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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00272077
		Study Code:	HOE901_3509
Generic drug name:	insulin glargine	**Date:**	10 March 2008

Title of the study:	Pilot study on glycaemic variability in type 2 diabetes mellitus patients with basal insulin and fixed Combo oral antidiabetic treatment. HOE901/3509	
Investigator(s):	One principal investigator and centre: Prof. Giancarlo De Mattia, Department of Internal Medicine, University of Rome "La Sapienza", Viale del Policlinico, 155, 00161, Rome, Italy. Phone number: +39 06 4940678; Fax number: +39 06 4940678; E-mail address: giancarlo.demattia@uniroma1.it	
Study center(s):	One single centre in Italy	
Publications (reference):	None	
Study period: Date first **patient** enrolled: 06/04/2005 Date last **patient** completed: 16/05/2006		**Phase of development:** IV
Objectives:	The primary objective of the study was to evaluate in explorative manner the coefficient of variability (CV) of fasting blood glucose calculated on SMBG values during the last 4 weeks before visit 3 (end of cycle 1) and visit 4 (end of cycle 2). The secondary objectives of the study were to assess the following outcome measures: glycaemic control, by measurement of HbA1c, fasting blood glucose, insulin and C-peptide; frequency of hypoglycaemias; change in body weight; final insulin dose; changes in lipid profile (serum total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides); changes in urinary albumin-to-creatinine ratio; results of a standard meal test; profile of patient which best fitted each of the algorithms with the dependent variable of change in HbA1c and independent variables of age, gender, race, tobacco use, diabetes complications, initial HbA1c, initial weight, duration of diabetes mellitus, general education and diabetes education; general safety (adverse event profile, other routine laboratory parameters).	
Methodology:	This was an open-label, national, single centre, randomised, controlled, cross-over exploratory study. The study duration was 26 weeks (following 2 to 7 days run-in), during which patients received a 24-week treatment period with both investigational study drugs, each administered for 12-weeks according to randomised sequences. Once eligibility was confirmed within maximum one week-time, patients performed	

	visit 2 (baseline visit) in which they were randomly allocated on sequence A or sequence B and the first study drug was administered for 12 weeks. Patients in sequence A continued their previous OAD fixed combo (glibenclamide 2.5 mg + metformin 400 mg, 2 or 3 tablets) treatment and started glargine insulin (at dinner-time). Patients in sequence B continued their previous OAD fixed combo (glibenclamide 2.5 mg + metformin 400 mg, 2 or 3 tablets) treatment and started NPH insulin (at bedtime). At the end of this period (visit 3) patients were switched to alternative drug, according to the cross-over study procedure, and a final visit (visit 4) was performed at the end of the second 12-week cycle.		
Number of patients:	Planned: 20	Randomized: 21	Treated: 20
Evaluated: Total A) Glargine → NPH B) NPH → Glargine	**Safety** 21 10 11	**Completed** 20 9 11	
Diagnosis and criteria for inclusion:	Male or female subjects aged 45 years or older; diagnosis of type 2 diabetes mellitus for at least 5 years; treatment with OADs in fixed combination (i.e. glibenclamide 2.5 mg + metformin 400 mg, 2 or 3 tablets, at stable dose in the last 3 months); HbA1c ≥ 8% and ≤ 11%; BMI > 27 and < 35 kg/m2; willingness and demonstrated ability to inject insulin; demonstrated ability to understand and comply with the study protocol procedures; demonstrated ability and willingness to perform SMBG; written informed consent.		
Investigational product: Dose: Administration:	The starting glargine insulin dose was 10 IU/day, to be titrated every 3 days according to the SMBG level based on the mean of the last 2 days of morning FBG values. Titration will be performed with the following dose-schedule algorithm: 2 Day Mean FBG > 180 mg/dl + 6 Units 2 Day Mean FBG 160-180 mg/dl + 5 Units 2 Day Mean FBG 140-159 mg/dl + 4 Units 2 Day Mean FBG 120-139 mg/dl + 2 Units 2 Day Mean FBG 100-119 mg/dl + 1 Units 2 Day Mean FBG 70-99 mg/dl No Change In Dosage 2 Day Mean FBG < 70 mg/dl Decrease 2 Units Uptitration will be stopped temporarily for one week after a case of severe hypoglycaemia unless there is a good explanation (e.g. omission of a meal) for the event. Glargine insulin was administered at dinner-time.		
Duration of treatment: 24 weeks (12 weeks in each cycle).		**Duration of observation:** 27 weeks	

