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Sponsor/company:	**sanofi-aventis**	**ClinialTrials.gov Identifier:**	**NCT00313937**
		Study Code:	**HOE901_4028**
Generic drug name:	**Insulin Glargine**	**Date:**	**February 14th, 2007**

Title

Multicenter, open, controlled, randomized (1:1), parallel group clinical trial of HOE 901 insulin analogue vs. NPH insulin: Effects on morning blood glucose (7:00 a.m. - 12:00 p.m.) in patients with type 1 diabetes mellitus who skip the morning meal during treatment with MDI (Multiple Daily Injection) basal/bolus insulin (prolonged fasting).

Investigator(s), study site(s)

Multicenter (4 centers in Germany)

Study duration and dates	The first subject was enrolled on 6 November 2001 and the last subject completed the study on 12 May 2004	**Phase** IV

Objectives

Primary objective: to compare metabolic control as measured by blood glucose (BG) upon arising from bed (7:00 - 12:00; 24 hour notation) in diabetes mellitus subjects type 1 who skipped the morning meal during treatment with MDI basal/bolus insulin. Primary efficacy criterion was the difference of change in BG between 7:00 and 11:00 between subjects on HOE 901 insulin analogue and NPH insulin.
Secondary objectives: evaluation between the two subject groups for BG (22:00 and 12:00) as well as for serum insulin, free fatty acids (FFA) and beta-hydroxybutyrate levels (7:00 - 12:00).
In addition, an evaluation of the Continuous Glucose Monitoring System (CGMS, MiniMed®) was performed between the two groups (continuous measurement of BG over a period of 14 hours starting at 22:00 on day 0).

Study design

Open, controlled, randomized (1:1), parallel group study of HOE 901 insulin analogue vs. NPH insulin in subjects who took meal-time regular insulin/short acting insulin analogue. The subjects passed through a stabilization phase after the randomization to

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HOE 901 insulin analogue or NPH insulin.
Once the subjects were stable, the assessments were scheduled. The assessment started in the evening of day 0 with regular insulin/short acting insulin analogue taken with the evening meal and HOE 901 insulin glargine or NPH insulin administered at bedtime. After the evening meal, the subjects stayed fasting. Blood glucose measurement started at 22:00 (day 0) after bedtime injection of HOE 901 insulin glargine or NPH insulin and continued during the night at 1:00, 3:00 and 5:00 (day 1).
The next morning, fasting BG value was determined between 6:00 and 7:00. If it ranged between 80 and 130 mg/dl, the subjects skipped the morning meal and the corresponding insulin injection. When BG did not exceed 220 mg/dl until 12:00, the subjects stayed in fasting condition and all insulin doses were held. Blood glucose, serum insulin, free fatty acids and beta-hydroxybutyrate were measured hourly from 7:00 to 12:00 on a continuous basis. After the last blood withdrawal at 12:00, the subjects had their first meal of the day and the corresponding insulin injection on investigator discretion. If the BG exceeded 220 mg/dl during the assessment phase, an insulin bolus was given for the subject's safety.

Number of subjects planned

With the assumption of a standard deviation of $\sigma = 40$ mg/dl, a difference of $\Delta = 30$ mg/dl in blood glucose change between the two treatment groups can be detected with $\alpha = 0.05$ (2-sided), and $\beta = 0.20$ with n = 29 subjects per group. Thus, 58 subjects were planned to be enrolled and treated with HOE 901 or NPH human insulin.

Inclusion criteria

Male and female subjects with type 1 diabetes mellitus, aged ≥ 18 years, who had been treated with MDI (Multiple Daily Injection) basal/bolus insulin, regular insulin/short acting insulin analogue + NPH insulin on a stable dose (no change > 10%) for at least four weeks prior to study entry, who had a HbA1c ≤ 11.5% (measured at visit 1) and a BMI ≤ 35 kg/m^2.
In addition, subjects had to have a fasting blood glucose value of 80 – 130 mg/dl (day 1: 6:00 – 7:00) before skipping breakfast.

