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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00272012
		Study Code:	HMR1964A_3507
Generic drug name:	insulin glulisine	**Date:**	28 November 2007

Title

26-week, open, randomized, national, multi-center clinical trial to compare the efficacy and safety of HMR 1964 given as a single injection at breakfast + insulin glargine + OAD vs. HMR 1964 given as a single injection at main meal + insulin glargine + OAD in type 2 diabetic patients for which glycemic control is suboptimal using insulin glargine + OAD alone.

Investigator(s), study site(s)

126 centers in Germany participated in this study.

Study duration and dates	The first subject was enrolled on 17 June 2004 and the last subject completed the study on 14 Sep 2006.	**Phase**	IIIb

Objectives

Primary objective:
The primary study objective was to compare efficacy of insulin glulisine once a day at breakfast versus insulin glulisine given once a day at main mealtime in combination with insulin Glargine plus OAD.
The study aimed to demonstrate the two-sided equivalence of the two therapy regimens with different injection times of insulin glulisine in terms of individual change of HbA_{1c} from baseline to endpoint.
Secondary objectives:
The secondary objectives of the study were to compare the efficacy and safety of insulin Glulisine once a day at breakfast versus insulin glulisine given once a day at main mealtime in combination with insulin glargine plus OAD.
For the secondary analysis of efficacy the two treatment arms were compared in terms of:
Baseline to endpoint change of fasting, pre-prandial, 2h-postprandial, mean daily and nocturnal blood glucose.
Baseline to endpoint change of fasting plasma glucose.
Responder rate of patients with baseline to endpoint decrease of HbA_{1c} 6.5 %.

(The response criteria was adapted from initially HbA_{1c} 7.0 % to HbA_{1c} 6.5 % according to protocol amendment 1; 08-Mar-2004).
For the analysis of safety the two treatment arms were compared in terms of:

- Change of body weight and body-mass-index.
- Hypoglycemic events
- Adverse events

Study design

National, multicenter, open, 1:1 randomized, parallel group study. The study consisted of a pre-screening phase (up to 2 weeks), a screening phase (between 1 and 3 weeks), a randomized treatment phase (24 weeks) and a follow-up phase (1 week).

Number of subjects planned

A total of at least 348 subjects (see Amendment no. 2) were planned to be enrolled and treated with insulin study medication.

Inclusion criteria

Subjects of both gender, aged ≥ 18 years with type 2 diabetes mellitus, previously treated with a combination therapy of insulin glargine plus OAD (excluding α-glucosidase inhibitors) for at least 3 months who show a pre-screening HbA1c value between > 6.5 % and ≤ 9.0 % and a fasting blood glucose value ≤ 120 mg/dl (6.6 mmol/l).
All subjects had to give informed consent at enrollment into the study and should be able and willing to perform blood glucose monitoring using the sponsor-provided blood glucose meter and subject diary at home. Females should be either not of childbearing potential or not pregnant and agreed to use reliable contraceptive measure for the duration of the study.

Treatments

Subjects enrolled in this study had to be previously treated for at least 3 months with a combination therapy of insulin glargine once daily plus OADs, except -glucosidase inhibitors, in the maximal tolerated OAD dose approved for the combined treatment with insulin according to local SPCs, but who failed to obtain good glycemic control prior to study start (pre-screening/visit 0, HbA_{1c} value between > 6.5 % and ≤ 9.0 %).
All patients had to continue their previous therapy regimen (insulin glargine plus OAD) unchanged as concomitant medication during the study period. The time of insulin glargine injection should not be altered, the injection dosage of insuline glargine should have been adjusted individually to target level FBG ≤ 100 mg/dl based on the investigator's experience.
At the end of the screening period the subjects were stratified to their main meal (breakfast, lunch or dinner) according to their highest 2h-postprandial blood glucose values shortly before randomization and than 1:1 randomized to one of the two HMR 1964 insulin (study insulin glulisine) therapy regimens (arms/groups): Subjects had to either inject HMR 1964 at breakfast (at breakfast arm) or at

the individual main mealtime (at main mealtime arm), which had been determined during the screening period. The subjects of each study arm had to inject insulin glulisine sc, od 0 to 15 minutes before the allocated mealtime of injection. The insulin glulisine dosage was individually titrated at the investigator's discretion with each subject to achieve the titration goal of 2h-pp BG ≤ 135 mg/dl (7.5 mmol/l), while avoiding hypoglycemia.
Investigators had to provide adequate training to the subjects enabling a safe and successful Patient's self-titration of insulin. The goal for all subjects was to reach the defined blood glucose targets without any increase of hypoglycemia.

Safety data

Serious adverse events and adverse events, including all forms of hypoglycemia (especially severe, nocturnal and symptomatic hypoglycemia) and local intolerance at the injection sites were analyzed.
The results of the standard clinical chemistry, the physical examination and the vital signs were evaluated for safety.

