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Sponsor/company:	**sanofi-aventis**	**ClinialTrials.gov Identifier:**	**NCT00046501**
		Study Code:	**HOE901_4030**
Generic drug name:	**Insulin Glargine**	**Date:**	**February 5th, 2007**

Study number HOE901/4030

Title

Morning Lantus® (insulin glargine [rDNA origin] injection) vs. intermediate-acting insulin twice daily as basal insulin in a multiple daily injection regimen with Humalog® (insulin lispro injection [rDNA Origin]) in pediatrics with type 1 diabetes mellitus: an active-controlled, open, randomized, gender-stratified, two-arm, parallel-group study.

Investigator(s), study site(s)

This was a multicenter study that was to be conducted at approximately 33 sites (22 US and 11 Canadian). The lead investigator was William Tamborlane, MD, Yale University, New Haven, CT.

Study duration and dates 2 December 2002 to 2 February 2005 | **Phase** IIIb

Objectives

The primary objective of the study was to compare the effects of insulin glargine and twice daily intermediate-acting insulin, when used as the basal insulin in a multiple daily injection (MDI) regimen with insulin lispro, on change in glycemic control from baseline to endpoint (last available post-treatment assessment) as measured by hemoglobin A1c (A1c).

The secondary efficacy objectives of the study were to assess whether there were differences in any of the following measures between subjects who received insulin glargine versus twice daily intermediate-acting insulin as the basal component in a MDI regimen with insulin lispro:

- Change from baseline to individual study time points in A1c
- Percentage of subjects achieving an A1c ≤7.0; percent of preteens (12 years and below) achieving 8%; teens (13-18 years) achieving 7.5%
- Change from baseline to endpoint in fasting self-monitored blood glucose (SMBG) for weekdays, weekends and weekday/weekend combined
- Change from baseline to endpoint in 8-point blood glucose profiles for weekdays, weekends, and weekday/weekend combined
- Change from baseline to endpoint in average basal insulin doses
- Change from baseline to endpoint in lipids (total cholesterol [TC], high-density lipoprotein cholesterol [HDL], low-density lipoprotein cholesterol [LDL], and triglycerides [TGs])
- Change from baseline to endpoint in urinary spot random microalbumin-to-creatinine (A/C) ratio

- Change from baseline to endpoint in glucose
- Exploratory analysis of the usefulness of interstitial fluid glucose monitoring using the Medtronic Minimed Continuous Glucose Monitoring (CGMS). The following CGMS variables were examined: mean, standard deviation (SD), MAGE, MValue, are about 120 mg/dL, minimum, maximum, time<70mg/dL, time<50mg/dL, time=40mg/dL, and variance associated with cycles of oscillation

The safety objectives of this study were to investigate the relative differences between insulin glargine and twice daily intermediate-acting insulin as the basal component in a MDI regimen with insulin lispro, from baseline to end of study, in the following:

- Occurrence of hypoglycemia
- Adverse events (AEs)
- Clinical values: physical examination, vital signs, change in age-adjusted body mass index (BMI)

The objectives of the educational run-in phase (screening to baseline) were to quantify the magnitude of change in the following: A1c, fasting SMBG, lipids, urinary spot random A/C ratio, occurrence of hypoglycemia, and age-related BMI.

The objectives for Health Related Quality of Life analyses were to (1) assess Health-related Quality of Life (HRQoL) among youths treated with insulin glargine relative to those treated with intermediate-acting insulin, (2) evaluate and compare the burden imposed on caregivers, and (3) measure the impact of an educational run-in period on HRQOL. Details regarding quality of life are provided in a separate analysis plan

Study design

Active-controlled, randomized, open-label, gender-stratified, two-arm, parallel-group comparison of insulin glargine with intermediate-acting insulin (NPH insulin or lente insulin) in a MDI regimen with insulin lispro. The study included a 1-month educational run-in period and 24 week treatment period.

Number of subjects planned

A total of 250 subjects were planned to be enrolled into the study in order to obtain 100 evaluable subjects per treatment arm; Finally out of 235 screened subjects 175 were randomized.

Inclusion criteria

Male and female subjects who were between 9 and 17 years-of-age, with a Tanner stage of ≥ 2, who had a diagnosis of type 1 diabetes mellitus for at least 1 year, for which they were treated with insulin only, and who had evidence of decreased insulin secretory capacity (fasting C-peptide concentration $\leq$0.5 mmol/L) and 7.0%$\leq$A1c$\leq$9.5% at screening.

