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Sponsor/company:	Sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00354939
		Study Code:	HOE901_4049
Generic drug name:	Insulin glargine	**Date:**	28 June 2007

STUDY SYNOPSIS

Study number HOE 901_4049

Title

SAFIR: 10-week, open, national, multicenter clinical trial to evaluate the **SAF**ety of HOE 901 insulin analogue in Type 2 Diabetes mellitus patients on **I**ntensified conventional therapy

Investigator(s), study site(s)

Multicenter: 125 centers in Germany
Coordinating Investigator: Prof R Zick, Lingen, Germany

Study duration and dates

The study took place between 01 October 2003 and 02 July 2004

Phase IV

Objectives

The primary objective of the study was to evaluate the difference in frequency of subjects with conventionally detected hypoglycemia through the subject compared to CGMS (continuous glucose measurement system) detected blood glucose values ≤ 60mg/dl [3.3 mmol/l] during CGMS measurement period after 8 weeks treatment with insulin glargine. Secondary objectives were to show the safety and efficacy of a treatment change to insulin glargine in subjects on intensified conventional therapy.

Study design

This study was an open, single-arm, national, multicenter clinical trial to evaluate the safety of insulin glargine in Type 2 diabetic patients on intensified conventional therapy (ICT) using the CGMS device from Medtronic MiniMed®.
The study consisted of a 2-week run-in phase followed by an 8-week insulin glargine treatment phase.

During the run-in phase subjects received basal NPH insulin (neutral protamine Hagedorn).
Thereafter, treatment was converted to insulin glargine with clinical visits at Week 0 + 3 days, Week 4, Week 4 + 3 days, Week 8 and Week 8 + 3 days (final examination). Intermediate phone contacts were scheduled at Week 2 and Week 6.

Number of subjects planned

Approximately 480 subjects were to be enrolled. It was assumed that at least 65% of the subjects were evaluable in a full analysis set evaluation.

Inclusion criteria

Type 2 diabetes mellitus patients aged ≥ 18 and ≤ 75 years, on stable treatment with NPH insulin and mealtime insulin for at least 3 months, with HbA_{1c} values ≤ 8.0% and able to perform continuous & self monitoring blood glucose profiles at home.

Treatments

During screening subjects continued with their previous individually titrated basal NPH insulin therapy (once or twice a day) in combination with at least one injection of mealtime insulin (either regular or short acting). During the 8-week treatment phase basal NPH insulin was replaced by insulin glargine, which was individually titrated according to a recommended predefined titration regimen to target fasting blood glucose (FBG) ≤ 100mg/dl.

Primary objective

Primary objective: difference in frequency of subjects with conventionally detected hypoglycaemia by the subject [at least one measurement ≤ 60mg/dl documented in the 8-point profile in the case record form (CRF) or documentation of symptomatic hypoglycemia in the CRF through Visits 8/9] compared to CGMS detected blood glucose values ≤ 60mg/dl during CGMS measurements (at least one measurement through Visits 8/9) after eight weeks of treatment with insulin glargine.

Safety data

Adverse events reported by the subject or noted by the investigator; vital signs.

Statistical procedures

The primary variable was compared using a confirmatory two-sided McNemar test of symmetry. The error level was fixed to α=0.05. The confirmatory analysis was performed on the full analysis set (FAS) population. In addition a descriptive analysis of the primary variable was presented which additionally included a 95% confidence limit for the percentage of subjects with hypoglycemia detected conventionally or hypoglycemic blood glucose values detected by CGMS.

The same analysis was performed exploratory on the per-protocol (PP) population for sensitivity purposes. Also for sensitivity the primary analysis (FAS) was repeated:

- After exclusion of all CGMS measurements, for which based on the CGMS optimal accuracy criteria were not fulfilled.
- After exclusion of all subjects receiving metformin as concomitant medication.

All secondary variables were analyzed descriptively either by sample statistics or contingency
tables.
All safety analyses were performed descriptively and were based on the safety analysis set (SAF).

Interim analysis

No interim analysis was performed.