Quality-of-life data

N/A

Statistical procedures

Throughout the analysis, continuous variables were summarized with mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, maximum, number of valid observations, number of missing observations and total number of observations. For specific variables 95 %-confidence intervals were calculated. For categorical data the frequency distributions were given. Missing values were treated as a separate category. Analyses were done on the FAS and the PPS in general and on the completers set for HbA_{1c} additionally. Analyses on HbA_{1c} were performed as secondary efficacy analyses if they were not part of the primary efficacy analysis.
The primary efficacy variable was the change in glycated hemoglobin HbA_{1c} from baseline to endpoint for each subject. The primary analysis tested the hypothesis of equivalence of the two insulin glulisine therapy regimens (injection at breakfast versus injection at main mealtime) for the primary efficacy variable at the two-sided level of $\alpha = 0.05$ and with an equivalence margin of $\varepsilon = 0.4$ % on the per-protocol set. The hypothesis was tested by means of an analysis of covariance (ANCOVA) model, considering therapy group and randomization stratum as fixed factors, and baseline HbA_{1c} as covariate. A two-sided 95 %-CI was derived for the difference in LS-means of the treatment arms [LS-mean (at breakfast arm) - LS-mean (at main meal arm)].
The two therapy regimens were considered equivalent if the 95 %-CI was completely within the interval] -0.4 %; +0.4 % [.
Sensitivity analyses were performed considering the comparison of subgroups, homogeneity of treatment effects across strata, violations of the model assumptions, and baseline imbalances as specified below.
Because the randomization made no difference between the therapy regimens for those patients stratified into the "main meal = breakfast" stratum as they always injected insulin glulisine at

breakfast, irrespective if they were randomized to the insulin glulisine at breakfast or insulin glulisine at main meal arm, the primary efficacy analysis was carried out comparing the following subgroups (group I,II,III)and pooled subgroups:

Group I were those patients who were stratified into the "main meal = breakfast" stratum and thus, irrespective of the randomization, injected insulin glulisine at breakfast,

group II were those patients who were stratified into the "main meal = lunch" or "main meal = dinner" stratum and were randomized to the at breakfast arm and subsequently injected insulin glulisine at breakfast and

group III were those patient who were stratified into the "main meal = lunch" or "main meal = dinner" stratum and were randomized to the at main-meal arm. These patients injected insulin glulisine at lunch or dinner, respectively.

Homogeneity of treatment effect across strata was assessed by adding the treatment-by-stratum interaction terms to the ANCOVA model.

Model assumptions of normality and homogeneity of regression for the ANCOVA model were checked by analysis of residuals and treatment-by-baseline evaluation, respectively. The assumption of *regression homogeneity* was evaluated by adding the treatment-by-baseline interaction term to the ANCOVA model.

Baseline imbalances were evaluated by adding the respective baseline value as factor or covariate. For the change of all continuous secondary variables, the same ANCOVA was performed as for the primary variable. Additionally, confidence intervals for baseline, endpoint and change values were reported together with the associated p-values. Categorical variables were compared between treatment arms by Cochran-Mantel-Haenszel tests (CMH) controlling for stratum. Event-based analyses were done reporting the number of events, the absolute and relative frequency of subjects for which the events occurred, and the total number of subjects.

Interim analysis

No interim analysis was performed.

In order to reassess the original assumptions for sample size calculation a blinded "Data Monitoring" on the basis of 158 subjects was performed.

Results – Study subjects and conduct

A total of 492 subjects were enrolled in the pre-screening phase of the study to confirm the eligibility of the subjects according to their initial HbA_{1c} and FBG status. Of those, 393 subjects were finally randomized and treated with the study insulin glulisine: 196 subjects were treated with insulin glulisine at breakfast and 197 subjects with insulin glulisine at main mealtime. After randomization 19 subjects in the at breakfast arm and 20 subjects in the at main meal arm prematurely discontinued the study. Respectively, a total of 354 subjects completed the study: 177 in the at breakfast arm and 177 in the at main mealtime arm.

Both treatment arms were comparable as regards demographic and anamnestic conditions and medical history. The treatment arms were comparable with respect to the history of type 2 diabetes and to the actual situation in terms of diabetic late complications as well as with regard to previous and concomitant antidiabetic medication. During the on-treatment period the daily dose of study

insulin glulisine, as well as that of concomitant insulin glargine was comparable between the two treatment arms.
The baseline HbA_{1c} value at the beginning of the insulin glulisine treatment phase (visit II) was homogenous for the two treatment arms. The mean baseline values of most of the secondary blood glucose parameters (fasting blood glucose, nocturnal blood glucose, mean daytime blood glucose, mean daily blood glucose as well as the parameters of circadian blood glucose profile) were also comparable in both treatment arms at the beginning of the insulin glulisine on-treatment phase.
More obvious baseline differences were clearly revealed only for the full analysis set (FAS) for the fasting blood glucose (FBG) and the 2h-pp BG after lunchtime. These differences were not seen for the per-protocol analysis set (PPS) and the completers analysis set (CoS). Thus, it seems unlikely that these few differences might have had any substantial influence on the evaluation of efficacy.