Treatments

Insulin glargine subcutaneously administered before breakfast for a treatment duration of 6 months

NPH insulin or lente insulin subcutaneously administered twice daily, before breakfast and in the evening, for a treatment duration of 6 months

Insulin lispro subcutaneously administered before each meal based on insulin:carbohydrate ratio and correction factor (proactive sliding scale) for a treatment duration of 6 months

Efficacy data

Primary efficacy data: A1c at baseline (week 0) and study endpoint (24 weeks, or last available post-randomization assessment).

Secondary efficacy data: fasting SMBG, 8-point blood glucose profiles, insulin doses, glucose, lipids (TC, HDL, LDL, and TGs), and urinary spot random A/C ratio.

In addition, interstitial fluid glucose was measured using CGMS.

Safety data

The safety data included the following: hypoglycemia, adverse events, laboratory values (standard blood chemistry, hematology and UA), and clinical values (physical examination, vital signs and weight)

Educational run-in data

Educational run-in data included A1c, fasting SMBG, lipids (TC, HDL, LDL, TGs), urinary spot random A/C ratio, hypoglycemia, and weight

Health Related Quality-of-life data

The Diabetes Quality of Life for Youths questionnaire and the Parents' Diabetes Quality of Life questionnaire, both modified versions of the Diabetes Control and Complications Trial instrument, were used to assess HRQOL in terms of physical symptoms/functioning, emotional state/psychological functioning, burden to caregiver, parent-pediatric communication, and anxiety.

Statistical procedures

The primary efficacy analysis comparing mean change in A1c from baseline (week 0) to week 24 (or the last post-randomization A1c if the subject did not have a week 24 visit) between groups was conducted using an analysis of covariance (ANCOVA) with treatment group, center (pooled), CGMS participation (presence or absence of CGMS data) and gender as main effects, and baseline value as a covariate (α=0.05, two-sided). Ninety-five percent confidence intervals (CIs) were computed for the adjusted mean difference between the treatment groups from the ANCOVA to test for noninferiority. Noninferiority was first assessed in the completer population. If noninferiority was concluded in the completer population, then noninferiority was to be assessed in the intention-to-treat (ITT) population. If noninferiority was concluded, superiority was to be assessed in the ITT population. Changes from baseline for secondary efficacy variables were analyzed in the same manner as described for the primary efficacy variable, however, the secondary efficacy analysis was one of superiority and the analysis population was the ITT population. The Cochran-Mantel-Haenszel test, controlling for center (pooled) and gender, was

used for the secondary efficacy analysis of the percentage of subjects achieving an A1c ≤7.0% at endpoint.

Interim analysis

No interim analysis was conducted for this study.

Results - Study subjects and conduct

The two treatment groups were equivalent in terms of study duration. There were no differences between the treatment groups in the baseline demography and disease states. Following is the summary table of subject accounting.

Characteristic	Statistic	GLAR		Intermediate acting-Insulin		P-value+
	Safety population					
Study duration (days)	Mean - SE	220.8	2.6	219.6	2.5	0.7438
Study drug duration (days)	Mean - SE	166.6	2.3	166.6	2.3	0.9917
Discontinued	No N - %	81.0	95.3	86.0	95.6	0.9342
	Yes N - %	4.0	4.7	4.0	4.4	.
Withdrawal Reason	Did not wish to continue N - %	3.0	1.7	2.0	1.1	.
	New or worsening AE N - %	0.0	0.0	1.0	0.6	.
	Other	1.0	0.6	1.0	0.6	.
	ITT(A1c) population					
Study duration (days)	Mean - SE	220.9	2.0	222.1	2.0	0.6701
Study drug duration (days)	Mean - SE	166.6	1.7	169.9	1.7	0.1718
Discontinued?	No N - %	80.0	95.2	82.0	97.6	0.4071
	Yes N - %	4.0	4.8	2.0	2.4	.
Withdrawal Reason	Other	3.0	1.8	1.0	0.6	.
	Completer population					
Study duration (days)	Mean - SE	224.1	1.6	223.0	1.5	0.6182
Study drug duration (days)	Mean - SE	170.1	0.8	171.1	0.7	0.3463
Discontinued?	No N - %	76.0	100.0	80.0	98.8	0.3327
	Yes N - %	0.0	0.0	1.0	1.2	.
Withdraw Reason	Other	0.0	0.0	1.0	0.6	.