Reference therapy: Dose: Administration:	 The starting NPH insulin dose was 10 IU/day, to be titrated according to the same procedures as for glargine. NPH insulin was administered at bedtime.
Criteria for evaluation: Efficacy:	**The primary variable** of the study was the CV of fasting blood glucose calculated on SMBG values during the last 4 weeks before visit 3 (end of cycle 1) and visit 4 (end of cycle 2). **The secondary efficacy variables** were: glycaemic control (HbA1c, fasting blood glucose, insulin and C-peptide), frequency of hypoglycaemias, body weight, final insulin dose, lipid profile (serum total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides), urinary albumin-to-creatinine ratio, standard meal test, results of CGMS.
Safety:	Safety variables were: adverse events, including severe hypoglycaemia, hypoglycaemia, and nocturnal hypoglycaemia, laboratory parameters (haematology and blood chemistry), physical examination and vital signs (systolic/diastolic blood pressure and heart rate).

Efficacy results:	**Primary efficacy variable:** CV of Fasting Blood Glucose measured in the SMBG A marked and statistically significant decrease from baseline (start of treatment) was observed with both drugs. The mean changes from baseline were -99.9 mg/dL (95% CI: -125.0 to -74.7) with glargine ($p<10^{-3}$) and -100.4 mg/dL (95% CI: -125.5 to -75.3) with NPH ($p<10^{-3}$). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.946). **Secondary efficacy variables:** • Results of SMBG <u>Mean Amplitude Glucose Excursion (MAGE) measured in the SMBG:</u> A non-significant decrease from baseline (start of treatment) was observed with both drugs. The mean changes from baseline were -17.0 mg/dL (95% CI: -34.5 to 0.6) with glargine (p = 0.058) and -13.1 mg/dL (95% CI: -31.4 to 5.3) with NPH (p = 0.152). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.603). <u>Mean Daily Blood Glucose measured in the SMBG:</u> A marked and statistically significant decrease from baseline was observed with both drugs. The mean changes from baseline were -40.9 mg/dL (95% CI: -57.0 to -24.8) with glargine ($p<10^{-3}$). and -43.9 mg/dL (95% CI: -59.9 to -27.8) with NPH ($p<10^{-3}$). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.701). <u>Standard deviation of Mean Daily Blood Glucose measured in the SMBG:</u> A decrease from baseline, which was significant with glargine, was observed with both drugs. The mean changes from baseline were -11.6 mg/dL (95% CI: -20.2 to -3.0) with glargine (p = 0.011) and -6.7 mg/dL (95% CI: -16.1 to 2.7) with NPH (p = 0.149). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.192). <u>Fasting Blood Glucose measured in the SMBG (glycaemic profile in the days of the visits):</u> A marked and statistically significant decrease from baseline was observed with both drugs. The mean changes from baseline were -45.1 mg/dL (95% CI: -64.8 to -25.4) with glargine ($p<10^{-3}$). and -54.8 mg/dL (95% CI: -74.2 to -35.5) with NPH ($p<10^{-3}$). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.261). <u>Blood Glucose after breakfast measured in the SMBG:</u> A marked and statistically significant decrease from baseline was observed with both drugs. The mean changes from baseline were -47.1 mg/dL (95% CI: -66.6 to -27.6) with glargine ($p<10^{-3}$). and -40.1 mg/dL (95% CI: -57.1 to -23.0) with NPH ($p<10^{-3}$). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.890). <u>Blood Glucose before lunch measured in the SMBG:</u> A marked and statistically significant decrease from baseline was observed with both drugs. The mean changes from baseline were -65.3 mg/dL (95% CI: -83.8 to -46.9) with glargine ($p<10^{-3}$). and -59.8 mg/dL (95% CI: -78.1 to -41.5) with NPH ($p<10^{-3}$). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.577).

Blood Glucose after lunch measured in the SMBG:

A marked and statistically significant decrease from baseline was observed with both drugs. The mean changes from baseline were -48.7 mg/dL (95% CI: -75.4 to -22.0) with glargine (p = 0.001) and -50.3 mg/dL (95% CI: -76.7 to -23.9) with NPH (p = 0.001). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.866).