Results – Efficacy

The baseline to endpoint HbA_{1c} improvement was shown to be very similar for the two treatment regimens with study insulin glulisine. The absolute baseline to endpoint reduction of HbA_{1c} was on average (LS-means) 0.3069 % for the at breakfast arm and 0.355 % for the at main meal arm.
The primary efficacy analysis performed on the per-protocol analysis set demonstrated statistically significant therapeutic equivalence of the two study insulin glulisine treatment regimens. The difference of HbA_{1c} [%] change for the adjusted means of the two treatment arms is |0.0481|. The corresponding two-sided 95%-CI of this difference is [-0.1151, 0.2113] being completely within the predefined equivalence margin] -0.4, +0.4 [. Thus, the two treatment arms can be considered equivalent. Additional analyses of the primary efficacy variable showed very similar results for the full analysis set (difference of adjusted means = 0.1305 %; 95 %-CI: [-0.0210, 0.2821]) and the completers set (difference of adjusted means = 0.0326 %;95 %-CI: [-0.1367, 0.2019]). This clearly confirmed the results with regard to equivalence of the two treatment regimens. Sensitivity analyses excluded relevant effects of stratum randomization on the baseline to endpoint treatment differences of HbA_{1c} change. Due to the stratified randomization, subjects with an individual main meal at breakfast were 1:1 assigned to the at breakfast arm and the at main meal arm. This might have favored a result towards equivalence of the two treatment arms because in both treatment arms 1/3 of all patients had main meal breakfast and were treated with study insulin glulisine at breakfast.
To evaluate the potential impact of the above described stratum effect on the results of primary analysis, additional analyses of subgroups of the per-protocol set were performed. The analyses compared pairwise e.g. those subjects who injected the study insulin glulisine at their individual main mealtime to those who injected the study insulin not at their individual main mealtime.
All pairwise comparisons of single or pooled subgroups showed only slight differences in the absolute baseline to endpoint change of HbA_{1c} (< ± 0.1 % - LS-means). Although, these differences are little higher when subgroups with injection at main mealtime vs injection not at main mealtime were compared the overall low differences imply that the stratum effect does not result in a relevant effect on the obtained intragroup baseline to endpoint HbA_{1c} changes in the two treatment arms. All 95% CI resulting from the comparison of subgroups or pooled subgroups were within the equivalence margin]-0.4%, 0.4%[.
In summary all results from the sensitivity analyses (considering the comparison of subgroups, homogeneity of treatment effects across strata, violations of the model assumptions, and baseline

imbalances) support the result of primary analysis The frequency of subjects with HbA1c ≤ 6.5 % was similar in the two treatment arms: At the study endpoint 27.78 % of the at breakfast arm and 33.77 % of the at main meal arm showed an individual HbA1c ≤ 6.5 % for the per-protocol set (p = 0.2094, CMH tests). Moreover, at baseline (visit II) more patients of the main meal arm (9.1%) already had an HbA1c ≤ 6.5%, compared to the breakfast arm (7.4%).

The two study insulin glulisine treatment regimens differed more obvious in some effects on the circadian blood glucose level. The mean change of BG 2h-pp after dinner, that of BG at bedtime and that of nocturnal BG was obviously less positive in the at breakfast arm as compared to the at main mealtime arm. In contrast, the mean change of blood glucose 2h-pp after breakfast and at lunchtime was clearly more positive in the at breakfast treatment arm as compared to the at main mealtime treatment arm. The results demonstrate a temporary blood glucose control that was most effective in the circadian period following the individual time of study insulin glulisine injection.

For the at breakfast injection group the BG control was more sufficient particularly during the morning until lunchtime period and for the at main mealtime group the BG control was more sufficient particularly during the after dinner and nocturnal period. However, the accumulated blood glucose parameters mean daytime BG, mean daily BG as well as mean 2h-postprandial BG after insulin glulisine injection were very similar for the two insulin glulisine treatment regimens and did not show any relevant differences.

In conclusion, the total effect on long-term and circadian blood glucose control can be assumed to be very similar for the two insulin glulisine treatment regimens.

Results – Safety

Hypoglycemia

The analyses of the on-treatment hypoglycemic events demonstrate that the individual risk of hypoglycemic events was comparable for the two insulin glulisine treatment arms. A comparable number of patients treated at breakfast (86 (43.88 %) and of those treated at main mealtime (89 (45.18 %) experienced hypoglycemia (p = 0.8571, CMH test). In contrast, the total number of hypoglycemic events differed more (at breakfast: N = 385, at main mealtime: N = 469) and the corresponding mean of hypoglycemic events per subject year was lower for subjects treated at breakfast (4.76 ± 9.69) as compared to the subjects treated at main mealtime (5.34 ± 13.44) (p = 0.7012, ANOVA).

