These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	**sanofi-aventis**	**ClinialTrials.gov Identifier:**	**Not applicable**
		Study Code:	**HOE901_4050**
Generic drug name:	**Insulin Glargine**	**Date:**	**February 14th, 2007**

Title

Assessment of Duration of Metabolic Effect of a Single Bolus of sc Injected Lantus™ Compared to NPH-Insulin (Protaphan™) in Patients with Type 2 Diabetes

Investigator(s), study site(s)

Principal investigator: Klaus Rave, MD, co-investigators: Leszek Nosek, MD, Oliver Klein, MD
Profil Institut für Stoffwechselforschung GmbH, D-41460 Neuss, Germany

Study duration and dates	07 April 2004 until 25 July 2005	Phase	IV

Objectives

Primary objective: To assess the duration of the metabolic effect of a sc injected single dose of either insulin glargine (Lantus™) or NPH-insulin (Protaphan™) on blood glucose control in patients with type 2 diabetes.

Secondary objectives: To evaluate the effect of insulin glargine (Lantus™) and NPH-insulin (Protaphan™) on suppression of endogenous glucose production, endogenous insulin secretion, and lipolysis

Study design

The study was a single-center, randomized, single-blind, two-way crossover trial with two subsequent dosage groups. The second dosage group was introduced by Amendment 2. Following the crossover part, an open study part with single placebo administration was added which was introduced by Amendment 3.

The crossover part of the study consisted of 4 trial periods: TP 0 (screening visit), TP 1 and 2, (treatment visits), and TP 3 (follow-up visit). The placebo part consisted of 3 trial periods: TP 0 (screening), TP 1 (treatment visit), and TP 2 (follow-up visit). During each treatment period subjects were hospitalized for about 32 hours and underwent an isoglycemic glucose clamp procedure with clamp levels of 130 mg/dL (before implementation of Amendment 2) or 90 mg/dL (after implementation of Amendment 2), respectively. During each clamp session blood samples were taken at predetermined time points for the assessment of pharmacodynamic (PD) and pharmacokinetic (PK) parameters.

Number of subjects planned

Originally, 20 subjects were planned to complete the study. By Amendment 2 the planned number was increased to 30 in total. According to Amendment 3, 10 subjects were enrolled into the open study part with placebo after 15 subjects had completed the crossover part of the study.

Inclusion criteria

Subjects with type 2 diabetes (for >6 months) of either gender between 40 and 65 years of age with a body mass index between 28 and 32 kg/m^2 (before implementation of Amendment 1) or 26 and 34 kg/m^2 (after implementation of Amendment 1), HbA_{1c} >7.5% and <9.5% (before implementation of Amendment 1) or >7.0% and <9.5% (after implementation of Amendment 1), fasting C-peptide >0.2 pmol/mL (before implementation of Amendment 3) or ≤0.4 pmol/mL in 5 subjects and >0.4 pmol/mL in 5 subjects (after implementation of Amendment 3), normal findings in the medical history and physical examination, normal laboratory values and normal ECG, blood pressure and pulse rate unless the investigator considered an abnormality to be clinically irrelevant. Female subjects had to be postmenopausal (for at least 2 years) or surgically sterilized, or had to use reliable contraceptive methods and to show a negative pregnancy test immediately prior to treatment.

Treatments

Insulin glargine (Lantus™): one single dose of 0.3 IU/kg (first group of subjects enrolled) and 0.5 IU/kg, (subjects enrolled after implementation of Amendment 2), injected subcutaneously in the abdominal or thigh region.

NPH-insulin (Protaphan™): two single doses of 0.3 IU/kg (first group of subjects enrolled) and 0.5 IU/kg (subjects enrolled after implementation of Amendment 2), injected subcutaneously in the abdominal or thigh region.

Placebo (sterile 0.9% NaCl solution): one single administration of 2 mL (subjects enrolled after implementation of Amendment 3), injected subcutaneously in the abdominal or thigh region.

