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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00565162
		Study Code:	HOE901_4041
Generic drug name:	insulin glargine	**Date:**	30 November 07

Title

INITIATE (INITiate Insulin by Aggressive Titration and Education): A multicentre, multinational, randomised, open study to establish the optimal method for initiating Lantus® (insulin glargine) therapy to determine metabolic and economic outcomes, safety, and satisfaction in subjects with Type 2 Diabetes Mellitus.

Investigator(s), study site(s)

Multinational (Finland, The Netherlands, Sweden and UK), multicenter (6 centers, two in Finland and UK).
Coordinating Investigator: Prof H Yki-Järvinen, Helsinki, Finland

Study duration and dates	The first subject was enrolled on 17 November 2003 and the last subject completed the study on 21 June 2005.	**Phase**	IV

Objectives

Primary: To determine whether insulin therapy with insulin glargine can be initiated as effectively by group education as by teaching each patient individually. Programs were defined as equally successful if the glycohemoglobin A_{1c} (HbA_{1c}) at the end of the study differed less than 0.5 %. Superiority of one program over the other was based on observing a clinically significant difference in glycemic control (absolute difference in HbA_{1c} reduction in the two education programs $\geq$0.5 %).

Secondary: The secondary objectives of the study were to compare between group and individual education:

1. Cost of initiation of insulin therapy including: time spent by a nurse on education, physician's time, number and duration of phone calls.
2. Change in the concentrations of serum total, HDL and LDL cholesterol, and serum triglycerides (visit 12 vs. visit 3).

3. Change in body weight and blood pressure (visit 12 vs. visit 3).
4. Change in the fasting plasma glucose concentration (visit 12 vs. visit 3).
5. Insulin dose at visit 12.
6. Change in subject's treatment satisfaction (measured by the Diabetes Treatment Satisfaction Questionnaire, DTSQ) (visit 12 vs. visit 2).
7. Incidence of symptomatic and nocturnal hypoglycemic episodes during the treatment period (between visit 3 and visit 12).

Study design

Open, randomized (1:1), two-arm parallel-group study. Subjects were assigned to one of the two pre-defined patient education programs (group and individual education). The study consisted of a screening period of up to 14 weeks and a 24-week treatment period.

Number of subjects planned

134 subjects (67 in both groups) were to be enrolled.

Inclusion criteria

Insulin-naive Type 2 Diabetes Mellitus subjects, aged ≥18 years and on stable oral anti-diabetic treatment for >6 months requiring basal long-acting insulin (HbA_{1c} >7.5 % and <12.0 %).

Treatments

Insulin glargine (HOE901, Lantus) administered by subcutaneous injection daily at bedtime for 24 weeks. The dosage was individually titrated to maintain fasting glucose concentration between 4.0 – 5.5 mmol/L. The starting dose was 10 IUs for all subjects, and the dose was increased by 2 IUs when fasting glucose exceeded 5.5 mmol/L for 3 consecutive days. All participants initially used 2 IUs increments but the increment could be altered. Insulin glargine was administered by using pre-filled disposable OptiSet pens. The treatment target for each subject was to achieve and maintain an HbA_{1c} of ≤7.0 %.

Efficacy data

Primary: HbA_{1c} (visit 12 vs. visit 3).
Secondary: Cost of initiation of insulin therapy including time spent by a nurse on education, physician's time, number and duration of phone calls; concentrations of serum total, HDL and LDL cholesterol, and serum triglycerides (visit 12 vs. visit 3); body weight (visit 12 vs. visit 3); blood pressure (visit 12 vs. visit 3); fasting plasma glucose concentration (visit 12 vs. visit 3); insulin dose at visit 12; and subject's treatment satisfaction measured by the DTSQ (DTSQs: visit 12 vs. visit 2; DTSQc: visit 12).

Safety data

Incidence of symptomatic, biochemical, severe and nocturnal hypoglycemia, adverse events, laboratory measurements, physical examination (at screening only) and vital signs, electrocardiogram (at screening only), ophthalmoscopy or retinal photographs (at screening only).

Statistical procedures

Primary: HbA_{1c} change from baseline (visit 12 vs. visit 3) was analyzed with an analysis of covariance (ANCOVA) model having the education program (group or individual) and center as fixed effects and the corresponding baseline value as the covariate. Two-sided 95% confidence interval for the difference between the education programs was estimated from the statistical model. The primary analysis was based on the per-protocol population.

Secondary: Cost of initiation of insulin therapy and insulin dose at visit 12 were analyzed with an analysis of variance (ANOVA) model having the education program (group or individual) and center as fixed effects. Serum lipids, body weight, blood pressure and fasting plasma glucose concentration and subject's treatment satisfaction were analyzed as described for the primary variable (ANCOVA model). DTSQ data were analyzed by using Mann-Whitney U test and Wilcoxon's sign rank test.

Safety: The proportion of patients with symptomatic, biochemical and nocturnal hypoglycemias and the number of hypoglycemic episodes were compared between the education programs using a Cochran-Mantel-Haenszel (CMH) test. Adverse events were analyzed with descriptive statistics. Other safety variables were analyzed with descriptive statistics and ANCOVA model.

Interim analysis

No interim analysis was performed.