Results - Study subjects and conduct

A total of 479 subjects were enrolled into the study and received study treatment. Of these, 447 (93.3%) subjects completed the study and 32 (6.7%) discontinued prematurely. The mean actual duration of treatment exposure to NPH insulin was 18.8 days. Subjects' exposure to insulin glargine was 59.5 days for patients who completed the entire study and 30.3 days for patients with premature discontinuation.

A total of 42 major protocol deviations in 40 subjects were documented in the full analysis population leading to an exclusion from the per-protocol analysis. NPH or mealtime insulin treatment less than 3 months before study start was reported as the most prominent reason (16 subjects), followed by prohibited concomitant medication (10 subjects), NPH insulin applied more than twice a day (8 subjects), $HbA_{1c} > 8\%$ (5 subjects) and instable ICT (3 subjects). All 479 subjects suited for study participation received at least one dose of study medication and were analyzed in the safety analysis set. Out of these, 112 subjects were identified as non evaluable due to the fact that no valid baseline or no valid post baseline CGMS data sets were available. The remaining 367 subjects were included into the full analysis set. The per-protocol analysis set included all subjects of the full analysis set, excluding those with major protocol deviations. This was the case in 40 subjects, thus leading to a per-protocol analysis set comprising 327 subjects.

The demographic characteristics were very similar in all of the different sets analyzed. The frequency of male subjects was somewhat higher compared to female subjects. Mean values with respect to subjects' age, weight and body mass index were symptomatic for a Type 2 diabetic subject population: mean age approaching 60 years and relevant elevation of mean body mass index to values of approximately 32 kg/m^2.

Results - Efficacy

Primary objective of the study was the difference in frequency of subjects with conventionally detected hypoglycemia by the subject compared to CGMS detected blood glucose values $\leq$ 60mg/dl during CGMS measurements after 8 weeks of treatment with

insulin glargine. At study endpoint, CGMS data evaluation revealed a proportion of 56.9% of the subjects with blood glucose values ≤ 60 mg/dl, whereas a considerably lower frequency (26.4%) of subjects with hypoglycemic events was identified by the 8-point profile measurement or subjects' individual documentation of symptomatic hypoglycemia in the CRF (corresponding percentages for baseline assessment were 52.9% versus 27.8%).

In 123 subjects (33.5%) at least one blood glucose value ≤ 60 mg/dl was detected with CGMS at Last Visit, but no hypoglycemic event was documented for the same time period with the conventional method. On the other hand there were only 11 subjects (3.0%) with conventionally detected hypoglycemia without any blood glucose value ≤ 60 mg/dl during the concomitant CGMS measurement.

The confirmatory analysis (McNemar test) showed significant differences between CGMS and 8-point profiles/documentation of symptomatic hypoglycemia with respect to the detection of hypoglycemic events with a p-value of <0.0001. The 95% confidence interval for the risk difference of 0.3052 was 0.2373 to 0.3730.

The analysis of several secondary objectives revealed a slight tendency towards increasing frequencies of hypoglycemic values between Baseline Visit and Last Visit (analysis of the percentage of hypoglycemia determined by CGMS, area under the curve and time, frequency of subjects with notable blood glucose measurements). Mean blood glucose values were reduced at all time-points of the 8-point-profile between Baseline Visit and Last Visit. Mean nocturnal blood glucose values were considerably lower at each time-point when analyzed by CGMS compared to the 8-point-profile in contrast to daytime blood glucose for which almost identical values were obtained from both CGMS and 8-point-profile measurement. In each case, blood glucose was reduced between Baseline Visit and Last Visit (p = <0.001, paired 2-sided t-test). Fasting blood glucose decreased by 10.1±27.8 mg/dl with a p-value of <0.001 for changes between Baseline Visit and Last Visit.

The initial HbA_{1c} value of 6.91±0.72% at Visit 1 was reduced during the overall study duration of 10 weeks. A mean change of -0.23±0.64% led to final value 6.67±0.80% at Visit 9 (p <0.001).

