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Sponsor / Company: sanofi-aventis	**Study Identifier:** NCT00115570
Drug substance(s): insulin glulisine	**Study code:** EFC6096 (HMR1964D-3001)

Title of the study: Efficacy and safety of insulin glulisine compared with insulin lispro in children and adolescents with type 1 diabetes mellitus: a 26-week, multicenter, open, parallel-group clinical trial.

Study center(s): 65 study centers located in 16 countries, including 12 European countries (Belgium, Denmark, Finland, France, Germany, Hungary, Netherlands, Norway, Romania, Russia, Sweden and Switzerland), USA, Argentina, Australia and South Africa.

Study period:
Date first patient enrolled: 12-Apr-2005
Date last patient completed: 03-Nov-2006

Phase of development: Phase III

Objectives:

Primary objective: To demonstrate non-inferiority of insulin glulisine compared to insulin lispro in the change in total glycated hemoglobin (GHb) from baseline to endpoint (week 26 or last observation on treatment) in children and adolescents with type 1 diabetes mellitus.

Secondary objectives: To compare insulin glulisine with insulin lispro in terms of secondary efficacy parameters (change in GHb at weeks 12 and 26, self-monitored blood glucose [SMBG] parameters, symptomatic hypoglycemia and insulin doses) and safety (adverse events [AEs], serious symptomatic hypoglycemia, clinical chemistry and hematology, as well as insulin antibodies), in children and adolescents with type 1 diabetes mellitus.

Methodology: Open, parallel group, controlled, 1:1 randomized study with a run-in phase of 4 weeks, a treatment phase of 26 weeks and a 24h follow-up period. Subjects were stratified within each center according to whether they were taking Neutral Protamine Hagedorn (NPH) insulin or insulin glargine as basal insulin at the time of randomization.

Number of patients: Planned: 560 Randomized: 572 Treated: 572
Evaluated for efficacy: 570 (modified intent-to-treat population) and 532 (per protocol population); for safety: 572

Diagnosis and criteria for inclusion: Girls or boys, 4 to 17 years of age, inclusive,

- presenting type 1 diabetes mellitus as established in the medical history, with diabetes onset ≥ 1 year prior to screening, uninterrupted insulin therapy for ≥ 1 year prior to screening, and HbA_{1c} measured at screening in the range of ≥ 6.0 and ≤ 11.0 %;
- being at screening on a stable insulin regimen that consisted of either NPH insulin or insulin glargine as basal insulin and willing to have multiple daily injections
- willing to perform the prescribed blood glucose (BG) monitoring and to complete a subject diary.

Investigational product: Insulin glulisine (3 mL cartridges and 10 mL vials): rapid-acting insulin analog
Dose: Individual titration based on the BG values

Administration: Subcutaneous (SC) injection between 0 to 15 minutes prior to a meal, at least twice daily (more injections were permitted according to investigator's judgement), in association with basal insulin therapy (NPH insulin or insulin glargine)

Duration of treatment:
Run-in phase: 4 weeks of treatment with rapid-acting insulin (insulin lispro) and basal insulin (NPH or insulin glargine).

Treatment phase: 26 weeks with rapid-acting insulin (insulin glulisine or insulin lispro) and basal insulin (NPH or insulin glargine; same as in the run-in phase)

Duration of observation: 31 weeks, from screening to the end of the follow-up period.

Reference therapy: Insulin lispro (3 mL cartridges and 10 mL vials): rapid-acting insulin analog

Dose: Individual titration based on the BG values

Administration: SC injection between 0 to 15 minutes prior to a meal, at least twice daily, in association with basal insulin therapy (NPH insulin or insulin glargine)

Coadministered therapy: Basal insulin: Neutral Protamine Hagedorn [NPH] insulin (3 mL cartridges and 10 mL vials) or insulin glargine (3 mL cartridges and 10 mL vials)

Dose: Individual titration based on the BG values

Administration: NPH: twice daily individually dosed SC injections in the morning and in the evening;
insulin glargine: once daily individually dosed SC injection in the evening;

Criteria for evaluation:

Efficacy:

Primary efficacy variable:
Change from baseline to endpoint in GHb (expressed as HbA_{1c} equivalents).
Endpoint was defined as the subject's last available measurement after start of treatment.

