8.5 IU at baseline and 21.8 ± 8.4 IU at the final visit. The mean daily dose in the overall treatment period was 18.7 ± 5.6 IU in the Lantus+Lyspro group and 21.3 ± 8.5 IU in the NPH+Lyspro group.
A small decrease of daily dose of regular or fast-acting insulin were observed in both groups. The mean daily dose in the Lantus+Lyspro group was 26.4 ± 8.4 IU at baseline and 22.8 ± 9.7 IU at the final visit; the corresponding mean daily dose in the NPH+Lyspro group was 25.5 ± 8.8 IU at baseline and 24.3 ± 9.3 IU at the final visit. The mean daily dose in the overall treatment period was 23.6 ± 9.4 IU in the Lantus+Lyspro group and 25.0 ± 8.3 IU in the NPH+Lyspro group.

Insulin antibodies (IAA):

The results at the last visit showed no changes from baseline in the Lantus+Lyspro group, compared to a non-significant increase in the NPH+Lyspro group. The mean changes from baseline at the last visit were -0.07 % in the Lantus+Lyspro group ($p = 0.954$) and 0.77 % in the NPH+Lyspro group ($p = 0.544$). The comparison between groups of changes at the last visit did not show statistically significant differences ($p = 0.637$).

Quality of life:

Of the 175 randomised patients, only those with complete data were analysed for the differences baseline-6 months of scores of the WED questionnaire: 113 (65.1%) were evaluated for impact, 114 (65.1) for the level of satisfaction, 108 (61.7%) for general worries and 111 (63.4%) for diabetes-related worries.

No statistically significant changes from baseline for any domain were observed in both groups at 3 and 6 months. The comparisons between groups of changes from baseline (Mann-Withney test) showed a statistically significant difference at 6 months for diabetes-related worries, due to an improvement in the Lantus+Lyspro group compared to the NPH+Lyspro group. This difference was maintained in the multivariate analysis with multiple linear regression . It is likely that the lower incidence of symptomatic hypoglycaemia and/or the better prediction of the basal glycaemia in the Lantus+Lyspro group, in comparison with the NPH+Lyspro group, produced a decrease of the level of diabetes-related worries. No statistically significant differences between groups were found in the other domains.

Body weight:

No substantial changes of body weight were observed in both groups. The mean changes from baseline at the last visit were 0.01 kg in the Lantus+Lyspro group ($p = 0.957$) and 0.39 kg in the NPH+Lyspro group ($p = 0.143$). The comparison between groups did not show statistically significant differences ($p = 0.318$).

Safety results:

Adverse events:

A total number of 52 adverse events (AEs), 27 in the Lantus+Lyspro group and 25 in the NPH+Lyspro group, were reported in a total of 32 patients, 19 (22.3%) in the Lantus+Lyspro group and 13 (15.1%) in the NPH+Lyspro group (p = 0.225 between groups).

Serious adverse events were reported only in 2 patients (2.3%) in the Lantus+Lyspro group: the events consisted of an accidental lesion of the Achilleous tendon in one patient and severe hypoglycaemia in another; both of them were not related to the study drug.

One patient in each group had drug-related adverse events: the event in the Lantus+Lyspro group consisted of hypoglycaemia due to an error in the glargine insulin administration, while the drug-related adverse event in the NPH+Lyspro group consisted of bilateral micro-aneurysm. None of the adverse events, related or not related with study drug, caused early study discontinuation.

Laboratory parameters:

The results of safety laboratory parameters did not show evidence of clinically significant changes for any parameter. Statistically significant changes from baseline were found in platelets count (small but significant decrease in the Lantus+Lyspro group), creatinine levels (increase in the NPH+Lyspro group) and HDL-cholesterol (small but significant decrease in the Lantus+Lyspro group). These changes have no clinical relevance.

Vital signs, ECG and physical examination:

The results of vital signs (heart rate and blood pressure), ECG and physical examination of the main body districts (including the examination of fundus oculi) did not show statistically or clinically significant changes. The examination of fundus oculi showed that one patient in the Lantus+Lyspro group and 3 in the NPH+Lyspro group with normal finding at baseline had abnormalities at the final visit; however, 1 and 3 patients in the two groups, respectively, had their baseline abnormalities resolved at the final visit.

Date of the report : 18 September 2006