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| **Sponsor/company:** | sanofi-aventis | **ClinialTrials.gov Identifier:** | NCT00174668 |
| | | **Study Code:** | HMR1964A_3504 |
| **Generic drug name:** | Insulin Glulisine | **Date:** | 27 November 2008 |

## Title

52-week, open, randomized, multinational, multicenter clinical trial comparing insulin glulisine in combination with insulin glargine in an intensified insulin regimen to a two-injection conventional insulin regimen in type 2 diabetes mellitus patients with poor glycemic control pretreated with a two-injection conventional insulin therapy.

## Investigator(s), study site(s)

66 centers in 16 countries participated in this study. The countries and numbers of centers in each country were: Australia (3), Belgium (3), Czech Republic (3), France (6), Germany (18), Ireland (0), Italy (2), Netherlands (1), Poland (4), Portugal (2), Romania (4), Slovakia (6), Spain (4), Sweden (3), Switzerland (1), and United Kingdom (6).

## Study duration and dates

The first patient was enrolled on 30 September 2004 and the last patient completed the study on 25 October 2007.

**Phase** IIIb

## Objectives

### Primary objective:

The primary study objective was to demonstrate superior efficacy of an intensified insulin regimen with insulin glulisine and insulin glargine to a two-injection conventional insulin regimen in terms of change in glycated hemoglobin $A_{1c}$ ($HBA_{1c}$) from baseline to endpoint.

### Secondary objectives:

Secondary study objectives were to compare the intensified insulin regimen with insulin Glulisine and insulin glargine to a two-injection conventional insulin regimen in terms of blood glucose (BG) profiles (fasting, pre-/postprandial (ppBG), nocturnal), BG and $HBA_{1c}$ response rates (predefined), fasting plasma glucose, hypoglycemic events, adverse events, change of late diabetes complications, weight, body-mass-index, course of total daily insulin dose and adjustment, blood lipid profile, microalbuminuria, standard lab and quality of life/treatment satisfaction.

## Study design

Multicenter, multinational, active controlled, open-label, randomized (allocation ratio 1:1), parallel-group trial. 8 weeks qualification phase (Visit 1 to Visit4) and 52 weeks treatment phase (Visit 5 to Visit 25) with a predefined "forced titration regimen" (8 weeks) in two treatment groups:

- Study arm with mealtime insulin glulisine 3x daily and insulin glargine 1x daily subcutaneously (s.c.).
- Control arm with a two daily injection conventional insulin therapy s.c. (premixed insulin: NPH (70%) plus regular insulin or insulin aspart (30%)).

Stratification for and continuation of a possible additional previous metformin therapy.
Patients previously treated with metformin should continue this unchanged in dose and frequency.
Insulin titration in both arms to targets of fasting and pre-prandial BG values of ≤100 mg/dl (5.6 mmol/l) as well as insulin titration to targets of ppBG values of ≤135 mg/dl (7.5 mmol/l) in order to achieve the study goal of an $HBA_{1c}$ ≤6.5%.

## Number of patients planned

To get a number of 268 planned patients (134 patients in each group) 310 patients were randomized for evaluation of the primary efficacy.

## Inclusion criteria

Diabetes mellitus patients, type 2 with poor glycemic control pretreated with a two-injection conventional insulin therapy, $HBA_{1c}$ value between 7.5% and 11%, aged 18 to ≤75 years, and BMI ≤38 kg/m².

## Treatments

*Study group*: During active treatment phase mealtime insulin glulisine 3x daily (TID) s.c. 15 min before the start of a meal and insulin glargine 1x daily (OD) s.c. at any time (but every day at the same time) according to BG.

*Control treatment group*: During active treatment phase two daily injections of conventional insulin therapy with premixed insulin: NPH (70%) plus regular insulin or insulin aspart (30%) s.c. according to BG.