Secondary efficacy variables:

- GHb (expressed as HbA_{1c} equivalents): change from baseline at week 12 and week 26, numbers/percentages of subjects reaching predefined categories of GHb (GHb<8.5%; decrease in GHb from baseline ≥0.7%), and numbers/percentages of subjects reaching age-specific glycated hemoglobin goals defined by the American Diabetes Association in 2005;
- SMBG variables: BG values from a 3-point profile (before breakfast, prior to and 2 hours after the main meal of the day) at weeks 4, 12, 18, 26 and endpoint;
- dosage of insulin preparations (rapid-acting insulin and basal insulin): change from baseline at weeks 4, 12, 18, 26, and endpoint;
- incidence and monthly rate of symptomatic hypoglycemic episodes (all, severe, nocturnal, and severe nocturnal episodes).

Safety: Adverse events, serious symptomatic hypoglycemia, clinical data (physical examination, height, body weight, vital signs), laboratory safety data (hematology and clinical chemistry), and insulin antibodies.

Statistical methods: Main efficacy analyses were performed on a modified intent-to-treat (mITT) population, defined as all randomized and treated subjects with a baseline and at least one efficacy evaluation on treatment. These analyses were also carried out for consistency on a per protocol (PP) population, defined as all mITT subjects with no major protocol violations. All safety analyses were performed on the safety evaluable population, defined as all subjects treated with study medication.

Efficacy:
The study was designed to show non-inferiority of insulin glulisine compared to insulin lispro in GHb change from baseline to endpoint with a pre-specified non-inferiority margin of 0.4%. To assess non-inferiority, the two-sided 95% confidence intervals (95% CIs) were computed for the adjusted mean difference between treatment groups from an analysis of covariance (ANCOVA) model with treatment, type of basal insulin at randomization and (pooled) center as fixed effects and baseline GHb as covariate.

The secondary efficacy variables GHb at week 12 and week 26, BG values, and insulin doses were analyzed using the same method as described above for the primary efficacy variable. The numbers of subjects reaching categories of GHb were compared using a logistic regression model with treatment and (pooled) center as fixed effects and baseline GHb as covariate. Symptomatic hypoglycemia was presented by frequency distribution; treatment groups were compared using the Cochran-Mantel-Haenszel test stratified by (pooled) center.

Safety:
The proportion of subjects with treatment emergent adverse events (TEAEs) [all, serious and possibly related TEAEs], overall and by system organ class (SOC), and the proportion of subjects with at least one episode of serious symptomatic hypoglycemic events were tabulated for each treatment group.

Summary:

Study population:

A total of 646 subjects entered the screening phase, of whom 572 were randomized and treated. There were 277 subjects treated in the insulin glulisine group, and 295 in the insulin lispro group. The mean age of the population was 12.5 years. At baseline, both treatment groups were well balanced for demographic and disease characteristics.

Efficacy results:

Subjects in both treatment groups had similar GHb levels at baseline. The adjusted mean change from baseline at endpoint in the mITT population was +0.10% (± 0.08) in the insulin glulisine group and +0.16% (± 0.07) in the insulin lispro group. The difference in the adjusted means for the change from baseline in GHb between the two treatments was equal to -0.06%, ie, almost zero, with a 95% CI of (-0.24; 0.12). The non-inferiority of insulin glulisine compared to insulin lispro was shown by the fact that the upper bound of this 95% CI was equal to 0.12%, well below the pre-specified non-inferiority margin of 0.4%.