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Treatments

Regular insulin/short acting insulin analogue was injected with the evening meal and HOE 901 insulin glargine or NPH insulin administered at bedtime. The next morning, all doses of insulin were held until 12:00 or until the BG exceeded 220 mg/dl.

Efficacy data

- Primary efficacy data: difference of change in blood glucose between 7:00 and 11:00 on day 1.
- Secondary efficacy data: group comparisons for blood glucose (22:00 on day 0 and 12.00 at day 1), serum insulin, free fatty acids and beta-hydroxybutyrate levels (7.00 - 12:00).
- Additional data: evaluation of the Continuous Glucose Monitoring System (CGMS, MiniMed®) (continuous measurement of BG over a period of 14 hours starting at 22:00 on day 0).

Safety data

- Adverse events, including symptomatic or severe hypoglycemia and reactions at injection sites, reported by the subject or noted by the investigator.
- Laboratory evaluations.
- Physical exams and vital signs.

Statistical procedures

Efficacy :

The primary efficacy analysis investigated the difference of change in blood glucose (day 1: 7:00 and 11.00) between subjects on HOE 901 insulin analogue and NPH insulin. To demonstrate the superiority of HOE 901 compared with NPH in terms of better metabolic control (BG), an analysis of covariance (ANCOVA) was used. Corresponding 95% confidence intervals for the estimated treatment effect were also calculated.

The primary study population was the full analysis set with all subjects that were randomized, received at least one study drug dose including screening/stabilization

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phase and had the primary efficacy variable (BG value) available at 7:00 and 11:00. All secondary variables were analyzed in an exploratory manner.

Safety :

Descriptive analyses were performed. The population eligible for safety analysis consisted of all subjects who received at least one dose of study medication incl. screening/stabilization phase.

Interim analysis

No interim analysis was performed for this study.

Results - Study subjects and conduct

90 subjects were randomized and 86 subjects received study medication. Four subjects in two study centers were withdrawn during the screening phase. 28 of the 86 subjects who received study medication were withdrawn prematurely. The distribution of reasons for withdrawal such as adverse events, blood glucose > 220 mg/dl on day 1, hypoglycemia, subject wish and compliance problems, was roughly the same in both treatment groups.

Subjects had a mean age of about 40 years (range: 18 – 75 years) and were mostly white. Slightly more male than female subjects participated in the study. There were no relevant differences between the treatment groups with respect to demographics and other baseline characteristics. The following table gives an overview of the analysis populations:

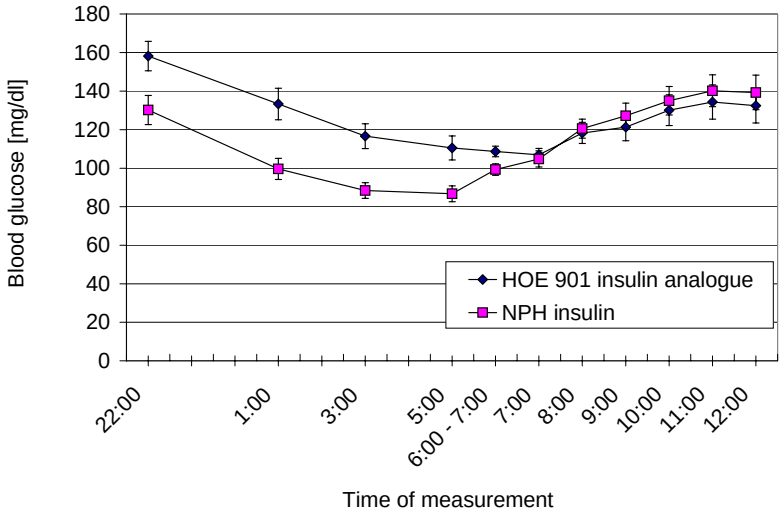
Number of subjects	Treatment as received		Treatment as randomized		
	HOE 901 group	NPH group	HOE 901 group	NPH group	Total
Safety analysis set	41	45	39	47	86
Full analysis set	30	30	28	32	60
Per protocol set	27	29	27	29	56

