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Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00311818
		Study Code:	HOE901_4040
Generic drug name:	insulin glargine	**Date:**	15 October 2007

Title

44-week, parallel, open, randomized, multinational, multi-center clinical trial to compare efficacy and safety of the combination therapy of an oral anti-diabetic drug treatment with either HOE901 insulin once daily or Lispro insulin analogue at mealtime in Type 2 Diabetes mellitus patients poorly controlled with oral anti-diabetic drug treatment

Investigator(s), study site(s)

67 centers (69 center numbers) in 10 countries participated in this study. Center numbers 205 and 912 as well as 305 and 913 were allocated to one center at a time. The countries and numbers of centers in each country were: Australia (3), Austria (7), Denmark (5), Germany (28), Italy (7), Netherlands (3), Norway (5), Poland (5), Spain (3), and Switzerland (3).

Study duration and dates	The first subject was enrolled on 25 June 2003 and the last subject completed the study on 31 May 2005.	**Phase**	IV

Objectives

Primary objective:
To compare efficacy of OAD combination therapy with either HOE901 insulin analogue once daily or Lispro insulin analogue at mealtime in terms of change in HbA_{1c} (baseline to endpoint).

Secondary objectives:
To compare the OAD combination therapy with either HOE901 insulin analogue once daily or Lispro insulin analogue at mealtime in terms of:

Efficacy:

- Frequency of subjects with HbA_{1c}: ≤ 6.5 %, 6.5 %< HbA_{1c} ≤ 7.0 %, 7.0 %<HbA_{1c} ≤ 8.0 % and HbA_{1c} > 8.0 % at endpoint

- Change in fasting blood glucose, FBG (baseline to endpoint)
- Frequency of subjects with: FBG ≤ 100 mg/dl (5.5 mmol/l), 100 mg/dl < FBG ≤ 126 mg/dl(7.0 mmol/l) and FBG > 126 mg/dl (7.0 mmol/l) at endpoint
- Change in nocturnal blood glucose (baseline to endpoint)
- Change in mean daytime blood glucose (baseline to endpoint)
- Change in mean daily blood glucose (baseline to endpoint)
- Change in blood glucose at the remaining time points of the 8-point-blood glucose profiles (baseline to endpoint)
- Change in fasting plasma glucose (baseline to endpoint and all visits)

Safety:

- Frequency of subjects with hypoglycemic events (overall, severe, nocturnal, symptomatic)

Subgroup analysis by region/country

Quality of life – patients' satisfaction

Dose of insulin

Adjustment of insulin

Body weight, body mass index

NEFA (measured at 10 German centers)

Lipid profile – cholesterol – total, HDL and LDL; triglyceride

Study design

Open, parallel, multi-center, multinational, randomized clinical trial. The study consisted of an up to 4 weeks screening phase followed by a 44 weeks treatment phase.

Number of subjects planned

To get a number of 334 planned subjects (167 subjects in each group) 420 subjects were randomized for evaluation of the primary efficacy.

Inclusion criteria

Diabetes mellitus patients, type 2, poorly controlled with oral anti-diabetic drug treatment (approved in combination with insulin according to local SPCs, not including use of a-glucosidase inhibitors) with HbA_{1c} value between 7.5 % and 10.5 % and FBG ≥ 120 mg/dl (6.6 mmol/l), age ≤ 75 years, and BMI ≤ 35 kg/m^2

Treatments

Subjects enrolled in this study failed in good metabolic control with OAD treatment and needed insulin to recover good metabolic control, $HbA_{1c} \leq 6.5$ %, according to current guidelines and requirements of Scientific Diabetes Societies (low cardiovascular risk according to the European Diabetes Policy Group).
Subjects were allowed to be previously OAD treated with any OAD(s) (approved in combination with insulin according to local SPCs, not including use of α-glucosidase inhibitors) at a stable dose for at least 3 months prior to study entry.
Insulin therapy was performed as a combination of previous OAD(s) in addition to either one injection of basal insulin (once daily, but every day at the same time) or short acting insulin at mealtime 3x daily.
During the screening phase at visit II, all subjects on sulfonylurea switched their sulfonylurea to the equivalent dose of glimepiride or continued with their previous glimepiride dose. The doses of all other OAD(s) were continued during the screening phase.
Subjects who were randomized to the combination therapy of HOE901 insulin analogue continued the OAD(s) in a stable dose at baseline (week 0) and started treatment with the addition of HOE901 insulin analogue (once daily, but every day at the same time). The HOE901 insulin analogue was titrated individually according to a predefined titration regimen to target FBG ≤ 100 mg/dl (5.5 mmol/l) (European Diabetes Policy Group).
Subjects who were randomized to the combination therapy of Lispro insulin analogue also continued the OAD(s) in a stable dose at baseline (week 0) and started treatment with the addition of Lispro insulin analogue at mealtime. The Lispro insulin analogue was titrated individually according to a predefined titration regimen to target pre-prandial glucose ≤ 100 mg/dl (5.5 mmol/l) and post-prandial glucose ≤ 135 mg/dl (7.5 mmol/l) (European Diabetes Policy Group; Ref. A desktop guide to Type 2 diabetes mellitus. European Diabetes Policy Group 1999.) Diabet Med. 1999 Sep; 16(9):716-30.)