Analysis of the numbers/percentages of subjects reaching predefined GHb categories shows a slightly higher percentage of subjects reaching GHb <8.5% at endpoint, in the insulin glulisine group (62.0%) compared to the insulin lispro group (57.4%). When considering the age-specific goals defined by the American Diabetes Association in 2005, a higher percentage of adolescents (13-17 years) reached GHb <7.5% at endpoint in the insulin glulisine group (31.1% versus 21.1%) and overall, for all age groups together, the percentage of subjects reaching their age-dependent GHb goals was significantly greater in the insulin glulisine group than in the insulin lispro group (38.4% versus 32.0%, p=0.0386).

Post-prandial glycemic control, as assessed by self-monitored blood glucose (SMBG) values and BG excursions, was similar in the two treatment groups at endpoint.

At endpoint, both groups showed an increase in daily total insulin doses compared with baseline (+2.53 ± 0.68 U/day in the glulisine group versus +4.91 ± 0.95 U/day in the lispro group, p=0.0074).

There were no noteworthy differences between the two treatment groups in the incidence of all symptomatic hypoglycemia, severe symptomatic hypoglycemia, and severe nocturnal symptomatic hypoglycemia. The incidence of nocturnal symptomatic hypoglycemia was higher in the insulin glulisine group than the insulin lispro group in the time period “entire treatment phase”; this between-group difference was mainly observed in the first month of treatment and decreased in the latter part of the treatment phase.

When GHb and hypoglycemia were analyzed in subgroups of subjects based on age, sex, race, duration of diabetes, basal insulin, and baseline GHb, the results observed in each subgroup were consistent with those seen in the population as a whole.

Safety results:

In general, both insulin glulisine and insulin lispro were well tolerated and overall, the kind, intensity and frequency of treatment-emergent adverse events (TEAEs) were similar in the two treatment groups. A total of 148 (53.4%) glulisine subjects and 173 (58.6%) lispro subjects had at least one reported TEAE. Possibly related TEAEs were reported in 25 (9.0%) glulisine and 28 (9.5%) lispro subjects. A total of 30 (10.8%) glulisine and 37 (12.5%) lispro subjects reported at least one serious TEAE.

There were no noteworthy differences between treatment groups in the number of subjects reporting hypoglycemia as a serious adverse event (SAE), including events of coma/unconsciousness or seizures associated with hypoglycemia. The percentage of subjects with hypoglycemia reported as SAEs was 7.2% in the insulin glulisine group, and 8.1% in the insulin lispro group.

There were no deaths during this study. One subject in the insulin glulisine group, with a previous history of injection site reaction (lipohypertrophy) which was ongoing at study entry, was withdrawn from the study due to a non-serious adverse event of injection site swelling.

Safety results (cont'd):

A slightly higher percentage of subjects in the insulin glulisine group than the insulin lispro group (8 subjects, ie 2.9%, versus 3 subjects, ie 1.0%) experienced potential systemic hypersensitive reactions, but none of these were considered to be possibly related to study medication nor led to discontinuation or change in the study medication. Most of these potential systemic hypersensitivity reactions (conjunctivitis allergic, rhinitis allergic, seasonal allergy) did not evoke adverse events that may indicate a hypersensitivity reaction to the insulin study medication, and most subjects had a previous history of the same reaction or of other allergic reactions. A slightly higher number of subjects in the insulin glulisine group experienced injection site abnormalities (10 subjects, ie 3.6%, versus 6 subjects, ie 2.0% in the insulin lispro group), but the number of subjects with possibly related injection site abnormalities was the same in the two treatment groups (5 subjects in each group).

No relevant abnormalities were observed for clinical laboratory parameters or vital signs.

The analyses of antibody data indicate that insulin glulisine does not elicit a significant anti-insulin antibody response and that there were no clinically notable effects associated with anti-insulin antibody formation in glulisine patients. In particular, overall, no correlation was found between crossreactive antibody levels and changes seen in GHb levels, insulin doses, or in symptomatic and severe symptomatic hypoglycaemia.

Issue date: 11-Mar-2008