During qualification phase, two-injection conventional insulin therapy with NPH (70%) plus regular insulin or insulin aspart (30%), according to previous therapy (NPH plus regular insulin or NPH plus rapid acting insulin (insulin lispro or insulin aspart)). An additional previous metformin therapy was continued throughout the trial in both arms.

## Efficacy data

$HBA_{1c}$, $HBA_{1c}$ response rates (predefined), fasting plasma glucose, self monitored BG (SMBG) values, BG response rates (predefined), body weight/body mass index (BMI), fasting blood lipid profile, urine albumin, total daily insulin dose, adjustment of insulin, late diabetes complications, quality of life/treatment satisfaction (by using the Diabetes Treatment Satisfaction Questionnaire, DTSQ).

## Safety data

Adverse events, standard lab tests, urine pregnancy test, vital signs, physical examination incl. insulin injection sites, hypoglycemic events.

## Statistical procedures

### Efficacy:

The primary efficacy analysis investigated the change of $HBA_{1c}$ from baseline to endpoint. To demonstrate the superiority of an intensified insulin regimen with insulin glulisine and insulin glargine over a conventional insulin regimen in terms of better glycemic control ($HBA_{1c}$), an analysis of covariance (ANCOVA) was used. Corresponding 95% confidence intervals for the adjusted estimated treatment difference were calculated.
The analysis for all secondary variables was done in an exploratory manner.
The primary study population was the modified full analysis set with all randomized patients that received at least one dose of study medication and had both baseline and at least one $HBA_{1c}$ value during treatment available.

### Safety:

The safety data for all treated patients were evaluated in a descriptive manner.

## Interim analysis

To reassess the original assumptions for the sample size calculation a blinded data monitoring on the basis of the first 100 patients was performed on 06 December 2005. The result allowed to reduce the total number of patients to be randomized from 372 (186 per treatment group) to 268 (134 per treatment group).

## Results - Study patients and conduct

A total of 401 patients were screened and enrolled in the qualification phase of the study. Of these patients 376 continued the qualification phase. During this period patients who had been treated with premixed insulin prior to study start switched to NPH plus regular insulin (70/30) if the previous therapy was NPH plus regular insulin (30/70 or 25/75) or to NPH plus insulin aspart (70/30) if the previous therapy was NPH plus insulin aspart (30/70 or 25/75). Due to screening failures in 66 patients, finally 310 patients were randomized and treated with insulin study medication: 153 patients were randomized to the glargine + glulisine treatment and 157 to the NPH 30/70 treatment. 131 of the patients of the glargine + glulisine group completed the study and so did 134 of the NPH 30/70 group.
Both treatment groups were comparable regarding their demographic and clinical conditions.
The patients in both treatment groups were comparable with respect to their history of type 2 Diabetes mellitus and their actual situation concerning diabetic late complications.
The baseline $HbA_{1c}$ at the beginning of the treatment phase (Visit 5) was homogeneous for the two treatment groups.
The frequencies of previous and concomitant diseases and surgeries were similar in both treatment groups.
The baseline daily dose of insulin was slightly lower in the glargine + Glulisine group (52.91 ± 23.45 IU (25.64 ± 13.46 IU glargine and 27.27 ± 12.11 IU glulisine)) than in the NPH 30/70 group (58.38 ± 26.80 IU). During the first 8 weeks of the treatment phase (= forced insulin titration period) the mean daily insulin dose was comparable. In the subsequent treatment period (= titration fine tuning period) the mean daily dose of insulin was higher in the glargine + glulisine group than in the NPH 30/70 group. The baseline to endpoint difference in mean daily insulin dose in the glargine + glulisine group was 45.08 ± 37.03 IU (19.34 ± 18.93 IU glargine and 25.99 ± 21.84 IU glulisine)and in the NPH 30/70 group 32.96 ± 30.50 IU. About 55-60% of the patients were treated with metformin in each of the treatment groups.