Blood Glucose before dinner measured in the SMBG:

A statistically significant decrease from baseline was observed with NPH, while the decrease with glargine was smaller and not significant. The mean changes from baseline were -13.4 mg/dL (95% CI: -36.4 to 9.7) with glargine (p = 0.238) and -32.1 mg/dL (95% CI: -53.8 to -10.4) with NPH (p = 0.006). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.075).

Blood Glucose after dinner measured in the SMBG:
The overall mean values were similar with the two drugs.

- HbA_{1c}

A marked and statistically significant decrease from baseline was observed with both drugs. The mean changes from baseline were -1.7 % (95% CI: -2.3 to -1.1) with glargine ($p<10^{-3}$) and -1.6 % (95% CI: -2.2 to -1.0) with NPH ($p<10^{-3}$). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.744).

- Meal test

Glucose:
A marked increase of mean glucose from the pre-test values up to 120 minutes was observed with both drugs at the start and at the end of each treatment cycle. In the multiple comparison, a marked and statistically significant decrease from baseline was observed with both drugs in the pre-test values; furthermore, a significant increase from baseline was also observed with NPH in values measured after 120 minutes (p = 0.002). The comparison between treatments of changes from the pre-test values showed statistically significant differences at 120 minutes ($p<10^{-3}$), due to the increase with NPH and the decrease with glargine.
The results of AUC showed a statistically significant increase from baseline with NPH and a smaller non-significant increase with glargine. The mean changes from baseline were 6.9 mg/dL*min (95% CI: -10.1 to 23.8) with glargine (p = 0.408) and 31.5 mg/dL*min (95% CI: 11.5 to 51.60) with NPH (p = 0.004). The comparison between treatments of changes from baseline showed a statistically significant difference (p = 0.024), due to a more marked increase with NPH compared to glargine.

Insulin:
A marked increase of mean insulin from the pre-test values up to 120 minutes was observed with both drugs at the start and at the end of each treatment cycle. In the multiple comparison, a marked and statistically significant increase from baseline was observed with both drugs in the pre-test values. The comparison between treatments of changes from the pre-test values showed a statistically significant difference at pre-test ($p<10^{-3}$) due to a greater increase

with glargine compared to NPH.

The results of AUC showed a statistically significant decrease from baseline with glargine and a smaller non-significant decrease with NPH. The mean changes from baseline were -61.5 mU/L*min with glargine (p = 0.002) and -31.8 mU/L*min with NPH (p = 0.070). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.109).

Glucagon:

A marked increase of mean glucagon from the pre-test values up to 60 minutes was observed with both drugs at the start and at the end of each treatment cycle, while values at 120 minutes slightly declined compared to values measured at 60 minutes. In the multiple comparison, a statistically significant increase from baseline was observed with NPH in values measured at 30 minutes (p = 0.000). The comparison between treatments of changes from the pre-test values did not show statistically significant differences at any time-point.

The results of AUC showed a non-significant increase from baseline with both drugs, which was slightly higher with NPH compared to glargine. The mean changes from baseline were 2.2 µg/L*min with glargine (p = 0.760) and 7.1 µg/L*min with NPH (p = 0.233). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.368).

C-peptide:

A marked increase of mean C-peptide from the pre-test values up to 120 minutes was observed with both drugs at the start and at the end of each treatment cycle. In the multiple comparison, a statistically significant increase from baseline was observed with both glargine and NPH in values measured at pre-test. The comparison between treatments of changes from the pre-test values showed statistically significant differences at pre-test (p = 0.004), due to the greater decrease with NPH compared to glargine.
The results of AUC showed a significant increase from baseline with NPH and a smaller non-significant increase with glargine. The mean changes from baseline were 17.6 µg/L*min with glargine (p = 0.096) and 39.1 µg/L*min with NPH (p = 0.002). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.090).

Fatty Free Acids:

A decrease of mean FFA from the pre-test values up to 120 minutes was observed with NPH at the start of the first cycle and at the end of the second, while no substantial changes from pre-test values were observed at the other time-points. In the multiple comparison, a statistically significant decrease from baseline was observed with both glargine and NPH in values measured at pre-test, while a significant increase from baseline was observed with glargine at 30 and 60 minutes p = 0.002 and $p<10^{-3}$, respectively) and with NPH at 60 minutes (p = 0.003). The comparison between treatments of changes from the pre-test values (level for significance = 0.017) showed a statistically significant difference at pre-test (p = 0.006), due to a greater decrease with glargine compared to NPH.

