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Sponsor / Company: sanofi-aventis **Drug substance(s):** insulin glulisine	**Study Identifier:** NCT00290979 **Study code:** EFC6167 (HMR1964A/3101)
Title of the study: 28-week evaluation of efficacy and safety of HMR1964 in subjects with type 1 diabetes mellitus; Lispro controlled, open, randomized, parallel group, comparative non-inferiority study, using Glargine as basal insulin.	
Study center(s): Multicenter study conducted at 24 sites in Japan.	
Study period: Date first patient enrolled: 16 Dec. 2004 Date last patient completed: 28 Mar. 2006	
Phase of development: Phase III	
Objectives: **Primary objective:** ● To evaluate non-inferiority in the efficacy of HMR1964 as compared with Lispro in terms of the change in hemoglobin A_{1C} (HbA_{1C}) from baseline to endpoint on a basal-bolus insulin regimen in subjects with type 1 diabetes mellitus. **Secondary objectives:** ● To compare HMR1964 with Lispro in terms of the change in baseline HbA_{1C} to every 4 week on-treatment, blood glucose values, insulin doses (rapid-acting, basal and total) and symptomatic hypoglycemia in subjects with type 1 diabetes mellitus; ● To compare the safety of HMR1964 with Lispro in subjects with type 1 diabetes mellitus; ● To assess the diabetes treatment satisfaction survey (QOL) data of HMR1964 and that of Lispro in subjects with type 1 diabetes mellitus.	
Methodology: Lispro controlled, open-label, 1:1 randomized (minimization method), parallel group, non-inferiority study. This study consisted of a 4-week screening phase, a 4-week Lispro and Glargine run-in phase, and a 28-week treatment phase.	
Number of patients: Planned: 250 (125 per treatment group) Randomized: 267 Treated: 267 Evaluated: 266 for efficacy, 267 for safety, 252 for Quality of Life	
Diagnosis and criteria for inclusion: The key inclusion criteria were as follows: ● Men or women with type 1 diabetes mellitus on an insulin regimen, with a body mass index (BMI) <35 kg/m^2, and a HbA_{1C} of ≥6.0% and ≤11.0% at screening; ● ≥18 years of age and ≤75 years of age; ● 2-hour postprandial serum C-peptide at screening <1.0 ng/mL; ● Subjects who had at least one year of continuous insulin treatment at the date of informed consent; ● Subjects who had been treated with bolus insulin before every meal and a basal insulin once or twice daily at least 12 weeks prior to informed consent.	

Investigational product: HMR1964 (insulin glulisine)

Dose: The starting dose for HMR1964 was determined after review of the clinical data at the last visit in the run-in phase, with appropriate adjustment to meet the titration goals. For subjects randomized to HMR1964, the dose was to be the same as the dose would have been if the subject had remained on Lispro administration. The titration goal was 2-hour postprandial blood glucose values of 128 to 172 mg/dL. The dose was adjusted appropriately by self-monitored blood glucose values, the symptoms and laboratory findings, with attention given to any events of hypoglycemia.

Administration: HMR1964 was self-injected subcutaneously immediately before (ie, 0 to 15 minutes) each meal using the insulin injection device for HMR1964.

Duration of treatment: 28 weeks

Duration of observation: 36 weeks (4-week screening phase, 4-week run-in phase, and 28-week treatment phase)

Reference therapy: Lispro

Dose: In the run-in phase, the dose of Lispro was initially determined in reference to the dose of bolus insulin in the prior treatment, and the titration goal was 2-hour postprandial blood glucose values of 128 to 172 mg/dL. The dose was adjusted appropriately by self-monitored blood glucose values, the symptoms and laboratory findings, with attention given to any events of hypoglycemia.
In the treatment phase, the starting dose for Lispro was determined after review of the clinical data at the last visit in the run-in phase, with appropriate adjustment to meet the titration goals. The titration goal was 2-hour postprandial blood glucose values of 128 to 172 mg/dL. The dose was adjusted appropriately by self-monitored blood glucose values, the symptoms and laboratory findings, with attention given to any events of hypoglycemia.

Administration: Lispro was self-injected subcutaneously immediately before (ie, 0 to 15 minutes) each meal using the insulin injection device for Lispro.

Basal insulin therapy: Glargine

Dose: In the run-in phase, the dose of Glargine was initially determined in reference to the dose of basal insulin in the prior treatment, and the titration goal was a fasting (pre-breakfast) blood glucose value of 95 to 128 mg/dL. The dose was adjusted appropriately by self-monitored blood glucose values, the symptoms and laboratory findings, with attention given to any events of hypoglycemia.
In the treatment phase, the starting dose for Glargine was determined after review of the clinical data at the last visit in the run-in phase, with appropriate adjustment to meet the titration goals. The titration goal was a fasting (pre-breakfast) blood glucose value of 95 to 128 mg/dL. The dose was adjusted appropriately by self-monitored blood glucose values, the symptoms and laboratory findings, with attention given to any events of hypoglycemia.

