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Sponsor/Company: sanofi-aventis **Drug substance(s):** insulin glulisine	**Study identifier:** NCT00290927 **Study Code:** EFC6168 (HMR1964A/3102)
Title of the study:	Evaluation of efficacy and safety of HMR1964 intensive therapy in subjects with type 2 diabetes mellitus not optimally controlled with oral hypoglycemic agents (OHA); OHA therapy controlled, open, randomized, parallel group, comparative (superiority), 16-week, multinational, multicenter study.
Study center(s):	Multinational, multicenter study conducted at 26 sites in Japan and 17 sites in Korea.
Study period: Date first patient enrolled: 25 Dec. 2003 Date last patient completed: 26 Dec. 2005	
Phase of development: Phase III	
Objectives:	**Primary objective:** ● To evaluate the superiority in the efficacy of combination of HMR1964 and continued OHA therapy as compared with continued OHA-only therapy in terms of the change in HbA_{1C} from baseline to endpoint in subjects with type 2 diabetes mellitus not achieving optimal glycemic control on OHA therapy. When the superiority of combination HMR1964 and continued OHA therapy is shown, the superiority in the efficacy of HMR1964 mono-therapy as compared with continued OHA-only therapy will be evaluated using the same method. **Secondary objectives:** ● To compare HMR1964 therapy (mono-therapy or in combination with continued OHA therapy) with continued OHA-only therapy in terms of the change in HbA_{1C} from baseline to weeks 4, 8, 12 and 16, consecutive change in HbA_{1C} every 4 weeks, plasma glucose parameters, and symptomatic hypoglycemia in subjects with type 2 diabetes mellitus. ● To evaluate the safety of HMR1964 in subjects with type 2 diabetes mellitus.
Methodology:	OHA therapy (sulfonylurea regimen or sulfonylurea + biguanide regimen), administered in a controlled, open, 1:1:1 randomized (minimization method), parallel group, superiority study. The study consisted of a 4-week screening phase and a 16-week treatment phase.
Number of patients:	Planned: 390 (130 per treatment group) Randomized: 393 Treated: 387 Evaluated: 387 for efficacy and for safety
Diagnosis and criteria for inclusion: The key inclusion criteria were as follows: ● Men or women with type 2 diabetes mellitus diagnosed at least one year prior to the study, with a body mass index (BMI) <30 kg/m^2, a HbA_{1C} of ≥8.0% and ≤11.0% at screening; ● Fasting serum C-peptide at screening ≥0.7 ng/mL; ● Subjects who had been on a stable regimen and at the following doses of sulfonylurea (SU) for at least 8 weeks prior to signing informed consent: Glibenclamide ≥5 mg/day Glimepiride ≥3 mg/day Gliclazide ≥80 mg/day In addition to receiving the above mentioned SU agents, subjects may have been treated with a biguanide at a stable dose for at least 8 weeks prior to signing informed consent. ● Subjects willing to administer three HMR1964 injections per day immediately prior to meals for a 16-week period.	