The results of AUC showed a significant increase from baseline with both drugs. The mean changes from baseline were 27.7 µg/L*min with glargine (p = 0.002) and 20.2 µg/L*min with NPH (p = 0.019). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.287).

- Continuous Glucose Monitoring System (CGMS)

- First day of CGMS with Glucoday® (24 hours)

Mean glycaemic profile for 24 hours:
Glycaemic levels measured in patients on glargine were lower than those measured in patients on NPH for most of time, both being lower than values measured in the 24 hours after baseline (start of treatment). The mean overall percentage of glucose levels > 180 mg/dL was 24.01 ± 16.73 after treatment with glargine and 28.25 ± 15.70 after treatment with NPH (p = 0.231 between treatments). The mean overall percentage of glucose levels < 54 mg/dL was 1.18 ± 3.12 after treatment with glargine and 1.52 ± 2.93 after treatment with NPH (p = 0.724 between treatments). The mean number of episodes of hypoglycaemia was 0.75 ± 1.02 after treatment with glargine and 0.65 ± 1.04 after treatment with NPH (p = 0.822 between treatments).

Glucose blood levels at different hours after lunch:
The mean AUC was 31.17 ± 3.80 mg/dL*6h after treatment with glargine and 30.46 ± 5.02 mg/dL*6h after treatment with NPH (p = 0.381 between treatments). The comparison between treatments of the results of blood glucose levels at different times after lunch in the ANOVA model showed a statistically significant difference at 6 hours, due to lower glycaemic values with glargine compared to NPH (p = 0.001). The comparison between treatments in the ANCOVA model showed a statistically significant difference at 5 hours (p = 0.040) and at 6 hours ($p<10^{-3}$), again due to lower glycaemic values with glargine compared to NPH.

AUC Meal Test (venous blood glucose) versus AUC Glucoday®:
The results of glucose levels in the meal test measured in the venous sample taken at the clinic and in the CGMS showed a marked increase from pre-test to values at 120 minutes at baseline (start of treatment) and with both drugs, with both methods of measurement. The comparison between the two methods in the ANOVA model showed a statistically significant difference at 60 minutes with glargine (p = 0.003) and at 60 minutes with NPH (p = 0.030), due to blood glucose levels measured in the CGMS lower than those measured in the venous blood samples. However, no significant differences between the two methods were found in the comparison of the overall mean glucose levels (p = 0.233). The mean values of AUC in the meal test (0-120 minutes) measured in the CGMS were lower than those measured in the venous blood samples at baseline, after treatment with glargine and after treatment with NPH (p = 0.014 for values measured on NPH and p = 0.049 and for the overall values).

Daily glycaemic profile:
The mean glucose levels measured before lunch were 152.4 ± 52.3 mg/dL after treatment with glargine and 142.9 ± 43.5 mg/dL after treatment with NPH (p = 0.500 between treatments). The mean glucose levels measured after lunch were 179.0 ± 44.9 mg/dL after treatment with glargine and 187.6 ± 64.2 mg/dL after treatment with NPH (p = 0.372 between treatments). The mean glucose levels measured before dinner were 128.8 ± 59.6 mg/dL after treatment with

glargine and 136.4 ± 71.6 mg/dL after treatment with NPH (p = 0.564 between treatments). The mean glucose levels measured after dinner were 189.5 ± 62.9 mg/dL after treatment with glargine and 188.8 ± 68.7 mg/dL after treatment with NPH (p = 0.948 between treatments). The mean glucose levels measured at bedtime were 174.3 ± 49.1 mg/dL after treatment with glargine and 198.0 ± 69.6 mg/dL after treatment with NPH (p = 0.311 between treatments). The mean glucose levels measured at night-time were 143.8 ± 61.9 mg/dL after treatment with glargine and 151.4 ± 58.9 mg/dL after treatment with NPH (p = 0.682).

Other analyses on CGMS in the first day:

No statistically significant differences between treatments were found in the analysis of the following parameters measured in the first 24 hours: mean glucose levels (p = 0.174), mean standard deviation of glucose levels (p = 0.291), mean minimum values of glucose levels (p = 0.338), mean maximum values of glucose levels (p = 0.639), mean maximum excursion of glucose levels (p = 0.730), mean overnight glucose levels (p = 0.650), and mean standard deviation of overnight glucose levels (p = 0.941).