Pharmacodynamic data

Blood glucose (BG), glucose infusion rate (GIR), C-peptide (CPEP), free fatty acids (FFA) and proinsulin were measured during the glucose clamp procedure, and the following pharmacodynamic characteristics were determined from the GIR vs. time and the respective concentration vs. time profiles:

Primary PD variable: Time to the end of the blood glucose controlling effect (T_{GCE})

Secondary PD variables: Time to the end of the glucose lowering effect (T_{GLE}) , time to start of glucose infusion ($t_{GIR\text{-}start}$), time to end of glucose infusion ($t_{GIR\text{-}end}$), time to recovery of suppressed endogenous glucose production (T_{SGP}), time to recovery of suppressed endogenous insulin secretion (T_{SIS}), area under the GIR vs. time curve from 0 to 24 hours (GIR-AUC(0-24h)), maximum value of the GIR vs. time curve (GIR_{max}), time to GIR_{max} (GIR-t_{max}), area under the BG concentration vs. time curve from 0 to 24 hours (BG-AUC(0-24h)), maximum BG concentration (BG_{max}), minimum BG concentration (BG_{min}), time to BG_{max} (BG-t_{max}), time to BG_{min} (BG-t_{min}), area under the CPEP concentration vs. time curve from 0 to 24 hours (CPEP-AUC(0-24h)), maximum CPEP concentration ($CPEP_{max}$), minimum CPEP concentration ($CPEP_{min}$), time to $CPEP_{max}$ (CPEP-t_{max}), time to $CPEP_{min}$ (CPEP-t_{min}), area under the FFA concentration vs. time curve from 0 to 24 hours (FFA-AUC(0-24h), maximum FFA concentration (FFA_{max}), minimum FFA concentration (FFA_{min}), time to FFA_{max} (FFA-t_{max}), and time to FFA_{min} (FFA-t_{min}).

Pharmacokinetic data

Concentrations of insulin glargine (Lantus™ administration) and human insulin (Protophan™ administration) in serum were determined during the glucose clamp procedure and the following pharmacokinetic parameters were derived from the insulin concentration vs. time profiles:

Area under the insulin concentration vs. time curve from 0 to 24 hours (INS-AUC(0-24h)), maximum insulin concentration (INS_{max}), and time to INS_{max} (INS-t_{max}).

Safety data

Clinical laboratory (hematology, clinical chemistry, urinalysis), vital signs, weight, 12-lead electrocardiogram (ECG), physical examination, and adverse events spontaneously reported by the subjects or observed by the investigator.

Statistical procedures

Descriptive statistical analyses were used for all variables. Statistical inferences for pharmacodynamic and pharmacokinetic variables were not performed.

Interim analysis

An informal interim analysis (data monitoring) of the study data was performed after the first 10 patients had been completed. Based on the evaluations of this analysis, it was decided to increase the doses of the study medication and extend the planned sample size to a maximum of 30 patients.

A second interim analysis (data monitoring) was done after 5 additional (in total 15) subjects had been completed. Based on the evaluations of this analysis, it was decided to add a group of 10 placebo-treated patients.

Results - Study subjects and conduct

Sixteen subjects (14 males and 2 females), between 42 to 64 years of age and with BMI ranging from 26.2 to 33.8 kg/m^2 were enrolled in the crossover part of the study and randomized to one of the treatment sequences (safety population). One participant terminated the study prematurely prior to completion of the second treatment session. This subject was included in the safety analysis but not in the PK/PD analysis. Therefore, the PK/PD population comprised 15 subjects, divided in the 1. PK/PD population (5 subjects dosed with 0.5 IU/kg of both insulins) and the 2. PK/PD population (10 subjects dosed with 0.3 IU/kg of both insulins). Ten subjects (7 males and 3 females), between 43 to 65 years of age and with BMI ranging from 27.6 to 33.6 kg/m^2 were enrolled in the placebo part of the study.

Results - Pharmacodynamic and pharmacokinetic results

Pharmacodynamic and pharmacokinetic results (arithmetic means±Std) obtained for the 5 treatments administered in this study.