Primary efficacy data:

- Change in HbA_{1c} from baseline to study endpoint

Secondary efficacy data:

- Response rates calculated from HbA_{1c} and FBG values
- Fasting blood glucose, nocturnal blood glucose, mean daytime blood glucose values, mean daily blood glucose values and 8-point blood glucose profile values
- Fasting plasma blood glucose values
- Daily insulin dose

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

Quality-of-life data were generated using the Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Statistical procedures

The primary analysis variable was the change in glycated hemoglobin- HbA_{1c} from baseline to study endpoint for each individual subject.
Treatment comparison of the changes in HbA_{1c} was done by confidence interval approach. Therefore, one-sided (97.5 %) confidence intervals were calculated for the treatment difference of the changes in HbA_{1c}. The two treatment groups were considered as therapeutically equivalent (i.e. HOE901 not inferior to Lispro) if the corresponding confidence interval was totally included in the one-sided equivalence region, i.e. the upper limit of the confidence interval was below $\varepsilon = 0.4$ %. The non-inferiority analysis was based on the per-protocol analysis set. After having demonstrated non-inferiority an additional superiority test (upper limit of confidence interval < 0) was done on the full analysis set. These analyses were interpreted in a confirmatory manner. The one-sided confidence limits for the non-inferiority test were calculated by using an analysis of covariance (ANCOVA) with treatment group, country and current metformin intake as fixed effects and the corresponding baseline value of HbA_{1c} as a covariate. Prerequisites of the ANCOVA were checked by adequate statistical methods.
A non-inferiority analysis was also conducted for the full analysis set and the completer's analysis set, and superiority analysis was also performed for the per-protocol and the completer's analysis set. These results were interpreted in a descriptive manner.
For all continuous secondary variables, the same ANCOVA was performed as for the primary variable. Categorical secondary variables were analyzed using Cochran-Mantel-Haenszel (CMH) tests adjusting for country and current metformin intake. All secondary objective variables were analyzed based on the full analysis set and the per-protocol analysis set. The rate of subjects with hypoglycemic episodes and number of episodes were analyzed based on the insulin safety population.
For the analyses of vital signs and laboratory values ANCOVA was used. The (L)PCAs of laboratory values and vital signs were analyzed using Fisher's exact test. Safety analyses were descriptive.
A subgroup analysis by country, type of concomitant OAD treatment, gender, age categories and BMI categories was conducted for HbA_{1c}, FBG, mean daytime blood glucose and frequency of subjects with hypoglycemia to identify potentially varying results in the subgroups.

Interim analysis

No interim analysis was performed.

Results - Study subjects and conduct

At total of 611 subjects was enrolled in the pre-screening phase of the study to confirm eligibility of subjects with regard to HbA_{1c}. Of these subjects 477 continued in the screening phase. During

this period patients who had been treated with other sulfonylurea urea derivatives prior to the study start switched to glimepiride. Finally, 415 subjects were randomized and treated with insulin study medication: 205 subjects were randomized to the HOE901 plus OAD treatment and 210 to the Lispro plus OAD treatment, 185 of the subjects of the HOE901 group completed the study and 182 of the Lispro group did so respectively.
Both treatment groups were comparable as regards demographic and anamnestic conditions.
The subjects in both treatment groups were comparable with respect to their history of type 2 Diabetes mellitus and to their actual situation concerning diabetic late complications.
The baseline HbA_{1c} value at the beginning of the screening phase (visit I) and the insulin treatment phase (visit III) was homogenous for the two treatment groups.
The frequencies of concomitant diseases and history of previous surgeries were similar in both treatment groups. Both treatment groups were comparable with regard to the daily dose of insulin, as well as with regard to the type and daily dose of concomitant OAD treatment during the study treatment period. More than 92 % of the subjects were treated with glimepiride and about 75 % were treated with metformin in both treatment groups.

Results - Efficacy

The primary efficacy variable was the change in glycated hemoglobin (HbA_{1c}) from baseline to study endpoint. The therapeutic equivalence (non-inferiority) of HOE901 once per day plus OAD treatment to Lispro three times per day at mealtime plus OAD was significantly demonstrated in the per-protocol analysis set for the change in HbA_{1c} from baseline to endpoint of the study.

