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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00783744
		Study Code:	HOE901_4027
Generic drug name:	Insulin Glargine	**Date:**	31 October 2008

Title

28-week, open, randomized, multinational, multicenter clinical trial to compare efficacy and safety of combination therapy of HOE901 insulin analogue plus glimepiride and metformin versus a two-injection conventional therapy with premixed insulin NPH 30/70 bid in type 2 diabetes mellitus patients poorly controlled with oral antidiabetic drug treatment.

Investigator(s), study site(s)

66 centers in 10 countries participated in this study. The countries and numbers of centers in each country were: Austria (5), Finland (1), France (4), Germany (35), Italy (5), Netherlands (3), Spain (5), Sweden (2), Switzerland (1), and United Kingdom (5).

Study duration and dates

The first subject was enrolled on 18 December 2001
The last subject completed the study on 27 August 2003.
Phase IIIb

Objectives

Primary objective:
To compare efficacy of combination therapy of HOE901 insulin analogue plus glimepiride and metformin versus 2 injections insulin monotherapy with premixed insulin NPH 30/70 bid in terms of change of HbA_{1c} (baseline to endpoint) to show non-inferiority of HOE901 insulin analogue plus glimepiride and metformin. If this could be demonstrated, additionally, superiority of HOE901 insulin analogue plus glimepiride and metformin should be investigated.

Secondary objectives:
To compare combination therapy of HOE901 insulin analogue plus glimepiride and metformin versus 2 injections insulin monotherapy with premixed insulin NPH 30/70 bid in terms of:
Efficacy:

- Frequency of subjects with HbA_{1c}: ≤ 7.0 % and > 7.0 % at endpoint
- Change of fasting blood glucose, FBG (baseline to endpoint)

- Frequency of subjects with: FBG ≤ 100 mg/dl (5.5 mmol/l), 100 mg/dl < FBG ≤ 120 mg/dl (5.5 mmol/l < FBG ≤ 6.6 mmol/l), 120 mg/dl < FBG ≤ 150 mg/dl (6.6 mmol/l < FBG ≤ 8.3 mmol/l) and > 150 mg/dl (> 8.3 mmol/l) at endpoint
- Change of nocturnal blood glucose (baseline to endpoint)
- Change of mean daytime blood glucose (baseline to endpoint)
- Change of fasting plasma glucose (baseline to endpoint and all visits)

Safety:

- Overall frequency of subjects with hypoglycemic events and overall frequency of hypoglycemic events
- Frequency of subjects with severe hypoglycemic events and frequency of severe hypoglycemic events
- Frequency of subjects with non-severe hypoglycemic events and frequency of non-severe hypoglycemic events
- Frequency of subjects with nocturnal hypoglycemic events and frequency of nocturnal hypoglycemic events
- Frequency of subjects with asymptomatic hypoglycemic events and frequency of asymptomatic hypoglycemic events
- Frequency of subjects with symptomatic hypoglycemic events and frequency of symptomatic hypoglycemic events

Subgroup analysis by region/country
Dose of insulin
Adjustment of insulin
Body weight, body mass index

Study design

Open, parallel, multicenter, multinational, randomized clinical trial. The study consisted of an up to 4 week screening phase followed by a 24 week treatment phase.

Number of subjects planned

It was planned to randomize a total of 420 subjects (210 subjects in each group) in order to have 334 subjects (167 subjects in each group) evaluable for the primary efficacy analysis.

Inclusion criteria

Diabetes mellitus patients, type 2, poorly controlled with oral antidiabetic drug treatment (glimepiride 3 or 4 mg od or any sulfonylurea similar to glimepiride 3 or 4 mg in combination with metformin in a dose at least similar to 850 mg once daily) with HbA_{1c} value ≥ 7.5 % to ≤ 10.5 % and FBG ≥ 120 mg/dl (6.6 mmol/l), age ≥ 35 to ≤ 75 years, and BMI ≤ 35 kg/m².