## Results Efficacy

The primary efficacy variable was the change in glycated hemoglobin ($HbA_{1c}$) from baseline to study endpoint. The superiority of glargine + glulisine versus a NPH 30/70 treatment regimen was significantly demonstrated in the modified full analysis set for the change in $HbA_{1c}$ from baseline to endpoint (adjusted means: -1.19% for the glargine + glulisine treatment group, -0.71% for the NPH 30/70 treatment group, difference: -0.48%, two-sided p = 0.0001). The supportive analysis of the primary endpoint in the per-protocol analysis set and the completers analysis set confirmed the results of the primary efficacy analysis.

At the endpoint clearly more patients in the glargine + glulisine treatment group (46.58%) reached the pre-defined target of $HbA_{1c}$ response ($HbA_{1c}$ ≤7.0%) than in the NPH 30/70 treatment group (27.92%, p = 0.0004, Cochran-Mantel-Haenszel test (CMH)). The frequency of $HbA_{1c}$ responders without nocturnal hypoglycemia at endpoint was more pronounced in the glargine + glulisine treatment group (26.03%) than in the NPH 30/70 treatment group (12.99%, p = 0.0031, CMH) as well as the frequency of $HbA_{1c}$ responders without confirmed/severe symptomatic nocturnal hypoglycemia was higher in the glargine + glulisine treatment group (31.51%) than in the NPH 30/70 treatment group (18.83%, p = 0.0063, CMH, modified full analysis set).
Further analyses of secondary objectives showed a baseline to endpoint decrease in all short-term metabolic variables (FPG, FBG, nocturnal BG, mean daytime BG, mean daily BG, mean preprandial BG, mean post-prandial BG, 8-point 24 hour BG profile) in both treatment groups. The mean decrease in nocturnal BG was similar in both treatment groups. The mean decreases in FPG, FBG and pre-prandial BG were slightly more pronounced in the glargine + glulisine treatment group than in the NPH 30/70 treatment group, but these treatment differences were not statistically significant. The mean decreases in mean daytime BG, mean daily BG and postprandial BG were more pronounced in the glargine + glulisine treatment group than in the NPH 30/70 treatment group (p < 0.05).
The course of circadian blood glucose regulation was different between the treatment groups at dinner and during the post-prandial periods. The mean decrease of blood glucose was clearly more pronounced in the glargine + glulisine treatment group than in the NPH 30/70 treatment group after breakfast (p = 0.0240), after lunch (p < 0.0001) and after dinner (p = 0.0003). Also at dinner time the treatment specific difference of blood glucose was clearly more pronounced in the glargine + glulisine treatment group (p = 0.0380). At night, in the morning, at lunch time and at bedtime the treatment group-specific differences of the changes in blood glucose were not statistically meaningful (p >0.05).
The mean increase in body weight and BMI was higher in the glargine + glulisine treatment group (weight: 3.59 kg, BMI: 1.26 kg/m²) than in the NPH 30/70 treatment group (weight: 2.19 kg, BMI: 0.81 kg/m², p = 0.0073 for weight and p = 0.0144 for BMI).
Mean cholesterol, LDL and triglycerides hardly changed from baseline to endpoint in both treatment groups (p>0.05 in both treatments for comparison between baseline and endpoint), while mean HDL decreased in both treatment groups (p < 0.05). In all these fasting lipid parameters there was no obvious difference between the treatment groups of the baseline to endpoint changes (p > 0.05).
Albumin in morning urine was measured to assess grade of microalbuminuria. The mean urinary albumin increased in both treatment groups between baseline and endpoint. The mean increase was not statistically different (p = 0.4815) between the glargine + glulisine treatment group (+22.89 mg/l, p = 0.0120) and the NPH 30/70 treatment group (+14.76 mg/l, p = 0.1849).
At the beginning of the study the situation concerning diabetic late complications was comparable between the treatment groups (p = 0.1138, CMH). 68.63% of the patients in the glargine + glulisine treatment group and 60.51% of the patients in the NPH 30/70 treatment group suffered from diabetic late complications. Diabetic neuropathy was the most common diabetic late complication followed by diabetic retinopathy and diabetic macroangiopathy in both treatment groups. At the end of the study the situation concerning diabetic late complications had hardly changed between the treatments (p =0.0516, CMH).