With regard to the different characteristics of hypoglycemic events most types of hypoglycaemic events occurred in a similar frequency in the two treatment arms. The total number of severe hypoglycemic events was low in the two treatment arms: 2 (1.02 %) subjects in the at breakfast arm and 5 (2.54 %) subjects in the at main mealtime arm (p=0.2708, CMH test). Almost all hypoglycemic events were non-severe without any clear difference of the frequency between the two treatment arms (p = 0.9348). Asymptomatic and nocturnal hypoglycemic events (confirmed by blood glucose measurement ≤ 60 mg/dl) differed more between the two treatment arms with a lower number of events per subject year for the at breakfast arm as compared to the at main mealtime arm (all p-values > 0.05%, CMH test or ANOVA).

In general, the two treatment arms revealed differences with regard to the circadian time of the occurrence of hypoglycemia. For those subjects treated at breakfast the relative number of

hypoglycemia was higher during the morning to lunchtime period between 9:00 am and 1:00 pm am as compared to those subjects treated at main mealtime. These subjects experienced a higher relative number of hypoglycemia during the afternoon to evening period between 6:00 pm and 11:00 pm. Thus, for the two treatment arms the individual risk of hypoglycemic events seems to be potentially higher during the circadian period after the injection of the study insulin.
The two treatment regimes of study insulin glulisine can be assumed to be comparable with regard to the global risk of hypoglycemic events. The results show no evidence for any obviously higher risk of hypoglycemic events depending on the insulin glulisine treatment regimen. Injection at breakfast did not increase the incidence of any type of hypoglycemic event or the individually experienced total number of events: The incidence and frequency of all types of hypoglycaemia were lower in the subjects treated at breakfast as compared to those treated at main mealtime.

Adverse events
The percentage of subjects with TEAE was similar for the two treatment regimens during the ontreatment
phase with study insulin glulisine. The overall incidence was 169 TEAEs in 87 of the subjects (44.39 %) treated at breakfast and 161 TEAEs in 92 of the subjects (46.70 %) treated at main mealtime. With regard to primary MedDRA® SOCs and preferred terms the relative incidences of TEAEs were similar in the two treatment regimens. Some of the MedDRA® SOC were slightly more frequently affected in the at breakfast arm (nervous system disorders, skin and subcutaneous tissue disorders, metabolism and nutrition disorders), some others were slightly more frequently affected in the at main mealtime arm (general disorders and administration site conditions, cardiac disorders). However, these differences were not much pronounced. The most frequently reported TEAE were nasopharyngitis (at breakfast: 5.61 %, at main mealtime: 6.09 %), bronchitis (at breakfast: 3.06 %, at main mealtime: 2.03 %), hypertension (at breakfast: 3.06 %, at main mealtime: 2.03 %) and back pain (at breakfast: 1.53 %, at main mealtime: 2.54 %).
Almost all of the TEAEs were reported without casual relationship to the study insulin and did not lead to premature termination of treatment with study insulin. A low number of TEAE were reported as being possibly related to the study insulin glulisine treatment: N = 2 (1.02 %) subjects treated at breakfast and N = 4 (2.03 %) subjects treated at main mealtime. The only possibly related TEAE reported more than once was weight increase that was reported for two subjects.
During the on-treatment phase 17 serious adverse events were reported in 10 (5.10 %) subjects treated at breakfast and 24 serious adverse events were reported in 18 (9.14%) subjects treated at main mealtime. No death was documented during this study. Only one of the serious TEAEs (hypoglycemia) experienced by one subject treated at main mealtime was assessed as being possibly related to the treatment (in addition, one further hypoglycemia was classified as serious but was not related to the treatment). TEAEs leading to withdrawal were rare and the number was comparable between the two treatment regimens. Withdrawal due to an TEAE occurred for N = 3 (1.52 %) subjects treated at breakfast and 2 (1.01 %) subjects treated at main mealtime.
The safety evaluation concerning vital signs and laboratory values did not reveal relevant findings.
In summary, the results of the safety analyses demonstrate the safe and well tolerated treatment with the study insulin glulisine once per day independent from the individual time of insulin glulisine injection (breakfast or main mealtime). The results reveal no evidence for an obvious different incidence of adverse events or adverse drug reactions between the two insulin glulisine treatment

regimens. The overall risk was explicitly not increased for subjects treated at breakfast as compared to those subjects treated at main mealtime with insulin glulisine.

Results Quality-of-life

Not applicable

Report Date

12 October 2007