Administration: Glargine was self-injected subcutaneously once daily at bedtime using the insulin injection device for Glargine.

Criteria for evaluation:

Efficacy: **Primary efficacy variable:**

- The change in HbA_{1C} from baseline to endpoint, where study endpoint is defined as the subject's last available value measured during the treatment phase.

Secondary efficacy variables:

- The changes in HbA_{1C} from baseline to weeks 4, 8, 12, 16, 20, 24 and 28;
- The consecutive changes in HbA_{1C} every 4 weeks from baseline to week 28;
- The changes in 2-hour postprandial plasma glucose (2h-PPG) from baseline to week 12, week 28 and endpoint;
- The consecutive changes in the 7-point blood glucose profile [preprandial and the corresponding 2-hour postprandial after breakfast, lunch and dinner, and at bedtime by self-monitoring of blood glucose (SMBG)] from baseline to week 12, week 28 and endpoint;

Criteria for evaluation (cont'd):

- Blood glucose excursion, computed as the difference between preprandial blood glucose value and the corresponding 2-hour postprandial (2 hours after the start of meal) blood glucose value [by SMBG] at baseline, week 12, week 28, and endpoint;
- The changes of insulin doses from baseline to weeks 4, 8, 12, 28 and endpoint;
- Symptomatic hypoglycemia.

Safety: Adverse events (including severe symptomatic hypoglycemia), laboratory values (hematology and biochemistry), antibodies (insulin antibodies and *E. coli* protein antibody), body weight, blood pressure (seated), standard 12-lead electrocardiogram (ECG), and fundoscopic examination.

Quality of Life: Quality of life (QOL) was assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Statistical methods: The primary variable, change in HbA_{1C} from baseline to endpoint, was analyzed by analysis of covariance (ANCOVA) model based on the intention-to-treat (ITT) population. The study was designed to show non-inferiority of HMR1964 compared to Lispro by estimating the upper limit of one-sided 97.5% (two-sided 95%) confidence interval (CI) of the adjusted mean difference between treatment groups, with a delta of 0.45% as the non-inferiority margin. In case non-inferiority was shown, superiority was to be evaluated.

Summary:

Efficacy results: HMR1964 was proved to be non-inferior to Lispro with respect to reduction in HbA_{1C} values from baseline to endpoint of the 28-week study period. Non-inferiority of HMR1964 in comparison to Lispro was shown by the fact that the upper boundary of the two-sided 95% CI (-0.09% ; 0.21%) was below the predefined non-inferiority margin of 0.45%. HMR1964 and Lispro showed very similar results in terms of mean HbA_{1C} values over time and number of subjects achieving the pre-defined HbA_{1C} categories.

There were no noteworthy differences between HMR1964 and Lispro for other measures of efficacy such as mean 2h-PPG over time, mean daily blood glucose (BG) profile at endpoint, blood glucose excursions, and change in mean daily rapid-acting insulin doses over time. For mean daily basal insulin doses over time, the HMR1964 group showed a statistically significant decrease in dose from baseline to endpoint ($P = 0.0132$).

More HMR1964 subjects than Lispro subjects experienced at least one symptomatic hypoglycemic episode during the study.

Safety results: There were no clinically significant differences between the two treatment groups in the incidence of treatment-emergent adverse events (TEAEs). For both groups, the most common related TEAEs were hypoglycemia (in approximately 4% of subjects in each group) and hypoglycemic coma (in approximately 2% of subjects in each group). The incidence of serious adverse events (SAEs) were also similar for the two groups. The most common SAEs were related to hypoglycemia (in 6.8% [9/132] of HMR1964 subjects and 4.4% [6/135] of Lispro subjects), and all non-hypoglycemia SAEs occurred in 1 or fewer subjects in each group. No deaths occurred during the study.

No noteworthy differences were observed in the production of insulin antibodies in the HMR1964 group. At endpoint, cross-reactive antibody levels decreased relative to baseline in HMR1964-treated subjects. No correlation between the formation of cross-reactive antibodies and HbA_{1C} values, insulin doses, and frequency of all symptomatic hypoglycemia or severe symptomatic hypoglycemia were detected in HMR1964-treated subjects. The percentage of subjects with increases in cross-reactive antibodies exceeding the 95% quantile was similar for the two treatment groups: 5.4% (7/130) of HMR1964 subjects; 4.5% (6/134) of Lispro subjects. At endpoint, human insulin-specific antibody levels decreased relative to baseline in HMR1964-treated subjects. A slight increase from baseline to endpoint in HMR1964-specific antibody formation was noted (+0.010%B/T).

Quality of life results: Assessment of treatment satisfaction score and perceived frequency of hyperglycemia and hypoglycemia by the DTSQ showed no changes from baseline to week 28 or endpoint in either treatment group.

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