Investigational product: HMR1964 (insulin glulisine)	
Dose:	HMR1964+OHA group: In the HMR1964+OHA group, prior OHA therapy was continued and HMR1964 was added. Titration started with ≥0.2 U/kg/day of HMR1964, and was adjusted individually thereafter based on blood glucose (BG) values, symptoms, and laboratory findings. HMR1964 doses were reviewed by the following titration algorithm: ● For 172 mg/dL <2-hour postprandial blood glucose (2h-PBG) (ie, self-monitoring of blood glucose [SMBG]) <200 mg/dL and no episodes of symptomatic hypoglycemia: increase dose of HMR1964 by at least 1 U at each of the appropriate meals; ● For 2h-PBG (SMBG) of ≥200 mg/dL and no episodes of symptomatic hypoglycemia: increase dose of HMR1964 by at least 2 U at each of the appropriate meals. The titration goal was a 2h-PBG value of 128 to 172 mg/dL while avoiding hypoglycemia. The PBG value was self-monitored. HMR1964 monotherapy group: Titration started with ≥0.2 U/kg/day of HMR1964, and was adjusted individually thereafter based on BG values, symptoms, and laboratory findings. HMR1964 doses were reviewed by the titration algorithm given above. The titration goal was a 2h-PBG value of 128 to 172 mg/dL while avoiding hypoglycemia. The PBG value was self-monitored.
Administration:	HMR1964 was administered via subcutaneous (SC) self injection using the insulin injection device (OptiPen® Pro1), 3 times daily, 0 to 15 minutes prior to each meal.
Duration of treatment:	16 weeks
Duration of observation:	20 weeks (4-week screening phase plus 16-week treatment phase)
Reference therapy:	oral hypoglycemic agents (OHA)
Dose:	OHA-only therapy group: Subjects were already on a stable dose and administration schedule of OHA for at least 8 weeks prior to informed consent, and the dose and administration schedule of OHA were maintained unless hypoglycemia or other safety concerns necessitated a reduction in OHA dose.
Administration:	OHA was self administered according to a stable dose and administration schedule, unless hypoglycemia or other safety concerns necessitated a reduction in the OHA dose.
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 change in HbA_{1C} from baseline to weeks 4, 8, 12 and 16; ● The consecutive changes in HbA_{1C} every 4 weeks from baseline to week 16; ● Plasma glucose excursion, computed as the difference between 2-hour postprandial plasma glucose (2h-PPG) and the corresponding fasting morning plasma glucose (FPG) values at baseline, week 8, week 16, and endpoint; ● The consecutive changes in FPG and 2h-PPG values from baseline to week 8, week 16, and endpoint; ● Symptomatic hypoglycemia.
Safety:	Adverse events (including severe symptomatic hypoglycemia), laboratory values (hematology and biochemistry), body weight, blood pressure (seated), standard 12-lead electrocardiogram (ECG), and fundoscopic examination.

Statistical methods:	Analysis of HbA_{1C} focused on the change from baseline to endpoint in the intention-to-treat (ITT) population. Comparison of HbA_{1C} change from baseline was done between the HMR1964+OHA group and the OHA-only group by the analysis of covariance (ANCOVA; one-sided significance level 2.5%). In case superiority was shown, comparison between the HMR1964 monotherapy group and the OHA-only group was to be done as a closed testing procedure.
Summary:	
Efficacy results:	The change from baseline to endpoint in HbA_{1C} was analyzed using the ITT population, and included only subjects with both baseline and post-baseline data. Baseline HbA_{1C} values were similar among the three treatment groups. Both groups of HMR1964-treated subjects had significantly larger reductions in the adjusted mean change from baseline to endpoint in HbA_{1C}: for HMR1964+OHA there was a 2.07% decrease, for HMR1964 monotherapy there was a 1.25% decrease, as compared to a 0.61% decrease among OHA-only subjects. Analysis showed that HMR1964+OHA was superior to OHA-only, with an adjusted mean change difference in HbA_{1C} of -1.46% ($P < 0.0001$). Further analysis showed that HMR1964 monotherapy was superior to OHA-only, with an adjusted mean change difference of -0.64% ($P < 0.0001$). Both groups of HMR1964-treated subjects had better 2h-PPG control than the OHA-only group. More subjects in the HMR1964 treatment groups reported at least one episode of symptomatic hypoglycemia in the entire treatment phase: 64.6% (84/130) of HMR1964+OHA subjects and 59.8% (76/127) of HMR1964 monotherapy subjects, as compared to 14.6% (19/130) of OHA-only subjects. Only one severe symptomatic hypoglycemia was reported in this study, in a subject in the HMR1964+OHA treatment group.
Safety results:	HMR1964, administered alone or in combination with OHA, was well tolerated. The type and frequency of treatment emergent adverse events (TEAEs) were generally similar among the three treatment groups. The percentage of subjects in each group with at least one TEAE was: 61.5% (80/130) of HMR1964+OHA subjects, 62.2% (79/127) of HMR1964 monotherapy subjects, and 62.3% (81/130) of OHA-only subjects. Serious TEAEs were reported in 6.9% (9/130) of HMR1964+OHA subjects, 2.4% (3/127) of HMR1964 monotherapy subjects, and 3.1% (4/130) of OHA-only subjects. Two deaths occurred during the study, one of which was due to a hepatocellular carcinoma in a 49-year old Korean male subject in the OHA-only group, and the other due to unknown causes while a 61-year old Korean male subject in the HMR1964+OHA treatment group was hiking alone and because no autopsy was performed.

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