Results - Efficacy

For the primary variable, the BG change between 7:00. and 11:00 on day 1, no statistically significant differences between the two treatment groups were observed (ANCOVA, p = 0.51; covariate: 7:00 BG value). The increase in mean BG between

7:00 and 11:00, however, appeared to be slightly less pronounced in the HOE 901 group: the mean BG increase between 7:00 and 11:00 was 27.5 ± 40.8 mg/dl in the HOE 901 group and 35.4 ± 45.9 mg/dl in the NPH group (full analysis set). The least squares (LS) mean difference between the two treatment groups was -7.6 mg/dl.
The following table shows the development of blood glucose after administration of the study drugs. At the beginning of the observation period (22:00), the mean blood glucose levels were considerably lower in NPH group than in the HOE 901 group. This difference was maintained until about 5:00 in the morning. From 5:00 to 7:00, blood glucose increased with NPH and further mildly decreased with HOE 901. Thereafter, the blood glucose profiles developed similarly with a comparable increase until 11:00. Descriptively, the increase was slightly less pronounced with HOE 901.

Mean blood glucose versus time curves (FA set)
Means ± SEMs



The mean serum insulin concentrations measured from 7:00 to 12:00 were slightly higher in HOE 901 group than in the NPH group. The mean concentrations of FFA (as

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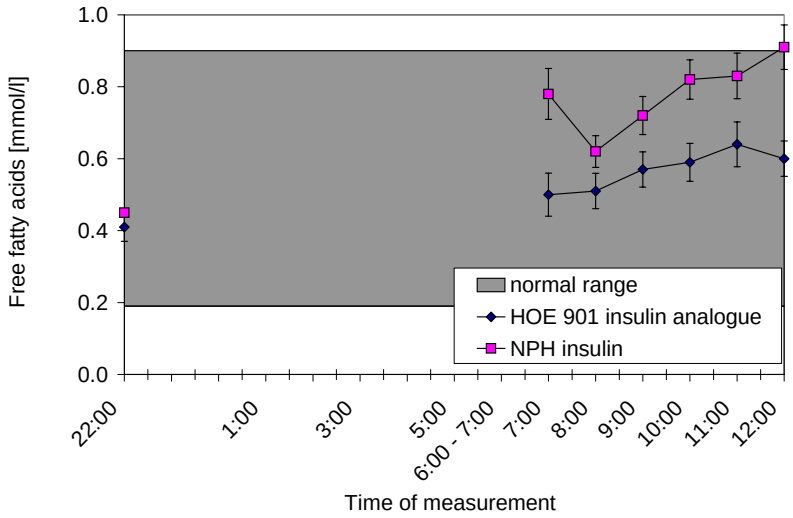
an indicator of lipolysis) and the ketone body beta-hydroxybutyrate (as an indicator of fatty acid degradation) were markedly lower with HOE 901.

Mean free fatty acids versus time curves (FA set)
Means ± SEMs



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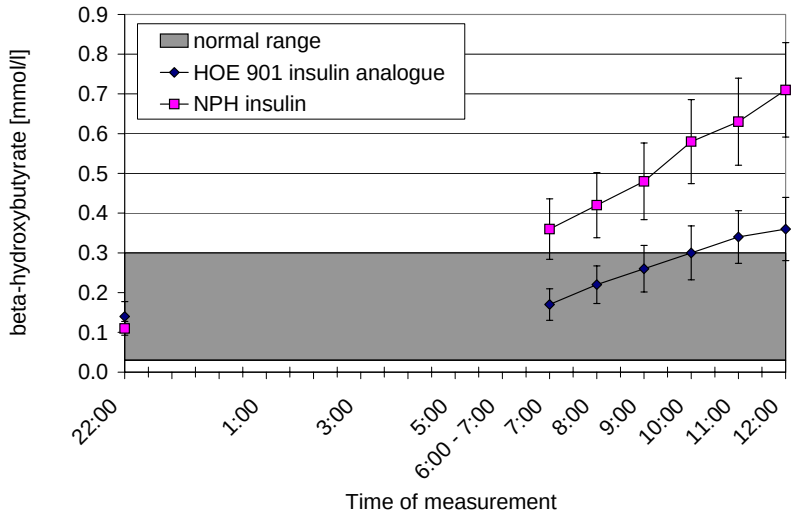
Mean beta-hydroxybutyrate versus time curves (FA set)
Means ± SEMs