- Second day of CGMS with Glucoday® (20 hours)

Mean glycaemic profile for 20 hours:
The mean glycaemic profile for 20 hours showed similar mean values measured in patients on glargine and in those on NPH. The mean overall percentage of glucose levels > 180 mg/dL was 20.84 ± 16.41 after treatment with glargine and 22.61 ± 23.56 after treatment with NPH (p = 0.756 between treatments). The mean overall percentage of glucose levels < 54 mg/dL was 1.26 ± 2.05 after treatment with glargine and 2.96 ± 5.46 after treatment with NPH (p = 0.161 between treatments). The mean number of episodes of hypoglycaemia was 0.50 ± 0.69 after treatment with glargine and 0.90 ± 1.21 after treatment with NPH (p = 0.203 between treatments).

Daily glycaemic profile:

The mean glucose levels measured before breakfast were 114.9 ± 59.8 mg/dL after treatment with glargine and 111.2 ± 36.8 mg/dL after treatment with NPH (p = 0.682 between treatments). The mean glucose levels measured after breakfast were 166.6 ± 49.1 mg/dL after treatment with glargine and 156.1 ± 40.9 mg/dL after treatment with NPH (p = 0.301 between treatments). The mean glucose levels measured before lunch were 110.6 ± 44.9 mg/dL after treatment with glargine and 118.0 ± 58.9 mg/dL after treatment with NPH (p = 0.652 between treatments). The mean glucose levels measured after lunch were 143.8 ± 40.8 mg/dL after treatment with glargine and 154.6 ± 68.0 mg/dL after treatment with NPH (p = 0.585 between treatments). The mean glucose levels measured before dinner were 130.6 ± 55.0 mg/dL after treatment with glargine and 138.8 ± 62.5 mg/dL after treatment with NPH (p = 0.535 between treatments). The mean glucose levels measured after dinner were 161.4 ± 42.7 mg/dL after treatment with glargine and 161.3 ± 82.8 mg/dL after treatment with NPH (p = 0.996 between treatments). The mean glucose levels measured at bedtime were 160.5 ± 63.1 mg/dL after treatment with glargine and 158.3 ± 70.9 mg/dL after treatment with NPH (p = 0.939 between treatments). The mean glucose levels measured at night-time were 142.6 ± 55.8 mg/dL after treatment with glargine and 131.6 ± 44.0 mg/dL after treatment with NPH (p = 0.612 between treatments).

Other analyses on CGMS in the second day:

No statistically significant differences between treatments were found in the analysis of the following parameters measured for 20 hours in the second day: mean glucose levels (p = 0.967), mean standard deviation of glucose levels (p = 0.757), mean minimum values of glucose levels (p = 0.942), mean maximum values of glucose levels (p = 0.912), mean maximum excursion of glucose levels (p = 0.930), mean overnight glucose levels (p = 0.875), and mean standard deviation of overnight glucose levels (p = 0.697).

- Hypoglycaemia

The number of patients with at least one episode of hypoglycaemia was 13 during treatment with glargine and 15 during treatment with NPH. The mean number of episodes/patient/month of hypoglycaemia was 1.04 with glargine and 2.12 with NPH. None of patients had severe hypoglycaemia with both investigational study drugs. The number of patients with at least one episode of nocturnal hypoglycaemia was 3 during treatment with glargine and 8 during treatment with NPH. The mean number of episodes/patient/month of nocturnal hypoglycaemia was 0.12 with glargine and 0.26 with NPH.

- Laboratory efficacy parameters (measured at clinic visits)

- Glucidic profile

Fasting blood glucose:

A marked and statistically significant decrease from baseline was observed with both drugs. The mean changes from baseline were -99.9 (95% CI: -125.0 to -74.7) with glargine ($p<10^{-3}$) and -100.4 (95% CI: -125.5 to -75.3) with NPH ($p<10^{-3}$). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.946).

Insulin levels:

A marked and statistically significant increase from baseline was observed with both drugs. The mean changes from baseline were 17.9 (95% CI: 11.8 to 24.0) with glargine ($p<10^{-3}$) and 9.9 (95% CI: 4.4 to 15.5) with NPH (p = 0.001). The comparison between treatments of changes from baseline showed a statistically significant difference (p = 0.028), due to a more marked increase with glargine compared to NPH.

C-peptide:
A marked and statistically significant decrease from baseline was observed with both drugs. The mean changes from baseline were -1.7 ng/mL (95% CI: -2.5 to -0.9) with glargine ($p<10^{-3}$) and -1.9 ng/mL (95% CI: -2.7 to -1.1) with NPH ($p<10^{-3}$). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.572).