This reduction resulted in a response rate ($HbA_{1c} \leq 7\%$) of 43.3% of those subjects whose baseline values exceeded the threshold value of $HbA_{1c} \leq 7\%$. A minor rate of response resulted from the analysis of fasting blood glucose at endpoint (8.5%).

The initial dose of insulin glargine at Visit 3 (24.2±15.2 IU) constantly increased during all study visits leading to a final daily dose of 30.4±19.1 IU at the Last Visit.
Body weight and body mass index slightly increased by 0.36±2.50 kg and 0.12±0.86, respectively.

Results - Safety

The frequency of subjects affected by adverse events was generally low. During the 2-week run-in phase with NPH insulin and the 8-week treatment phase with insulin glargine, 37 (7.7%) and 115 (25.3%) of the subjects experienced adverse events.

MedDRA primary system organ classes with frequencies of >5% of subjects under insulin glargine affected by adverse events were infections and infestations (7.7%) and general disorders and administration site conditions (5.5%). The majority of adverse events was restricted to single subjects only. Among all adverse events, only 4 MedDRA preferred terms were identified with frequencies of >1%, none of them as 'possibly related' to study treatment. Most frequent treatment emergent adverse event was influenza like illness reported in 4.2% of the subjects during treatment with insulin glargine, followed by bronchitis (1.8%), respiratory tract infection (1.5%) and diarrhea (1.1%).

Treatment emergent adverse events with an intensity assessment of 'severe' were restricted to 1 single case under treatment with NPH insulin (hypoglycemic coma) and to 13 cases under treatment with insulin glargine (acute myocardial infarction, eye disorder, ascites, small intestine ulcer, drug chemical incompatibility, hepatic cirrhosis, bronchitis, back pain, spondyloarthropathy, carcinoma, hyperhidrosis, joint prosthesis user and hypertensive crisis).

Adverse events were assessed as possibly drug related by the investigators during treatment with NPH insulin and during treatment with insulin glargine in 5 subjects each. For NPH, the events were: seasonal allergy (itching, rash), arrhythmia, muscular weakness, skin reaction and hypoglycemic coma. For insulin glargine, the events were: arrhythmia, weight increased, exanthem and hyperhidrosis twice.

In total, 3 subjects experienced a serious adverse event during treatment with NPH insulin and 13 subjects during treatment with insulin glargine. No accumulation of any specific adverse event was observed. A possible relationship to therapy was rated for the serious adverse events 'arrhythmia' for one patient during treatment with NPH insulin and for another patient during treatment with insulin glargine, 'hypoglycemic coma' (during treatment with NPH insulin) and 'muscular weakness' (during treatment with NPH insulin).

During treatment phase with insulin glargine, one serious adverse event (hepatic cirrhosis) led to death of the subject (center 12, subject 4). A relationship to the study treatment was not assumed.

In total, 5 subjects prematurely discontinued the study due to the occurrence of adverse events, 3 subjects during NPH insulin treatment (2 cases of seasonal allergy, road traffic accident) and 2 subjects during treatment with insulin glargine (osteoarthropathy, carcinoma).

Symptomatic hypoglycemia was reported by 24.4% of the subjects during the 2-week screening period with NPH insulin treatment and by 38.9% of the subjects during the 8-week active treatment period with insulin glargine. Severe symptomatic hypoglycemia occurred in only 3 subjects each during treatment with NPH insulin and insulin glargine. The mean number of episodes of overall symptomatic hypoglycemia per subject during NPH insulin treatment and treatment with insulin glargine was 0.46±1.03 and 1.32±3.11, respectively, of nocturnal symptomatic hypoglycemia 0.15±0.50 and 0.30±0.97 and of daytime symptomatic hypoglycaemia 0.32±0.79 and 1.01±2.77. A longer mean duration of symptomatic hypoglycemia was determined for subjects during NPH insulin treatment (37.8±58.0 min versus 31.0±27.9 min). This was also the case for nocturnal (32.4±40.6 min versus 29.1±21.1 min) and daytime symptomatic hypoglycemia (39.6±61.3 min versus 32.6±30.9 min).

Date of report
14 April 2005