Whereas the beta-hydroxybutyrate levels of the HOE 901 group remained in the normal range (0.03 to 0.30 mmol/l) until 10:00, the beta-hydroxybutyrate levels of the NPH group interestingly exceeded the upper normal range already at the first measurement of the morning at 7:00. At 8:00, the NPH group reached pathological levels (> 0.5 mmol/l [1]), but the HOE 901 group's beta-hydroxybutyrate levels did only increase up to 0.36 mmol/l at 12:00.

Comparison of methods of measurement for blood glucose

The subcutaneous sensor continuously monitors interstitial glucose levels. The glucose monitor acquires, displays and stores signals from the subcutaneous glucose sensor, whereas the measurement of capillary blood glucose determines the glucose concentration in the capillary blood. The CGMS was calibrated to the capillary blood glucose measurements, however concentration of interstitial glucose can differ from

capillary blood glucose due to the faster increase or decrease of glucose in capillary blood in comparison to the interstitial fluid. Therefore the minimal invasive method for blood glucose determination compared to the conventional method at distinct point of time could not be sufficiently assessed because the scatter plots showed varying scatters of data points for different assessment times.

Results - Safety

In total, 15 subjects experienced adverse events (AEs) while being on treatment, eight subjects (19.5%) in the HOE 901 group and seven subjects (15.6%) in the NPH group. No pre-treatment AEs were reported. None of the documented AEs were considered as possibly related to the administration of the study drug. Two subjects were withdrawn due to AEs; one subject of the NPH group was withdrawn because of a febrile infection and one subject of the HOE 901 group because of hypoglycemia. One AE – diabetic foot in a subject of the HOE 901 group – was classified as serious, but was not related to study medication. Deaths were not reported.
The following table gives an overview of all AEs observed during the study.

Adverse events (MedDRA preferred terms) during on-treatment period (SA set)

Number of subjects	HOE 901 group (N = 41)		NPH group (N = 45)		Total (N = 86)	
	N	%	N	%	N	%
Hypertension	2	4.9	2	4.4	4	4.7
Diabetic nephropathy	2	4.9	1	2.2	3	3.5
Headache	1	2.4	1	2.2	2	2.3
Microalbuminuria	2	4.9	-	-	2	2.3
Influenza like illness	1	2.4	-	-	1	1.2
Febrile infection	-	-	1	2.2	1	1.2
Gastrointestinal infection	-	-	1	2.2	1	1.2
Urinary tract infection	-	-	1	2.2	1	1.2
Glomerular filtration rate increased	-	-	1	2.2	1	1.2
Diabetic foot	1	2.4	-	-	1	1.2
Diabetic ketoacidosis	-	-	1	2.2	1	1.2
Hyperglycemia	-	-	1	2.2	1	1.2
Hypoglycemia	1	2.4	-	-	1	1.2
Depression	1	2.4	-	-	1	1.2
Albuminuria	-	-	1	2.2	1	1.2
- Number of subjects with AEs -	8	19.5	7	15.6	15	17.4

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Fifty eight out of 86 subjects (67.4%) suffered from hypoglycemia or hypoglycemia related symptoms (HOE 901 group: 30 of 41 (73.2%); NPH group: 28 of 45 (62.2%)). The most common symptoms were hyperhidrosis, tremor and nervousness. There was one case of severe hypoglycemia in the HOE 901 group presenting with asthenia and tremor. Asymptomatic hypoglycemia was observed in about 50% of the subjects of both groups.
In conclusion, the medications were safe and well tolerated. The incidence of hypoglycemic events and other adverse events was similar in both treatment groups.