@@ pa4 -- zpa4_6.sas; @@pa5 -- zpa4_6.sas; pa6 -- zpa4_6.sas;
SE = standard error; AE = adverse event
+ P-Value for continuous variables from an ANOVA with treatment; categorical variables from a Cochran-Mantel-Haenszel, stratified by site and gender

Results – Efficacy

Glargine is non-inferior to intermediate acting insulin, as established by the change from baseline to endpoint in HbA1c. Noninferiority was established in both the ITT and completer populations.

Superiority for the primary endpoint was not established. At the end of treatment in both ITT and completer populations, neither insulin glargine nor intermediate acting insulin were significantly different at the endpoint from the baseline in controlling A1c values for pediatric subjects with type 1 diabetes.

However, the model from an additional method of analysis showed that glargine therapy would provide superior overall glycemic control over intermediate acting therapy for subjects with baseline A1c 7.9% and 9.3%.

A numerically larger number of glargine-treated subjects than intermediate acting-treated subjects responded to therapy by reaching A1c values ≤7 and ≤8%. This was consistent in both the pre-teen and teen subgroups.

At endpoint, neither treatment group had a significant lowering in fasting SMBG, either during weekdays, weekends or weekdays/weekends combined. However, significant treatment difference, for fasting SMBG, in favor of glargine therapy were observed during weekdays at week 12, weekend days at week 18, and combined at week12.

In the 8-point BG analysis combining weekend and weekday data at week 24, glargine subjects responded significantly better than intermediate acting subjects 2 hours after breakfast. This effect came from the weekend analysis, as the weekday analysis was not significantly different.

The 6-month long pharmacotherapy with add-on glargine or intermediate acting insulin did not impart any statistically significant or clinically relevant changes at endpoint or at any intermediate visit time-point in the lipid profile from baseline, nor did it reveal any treatment difference in renal testing by A/C ratios. Glargine subjects, however, were able to significantly lower their glucose values.

CGMS

The subset of subjects that had CGMS data was representative of the larger study sample. Comparisons between CGMS subjects and non-CGMS subjects showed no real differences, and non-CGMS results for the subset of subjects with CGMS data were similar to results for the larger study sample.

For the 24-hour data category, no differences between treatments were found in mean CGMS sensor values. For CGMS variability measurements of standard deviation, MAGE and M Value, glargine subjects showed significantly more reduction throughout the duration of treatment than did IA subjects. This improvement in variability was seen most strongly in the morning and slightly in the afternoon; no treatment difference was seen nocturnally.

Results found in the first continuous data seen here paralleled results found in the 24-hour data category for mean and variability in CGMS.

Dosing

AM dosing was well tolerated. This was evidenced by the maintenance of AM for most subjects, very few severe hypos. Glargine subjects had lower levels of basal dose than did intermediate-acting subjects through out the study. While both treatment groups increased their basal dose, the difference between groups remained relatively constant. Glargine subjects had a higher bolus/basal ratio than did intermediate acting subjects, at the end of the study.

Educational Run-in conclusions

During the educational run-in phase of the study, subjects' A1c levels significantly improved from screening, as did total cholesterol levels.

Results – Safety

There were numerically more subjects reporting both TEAEs and treatment related TEAEs in the GLAR group than subjects in the intermediate acting group. There were statistically significantly more GLAR subjects reporting skin and subcutaneous tissue disorders. Infection and infestations was the biggest contributor of TEAE for both the glargine and intermediate acting treatment groups.

Significantly more glargine-treated subjects reported metabolism and nutrition disorders as serious adverse events compared with intermediate acting-treated subjects.

There was no coma or seizure, with or without hypoglycemia, reported in this study.

Nearly all subjects experienced a confirmed clinically relevant hypoglycemic event after randomization. The percentages of subjects having hypoglycemic events were numerically similar for most levels. However, there were numerically more GLAR subjects than intermediate acting subjects reporting severe events although there were no statistically significant differences between the treatment groups for any hypoglycemic cutoff level.

Glargine-treated subjects showed statistically larger annualized hypoglycemic event-rates for events with blood glucose <70 mg/dL. The annualized hypoglycemic event rate for blood glucose < 50 mg/dl or < 36 mg/dl was not statistically different.

There were no between-group treatment differences in the change of vital signs or BMI after 24 weeks of therapy.

Results - Health Related Quality-of-Life (HRQoL) data

Generally there was no difference in health-related quality of life in youths or parents of youths treated with insulin glargine relative to those treated with intermediate-acting insulin. The general trend was that pediatrics showed improvement in the life satisfaction domain; however worsened in the disease impact and diabetes-related worries domains somewhat after treatment with insulin glargine while pediatrics treated with intermediate-acting insulin showed improvement in all three

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