- Lipid profile

Total cholesterol:

A small non-significant increase from baseline was observed with both drugs. The mean changes from baseline were 5.7 mg/dL (95% CI: -11.6 to 23.0) with glargine (p = 0.497) and 1.1 mg/dL (95% CI: -21.0 to 23.1) with NPH (p = 0.920). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.562).

HDL-cholesterol:
A statistically significant increase from baseline was observed with NPH, compared to a small non-significant increase with glargine. The mean changes from baseline were 2.2 mg/dL (95% CI: -1.2 to 5.5) with glargine (p = 0.186) and 4.1 mg/dL (95% CI: 1.0 to 7.2) with NPH (p = 0.012). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.174).

LDL-cholesterol:
A small non-significant increase from baseline was observed with both drugs (more markedly with glargine). The mean changes from baseline were 4.1 mg/dL (95% CI: -9.7 to 17.9) with glargine (p = 0.540) and 0.6 mg/dL (95% CI: -52.9 to 54.0) with NPH (p = 0.983). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.554).

Triglycerides:
A non-significant decrease from baseline was observed with both drugs (more markedly with NPH). The mean changes from baseline were -16.6 mg/dL (95% CI: -47.5 to 14.4) with glargine (p = 0.277) and -31.6 mg/dL (95% CI: -64.2 to 1.0) with NPH (p = 0.057). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.376).

- Body weight and BMI:

Body weight:
A statistically significant increase from baseline was observed with both drugs. The mean changes from baseline were 2.5 kg (95% CI: 0.8 to 4.2) with glargine (p = 0.007) and 3.0 kg (95% CI: 1.5 to 4.6) with NPH (p = 0.001). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.328).

BMI:
A statistically significant increase from baseline was observed with both drugs. The mean changes from baseline were 0.9 kg/m^2 (95% CI: 0.3 to 1.5) with glargine (p = 0.005) and 1.1 kg/m^2 (95% CI: 0.5 to 1.6) with NPH (p = 0.001). The comparison between treatments of changes from baseline did not show statistically significant differences (p = 0.371).

- Insulin dosage

The mean daily doses with glargine were 34.0 ± 17.8 U/L at the end (i.e. last 4 weeks) of the first cycle, 24.6 ± 16.0 U/L at the end (i.e. last 4 weeks) of the second cycle, and 28.8 ± 17.1 U/L as total. The mean doses with NPH were 24.8 ± 21.1 U/L at the end (i.e. last 4 weeks) of the first cycle, 46.7 ± 26.6 U/L at the end (i.e. last 4 weeks) of the second cycle, and 34.7 ± 25.6 U/L as total.

Safety results:	Adverse events: A total number of 5 adverse events (AEs) were reported in 4 patients. One event in 1 patient started during the screening phase, while the other 4 events started in 3 patients under treatment with glargine. The comparison between treatments of the frequency of AEs did not show statistically significant differences (p = 0.248). The AEs started during the treatment phase with glargine consisted of diabetic retinopathy and atrial fibrillation in one patient, hypertensive retinopathy in another and rib fracture in the third one. However, none of the AEs started during the treatment phase was considered as related with study drug, was serious or of severe intensity, or caused study discontinuation. Both patients that developed retinopathy had underlying arterial hypertension. Laboratory parameters: The results of safety laboratory parameters (haematology and blood chemistry) did not show evidence of clinically significant changes for any parameter. A statistically significant increase from baseline of WBC count was observed following treatment with NPH, while a small increase in neutrophils count with NPH coupled with a small decrease with glargine determined a statistically significant difference between treatments. Furthermore, a small but significant increase from baseline of sodium was reported with both glargine and NPH. The results of urinalysis showed a small but statistically significant decrease of urine specific gravity with glargine (without statistically significant differences between treatments). A decrease of the mean urinary albumin/creatinine ratio was also observed following treatment with glargine, while a trend towards normalisation of the presence at baseline of urine glucose and proteins was observed with both study drugs. The results of safety laboratory parameters in terms of low/normal/high values based on normal range did not show evidence of marked changes from baseline or differences between treatments. Vital signs: The results of vital signs (heart rate and blood pressure) did not show statistically significant changes, apart from an increase from baseline of SBP following treatment with NPH. However, the comparison between treatments of changes from baseline of SBP did not show statistically significant differences.
Date of report:	15 May 2007