## Results Safety

### Hypoglycemia

About 25 to 30% of the patients experienced hypoglycemic events during the qualification phase and only one patient in the NPH 30/70 treatment group experienced two hypoglycemic events in the post-treatment period.
During the treatment phase the number of patients with hypoglycemic events was similar in both treatment groups (75.82% versus 73.89%, p = 0.5641, CMH). The total number of hypoglycemic events and the mean number of hypoglycemic events per patient were lower in the glargine + glulisine treatment group (n = 1972, 12.89 events per patient) than in the NPH 30/70 treatment group (n = 2760, 17.58 events per patient, p = 0.1919).
For all types of hypoglycemic events, the number of affected patients was similar in both treatment groups, while the number of hypoglycemic events or the number of hypoglycemic events per patient year was lower in the glargine + glulisine treatment group than in the NPH 30/70 treatment group. However, the treatment differences for hypoglycemic events per patient or per patient year were not statistically different (p > 0.05, ANOVA). In both treatment groups most of the hyperglycemic events were non-severe (about 75% in each treatment group), confirmed by BG ≤60 mg/dl (about 70% in each treatment group) and/or symptomatic (about 65% in each treatment group). About 40% of the patients experienced nocturnal hypoglycemic events in each treatment group.

### Adverse events

The frequency of patients with adverse events during the treatment phase was comparable in both treatment groups. In the glargine + glulisine treatment group 90 patients (58.82%) experienced 328 adverse events and in the NPH 30/70 treatment group 95 patients (60.51%) experienced 371 adverse events. Most of the adverse events described infectious diseases or its symptoms in both treatment groups.
Possibly related treatment emergent adverse events were reported more frequently in the glargine + glulisine treatment group than in the NPH 30/70 treatment group: 19 adverse events in 15 patients (9.80%) versus 7 adverse events in 6 patients (3.82%).
The frequency of adverse events leading to withdrawal was higher in the glargine + Glulisine treatment group (9 events in 7 patients (4.58%)) compared to the NPH 30/70 group (4 events in 3 patients (1.91%)).
A similar number of serious adverse events was reported in both treatment groups. In the Glargine + glulisine treatment group 26 patients (16.99%) experienced 35 serious adverse events and in the NPH 30/70 treatment group 24 patients (15.29%) experienced 37 serious adverse events. Five of the reported serious adverse events (3 cases of hypoglycaemia, oedema peripheral, transient ischaemic attack) were assessed to be related to the glargine + glulisine study medication and one serious adverse event (hypoglycemia) was assessed to be related to the NPH 30/70 study medication. During the treatment phase one patient of the glargine + glulisine treatment group died (sudden death) and one patient of the NPH 30/70 treatment group died (colon neoplasm, intestinal operation). None of these adverse events that resulted in death were assessed as possibly related. Additionally, three patients died during the pre-treatment phase (myocardial infarction, completed suicide, sudden death.
The safety evaluation concerning vital signs and laboratory values did not reveal any relevant findings for the glargine + glulisine treatment group or the NPH 30/70 treatment group.

## Results - Quality-of-life

The mean baseline to endpoint improvement of the total score for diabetic treatment satisfaction seemed to be more pronounced in the glargine + glulisine treatment group than in the NPH 30/70 treatment group, but this difference was not statistically confirmed (p = 0.1386). The single item for the assessment of feeling unacceptably high blood glucose was slightly more improved for the glargine + glulisine group compared to the NPH 30/70 group. Also this treatment difference was not statistically confirmed (p = 0.0906).

## Date of Report

29-Oct-2008