A significant superiority of one of the two treatments for the change in HbA_{1c} could not be demonstrated in the modified full analysis set (difference: 0.1374 %; two-sided $p = 0.0908$).
In the modified full analysis set the adjusted mean baseline to endpoint reduction in HbA_{1c} was 1.69 % for the HOE901 treatment group and 1.82 % for Lispro treatment group. At the endpoint 58.00 % of the subjects of the HOE901 treatment group and 67.65 % of the subjects of the Lispro treatment group reached the pre-defined target of HbA_{1c} response ($HbA_{1c} \leq 7.0$ %). ($p = 0.0455$, CMH). These results were confirmed by the results of the per-protocol and the completer's 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, 8-point 24 hour BG profile) in both treatment groups.
In spite of similar long-term efficacy, both treatments feature different effects on the course of circadian blood glucose regulation. Whilst the HOE901 treatment provided superior blood glucose control during the night period and in the morning time the Lispro treatment provided a better control of postprandial rise of blood glucose particularly after the lunch and after the dinner period. The results of blood glucose monitoring at 3 o'clock and that of FBG were explicitly more improved in the HOE901 treatment group compared to the Lispro treatment group ($p = 0.0017$ and $p < 0.0001$ respectively). In contrast, the baseline to endpoint change of the blood glucose postprandial showed obviously less pronounced decrease among the HOE901 group compared to the Lispro group after breakfast ($p = 0.0421$), after lunch ($p < 0.0001$) and after dinner ($p < 0.0001$). At lunch and dinner time the treatment specific differences of blood glucose were comparable and less pronounced ($p > 0.05$).

In consequence of the improvement of the circadian blood glucose regulation both treatments resulted in a comparable control of blood glucose over the whole day. The baseline to endpoint decrease of mean daily blood glucose and that of mean daytime blood glucose were similar although the differences were clear between the treatment groups ($p < 0.05$).

Results - Safety

Hypoglycemia

In the on-treatment phase the percentage of subjects with any hypoglycemic events was impressively lower in the HOE901 plus OAD group (66.34 %) than in the Lispro plus OAD group (89.15 % ($p < 0.0001$, CMH).
In addition, the overall incidence of any hypoglycemic events and the mean number of hypoglycemic events per subject were definitely lower in the HOE901 treatment group (n= 876 events / 4.27 events per subject) than in the Lispro treatment group (n= 4125 events / 19.46 events per subject).

For all types of hypoglycemic events except nocturnal hypoglycemic events, the number of affected subjects as well as the number of hypoglycemic events or the number of hypoglycemic events per patient year was vastly lower in the HOE901 treatment group than in the Lispro treatment group. Clear differences could be demonstrated for the frequencies of non-severe events per patient year ($p < 0.0001$, CMH) as well as for frequencies of symptomatic ($p < 0.0001$, CMH) hypoglycemic events (whether confirmed by blood glucose measurement or not) and for the frequency of asymptomatic hypoglycemic events ($p < 0.0001$, CMH). The overall frequency of subjects with nocturnal hypoglycemic events was higher for the HOE901 treatment group. The difference was less pronounced for the nocturnal hypoglycemia confirmed by blood glucose measurement compared to the number of nocturnal hypoglycemic events overall. Whilst the difference between treatment groups was obvious for the overall number of reported nocturnal hypoglycemia ($p = 0.0280$; CMH), the difference was less striking for those events confirmed by blood glucose measurement ($p = 0.2557$; CMH). The corresponding analysis of the mean number of nocturnal hypoglycemic events per subject revealed a less pronounced difference between the two treatment groups. The mean of overall nocturnal hypoglycemic events per subject was 0.42 (HOE901) versus 0.27 (Lispro) and that of confirmed nocturnal hypoglycemic events was 0.25 (HOE901) versus 0.21 (Lispro ($p = 0.0709$ (overall nocturnal hypoglycemia) and $p = 0.5190$ (confirmed nocturnal hypoglycemia)).

The number of subjects with severe hypoglycemic episodes was lower in the HOE901 treatment group ($N = 5$) compared to the Lispro treatment group ($N = 11$) ($p = 0.1444$, CMH).

The percentage of subjects with adverse events during the insulin treatment phase was comparable in both treatment groups. In the HOE901 treatment group 135 subjects (65.85 %) experienced 421 adverse events and in the Lispro treatment group 124 subjects (58.49 %) experienced 453 adverse events.
Possibly related treatment emergent adverse events were reported in similar numbers in both treatment groups: 5 adverse events in 4 subjects (1.95 %) from the HOE901 treatment group and 6 adverse events in 5 subjects (2.36 %) from the Lispro treatment group had been reported.

Adverse events leading to withdrawal were rare; the frequency was lower in the HOE901 treatment group (N = 2 (0.98 %)) compared to the Lispro group (N = 4 (1.89 %)).

The safety evaluation concerning vital signs and laboratory values did not reveal any evidence for relevant findings for the HOE901 plus OAD treatment group or the Lispro plus OAD treatment group.

Results - Quality-of-life

The mean baseline to endpoint improvement of total score for diabetic treatment satisfaction was obviously more pronounced for the HOE901 treatment group compared to the Lispro group ($p < 0.0001$). Inaddition the single item for the assessment of feeling unacceptably high blood glucose was markedly more improved for the HOE901 group compared to the Lispro group ($p = 0.0036$). In contrast the single assessment of feeling unacceptably low blood glucose was obviously less aggravated for the HOE901 group compared to the Lispro group ($p < 0.0001$).

Date of report

6 January 2006