Treatments

Subjects who were enrolled in this study failed in good metabolic control with OAD treatment and needed insulin to recover good metabolic control, HbA_{1c} ≤ 7.0 %, according to current guidelines and requirements of Scientific Diabetes Societies. Subjects were allowed to be previously OAD treated with any sulfonylurea (similar to glimepiride 3 or 4 mg or glimepiride 3 or 4 mg od) in

combination with metformin in a dose at least similar to 850 mg od at a stable dose for at least 1 months prior to study entry.
Insulin therapy was performed as a combination of basal insulin in the morning in addition to previous OAD (see above) or as 2 injection insulin monotherapy with premixed insulin NPH 30/70 bid.
During the screening phase at visit II, all subjects switched their sulfonylurea to glimepiride 3 or 4 mg or continued with previous glimepiride 3 or 4 mg. Subjects who took 500 mg tablets of metformin changed to 850 mg tablets, maintaining a similar total daily dose. Subjects who took 850 mg tablets of metformin continued with their previous dose.
Subjects who were randomized to the combination of HOE901 insulin analogue plus glimepiride and metformin therapy continued with glimepiride 3 or 4 mg od and metformin at least 850 mg od in a stable dose at baseline (week 0) and started treatment with the addition of HOE901 insulin analogue in the morning. The HOE901 insulin analogue was titrated individually (investigator and patient based) according to a predefined titration regimen to target FBG ≤ 100 mg/dl (5.5 mmol/l) (European Diabetes Policy Group).
In the premixed insulin arm NPH 30/70 bid, all OADs had to be discontinued at baseline visit (week 0) and insulin treatment with premixed insulin was started. The dose of premixed insulin, given before breakfast and before dinner, was also titrated individually (investigator based) to target of pre-prandial BG ≤ 100 mg/dl (5.5 mmol/l).

Efficacy data

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, nocturnal and mean daytime blood glucose 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 and hematology, the physical examination and the vital signs were evaluated for safety.

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 therapeutical equivalent (i.e. HOE901 plus glimepiride and metformin not inferior to NPH 30/70 bid) 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 ε=0.4 %. The non-inferiority analysis was based on the per-

protocol analysis set. 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 noninferiority test were calculated by an analysis of covariance (ANCOVA) with treatment and country (Germany and pooled remaining European countries) 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 completers analysis set, and superiority analysis was also performed for the per-protocol and the completers 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. All secondary objective variables were analyzed based on the full analysis set, the per-protocol analysis set and the completers analysis set, the rate of subjects with hypoglycemic episodes and number of episodes was analyzed based on the safety population.
Laboratory variables were analyzed using the Friedman test and Wilcoxon signed rank test.
For the analyses of vital signs ANCOVA was used. All further safety analyses were descriptive.
An analysis by country (Germany vs. pooled remaining European countries), gender, age categories and BMI categories was conducted for HbA_{1c}, FBG, mean daytime blood glucose and rate 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 66 sites a total of 511 subjects were enrolled in the study, 371 of them were randomized.
178 subjects were randomized to the HOE901 plus glimepiride and metformin group and 193 to the NPH 30/70 bid group.
Both treatment groups were comparable as regards demographic and anamnestic conditions.
Fewer female subjects than male subjects were included in the study in both treatment groups.
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 HbA1c values at the beginning of the screening phase (visit I) and the insulin treatment phase (visit III) were homogenous for the both treatment groups.
The frequencies of concomitant diseases and history of previous surgeries were similar in both treatment groups. In the HOE901 plus glimepiride and metformin group the mean daily insulin starting dose was 9.9 IU, in the NPH 30/70 bid group the mean insulin starting dose was 10.3 IU at breakfast and at dinner.
The majority of subjects in the HOE901 plus glimepiride and metformin group took a low daily dose of the OAD stated in the protocol: 111 (62.71 %) subjects were treated with the lowest recommended dose of 3 mg glimepiride per day and 118 (66.67 %) subjects with low doses of 850 mg metformin bid.

Results - Efficacy

The primary efficacy variable was the change in glycated hemoglobin (HbA1c) from baseline to study endpoint. The therapeutic equivalence (non-inferiority) of HOE901 plus glimepiride and metformin to NPH 30/70 bid was demonstrated in the per-protocol analysis set for the change in HbA1c from the baseline to the endpoint of the study (difference between adjusted means: -0.2961%; two-sided 95% confidence interval: [-0.4761%, -0.1161%]). Furthermore a significant superiority of the HOE901 plus glimepiride and metformin treatment group compared to the NPH 30/70 bid treatment group for the change in HbA1c was demonstrated in the full analysis set (difference between adjusted means: -0.3385%; two-sided 95% confidence interval: [-0.5218%, -0.1551%]).