Results – Study subjects and conduct

One-hundred-and-twenty-one patients were randomized to the 2 education programs and received insulin glargine therapy (Group 58, Individual 63). Eight patients (4 in both groups) were excluded from the Per-Protocol (PP) analysis which thus included 113 (Group 54, Individual 59) patients. The treatment groups were well balanced with respect to demographic and other baseline characteristics. 75 patients (62%) were males and 46 (38%) females. The mean (SD) age was 58.4 (9.6) years in the group education group and 57.6 (9.0) years in the individual education group. The treatment groups were comparable with respect to their history of type 2 diabetes mellitus. The mean (SD) duration of disease was 7.2 (4.5) years in the group education group and 8.3 (5.7) years in the individual education group. Also HbA_{1c} and fasting plasma glucose (FPG) values at screening were comparable in the two groups. All patients were on oral antidiabetic drug (OAD) treatment when recruited into the study and most were receiving a combination of insulin secretagogue and metformin.

Results – Efficacy

HbA_{1c} decreased quite similarly and statistically significantly in both treatment groups ($p<0.001$ in both groups). In the group education group mean (SD) HbA_{1c} decreased from 8.80 (1.58) % at baseline (visit 3) to 6.83 (0.92) % at week 24, and in the individual education group from 8.60 (1.39) % to 6.76 (0.82) % (PP analysis). The mean (SD) decreases (from visit 3 to visit 12) were 1.97 (1.50) % and 1.85 (1.32) % in the group education and individual education groups, respectively. There was no significant difference between the groups. The 95% CI for the estimated treatment difference (0.0371) between the groups (group vs. individual) for the change from baseline to the last visit was from –0.2442 to 0.3183 %. Analysis of the ITT population gave almost identical results.

Group education patients required less time by nurses and physicians than patients in the individual education group ($p<0.001$). Mean (SD) total times were 2.34 (0.93) and 4.40 (1.66) h, respectively. The 95% CI for the estimated treatment difference (-2.24 h) between the groups (group vs. individual) was from –2.61 to –1.87. There was a significant difference in serum total cholesterol levels (visit 12 vs. visit 3) between the groups ($p=0.0406$). This was due to a significant ($p=0.0074$) reduction from 5.03 (0.96) mmol/L at visit 3 to 4.80 (0.98) mmol/L at visit 12 in the individual education group. The 95% CI for the ratio (group vs. individual, log-transformed data) was from 1.0021 to 1.1000. There were no significant differences between the groups in serum HDL cholesterol, serum LDL cholesterol or serum triglyceride levels (visit 12 vs. visit 3) between the groups. Body weight increased during the study in both groups. Mean (SD) increase from baseline was 3.7 (4.8) kg in the group education group and 2.2 (2.8) kg in the individual education group and the difference between the groups was statistically significant ($p=0.0423$). The 95% CI for the estimated treatment difference (1.50 kg) between the groups (group vs. individual) was from 0.05 to 2.95 kg. There were no significant differences between the groups in systolic and diastolic blood pressure between the groups. Mean (SD) FPG decreased from 12.74 (3.96) at baseline to 7.12 (2.24) mmol/L at visit 12 in the group education group and from 11.87 (2.67) to 6.74 (2.63) mmol/L in the individual education group. The decreases were significant in both treatment groups ($p<0.001$) but there were no significant differences between the groups. The 95% CI for the estimated treatment difference (0.14 mmol/L) between the groups (group vs. individual) was from –0.78 to 1.07 mmol/L. There were no significant differences in insulin dose at visit 12 between the groups. Mean (SD) dose was 56.4 (37.3) IU in the group education group and 61.9 (40.3) IU in the individual education group. The 95% CI for the estimated treatment difference (–3.4 IU) was from –17.3 to 10.4 IU. Treatment satisfaction as measured with the DTSQ increased comparably in the two study groups. There were no significant differences between the groups in the total score or any of the individual questions.

Mean (SD) daily FPG decreased from 11.08 (3.16) at week 0 to 6.16 (1.65) mmol/L at week 23 in the group education group and from 10.29 (2.48) to 6.30 (1.24) mmol/L in the individual education group. There were no significant differences between the groups. Three baseline parameters, i.e. weight, HbA_{1c} and ALT predicted 37.3% ($p<0.001$) of the variation in insulin dose at visit 12.

Results – Safety

There were no significant differences between the groups in the number of patients with symptomatic or biochemical hypoglycemia or in the number of hypoglycemic episodes. Twenty three subjects (39.7%) experienced 72 episodes of symptomatic hypoglycemia in the group education group and 28 subjects (44.4%) 88 episodes in the individual education group. The number of patients and episodes of biochemical hypoglycemia increased relatively similarly in both groups as a function of the cutt-off value. Six subjects (10.3%) experienced 7 episodes of nocturnal hypoglycemia in the group education group and 7 subjects (11.1%) 11 episodes in the individual education group. There were no significant differences between the groups in the number of patients or episodes.

Twenty eight patients (48.3%) in the group education group and 31 patients (49.2%) in the individual education group had at least one adverse event during the course of the study. The number of adverse events was 47 and 60, respectively. There were no episodes of severe hypoglycemia recorded as adverse events during the study. The most common adverse events in both groups were related to various infections and musculoskeletal and connective tissue disorders. There were no clear differences in the number or type of adverse events between the two groups. All adverse events except one were considered not related to study treatment, and most adverse events were graded as mild or moderate. Two adverse events in the individual education group were graded as severe. One patient discontinued study treatment due to an adverse event (local irritation at the injection site). Four patients (group 1, individual 3) had serious adverse events during the course of the study.

There were no evident drug-induced changes in the various laboratory safety parameters. No major changes in vital signs occurred during the course of the study and there were no significant changes from baseline.

Report Date

12 May 2006