In the full analysis set the adjusted mean baseline to endpoint reduction in HbA1c was 1.64 % for the HOE901 plus glimepiride and metformin treatment group and 1.31 % for NPH 30/70 bid treatment group. At the endpoint 49.4 % of the subjects of the HOE901 plus glimepiride and metformin group and 39.0 % of the subjects of the NPH 30/70 bid group reached the pre-defined target of HbA1c response (HbA1c $\leq$ 7.0 %). The difference in the responder rates between both treatment groups was close to reach statistical significance for the full analysis set ($p = 0.0596$, CMH) and for the completers analysis set ($p = 0.0839$, CMH), but was significant for the per-protocol analysis set ($p = 0.0495$, CMH).

The analyses of secondary objectives showed a decrease in all short-term metabolic variables (FPG, FBG, mean daytime BG, nocturnal BG, resulting 8-point 24 hour BG profile) and the long-term measurement of metabolic control (HbA1c) in both treatment groups.

At the endpoint 31.6 % of the subjects of the HOE901 plus glimepiride and metformin group and 15.0 % of the subjects of the NPH 30/70 bid group reached the pre-defined target of FBG response (FBG $\leq$ 100 mg/dl). The difference in the responder rates between both treatment groups reached significance for the full analysis set ($p < 0.0001$, CMH).

In addition the decrease of all BG variables was more pronounced in the HOE901 plus glimepiride and metformin group compared to the NPH 30/70 bid group. The values obtained for each variable at endpoint were closer to the normal range for blood glucose in the HOE901 plus glimepiride and metformin group compared to the NPH 30/70 bid group. For most of the BG variables further tests revealed significant differences in the decrease from baseline to endpoint between both treatment groups. For the changes from baseline to endpoint for mean fasting blood glucose the difference of adjusted means for treatment groups was –17.00 mg/dl. The corresponding two-sided 95% confidence interval is [-23.66 mg/dl , - 10.35 mg/dl].

Results - Safety

Hypoglycemia

In the on-treatment phase the percentage of subjects in the HOE901 plus glimepiride and metformin group with any hypoglycemic events was lower (61.58 %) compared to the NPH 30/70 bid group (67.20 %). However the difference was non-significant between both treatment groups ($p = 0.2838$, CMH).

The overall incidence of any hypoglycemic events and the mean of overall number of hypoglycemic events per subject were significantly lower in the HOE901 plus glimepiride and metformin group (n = 527 events / 2.98 events per subject) compared to the NPH 30/70 bid group (n = 1199 events / 6.34 events per subject).

In all types of hypoglycemic events (severe, non-severe, symptomatic, asymptomatic and nocturnal) the number of related subjects was lower in the HOE901 plus glimepiride and metformin group compared to the NPH 30/70 bid group. Significant differences between both treatment groups were shown for the number of subjects with nocturnal hypoglycemic events (HOE901 plus glimepiride and metformin group 15.82 % vs. NPH 30/70 bid group 28.57 %; p = 0.0045, CMH) and for the number of subjects with asymptomatic hypoglycemic events (HOE901 plus glimepiride and metformin group 27.12 % vs. NPH 30/70 bid group 37.04 %; p = 0.0366, CMH).
The number of subjects with severe hypoglycemic episodes was lower in the HOE901 plus glimepiride and metformin group (N = 1) compared to the NPH 30/70 bid group (N = 5); this difference was not significant between both treatment groups (p = 0.1262, CMH).
In all types of hypoglycemic events (except severe hypoglycemic events) the number of reported events and the mean number of hypoglycemic events per subject were significantly lower in the HOE901 plus glimepiride and metformin group compared to the NPH 30/70 bid group.
The percentage of subjects with adverse events during the insulin treatment phase was comparable in both treatment groups. In the HOE901 plus glimepiride and metformin group 89 subjects (50.28 %) experienced 222 adverse events and in the NPH 30/70 bid group 92 subjects (48.68 %) experienced 234 adverse events.
Possibly related treatment emergent adverse events were reported in similar numbers in both treatment groups: 10 adverse events in 8 subjects (4.52 %) from the HOE901 plus glimepiride and metformin group and 12 adverse events in 10 subjects (5.29 %) from the NPH 30/70 bid group had been reported.
Adverse events leading to withdrawal were rare; the frequency was lower in the HOE901 plus glimepiride and metformin group (N = 1 (0.56 %)) compared to the NPH 30/70 bid group (N = 6 (3.17 %)).
The safety evaluation concerning vital signs and laboratory values did not reveal any evidence for a relevant finding for the HOE901 plus glimepiride and metformin group.

Report Date

10 May 2004