Variable	Lantus™		Protaphan™		Placebo
	0.5 IU/kg[a]	0.3 IU/kg[b]	0.5 IU/kg[a]	0.3 IU/kg[b]	0.9% NaCl[c]
Pharmacodynamics					
$t_{GIR\text{-}start}$ [h]	1.25±0.81	0.55±0.41	1.69±1.26	0.68±0.54	1.58±2.05
$t_{GIR\text{-}end}$ [h]	6.83±2.72	10.02±8.49 (N=7)	8.56±4.57 (N=4)	11.99±7.89	12.13±8.39 (N=9)
T_{GCE} [h]	N/A (N=0)	10.66±10.34 (N=2)	N/A (N=0)	18.43 (N=1)	8.69±3.50 (N=2)
T_{GLE} [h]	5.58±2.98	9.40±8.62 (N=7)	6.93±4.34 (N=4)	11.32±7.99	10.69±7.81 (N=9)
T_{SGP} [h]	N/A (N=0)	1.00 (N=1)	1.50±0.71 (N=2)	N/A (N=0)	N/A (N=0)
T_{SIS} [h]	18.00 (N=1)	4.00±4.12 (N=5)	8.00±8.45 (N=4)	1.00±0.00 (N=2)	3.00 (N=1)
GIR-AUC(0-24h) [mg/kg]	878±552	1208±514	643±463	1172±544	221±204
GIR_{max} [mg/min/kg]	4.46±1.65	5.33±1.48	4.32±2.15	4.78±1.12	2.99±1.40
GIR-t_{max} [h]	4.69±2.92	12.71±8.81	9.97±7.56	10.17±8.31	12.09±8.90
BG-AUC(0-24h) [h*mg/dL]	2193±78	3154±23	2203±49	3179±67	2520±432
BG_{max} [mg/dL]	135.6±18.9	169.4±17.7	145.4±25.8	177.6±12.7	154.7±34.4
BG_{min} [mg/dL]	57.6±10.6	84.2±17.0	63.4±9.5	87.2±16.6	62.3±8.3
BG-t_{max} [h]	8.95±4.84	12.38±5.54	9.73±3.39	16.30±5.21	12.20±6.92

Variable	Lantus™		Protaphan™		Placebo
	0.5 IU/kg[a]	0.3 IU/kg[b]	0.5 IU/kg[a]	0.3 IU/kg	0.9% NaCl[c]
BG-t_{min} [h]	12.14±10.01	13.46±8.62	9.75±4.88	11.31±5.25	8.16±8.25
CPEP-AUC(0-24h) [h*ng/mL]	35.80±25.17	31.16±11.19	33.70±25.79	32.42±14.28	36.90±23.21
$CPEP_{max}$ [ng/mL]	2.25±1.24	1.78±0.59	2.26±1.49	1.85±0.79	2.12±1.29
$CPEP_{min}$ [ng/mL]	1.06±0.77	0.87±0.43	0.90±0.67	0.92±0.51	0.90±0.69
CPEP-t_{max} [h]	1.00±2.24	3.30±3.95	0.80±1.79	11.70±10.64	14.60±6.79
CPEP-t_{min} [h]	7.20±3.56	9.30±6.34	10.80±6.61	8.30±5.21	5.90±6.76
FFA-AUC(0-24h) [h*mg/L]	11538±2680	15163±2915	11474±2240	15269±2836	19871±3678
FFA_{max} [mg/L]	535.8±140.6	708.0±125.8	552.6±87.8	740.2±151.2	937.3±178.4
FFA_{min} [mg/L]	442.0±95.4	575.0±119.0	421.6±73.9	571.0±117.6	740.1±147.7
FFA-t_{max} [h]	10.40±7.13	3.00±4.85	3.60±3.91	4.70±6.38	10.40±8.47
FFA-t_{min} [h]	12.60±6.31	14.70±6.24±	18.80±4.87	15.50±6.69	7.20±7.32
Pharmacokinetics					
INS-AUC(0-24h) [h*µIU/mL]	585.6±372.8 (N=4)	614.9±333.5	878.1±688.3	577.3±271.6	407.2±372.6
INS_{max} [µIU/mL]	30.21±14.44 (N=4)	34.33±21.84	52.64±42.99	35.06±16.75	25.39±17.43
INS-t_{max} [h]	3.50±1.00 (N=4)	7.00±4.67	3.60±0.89	5.10±2.51	6.00±4.59

[a] 1.PK/PD population (N=5) / [b] 2. PK/PD population (N=10) / [c] Placebo subjects (N=10). In case the number of observations is below 5 or 10, respectively, the referring number is indicated in brackets.

Due to the small metabolic response observed during the glucose clamp experiments after administration of Lantus™ as well as of Protaphan™, the primary PD variable, T_{GCE}, could not be assessed. Secondary PD variables and PK variables exhibited inconsistent results - except for free fatty acid serum concentration. A dose-dependent decrease of free fatty acid AUCs suggests a dose-dependent inhibition of lipolysis to a comparable extent after administration of both insulins.

Results – Safety

Sixteen insulin-treated subjects and 10 placebo subjects were included in the safety analysis. All treatments were considered to be safe and well tolerated. No adverse events were reported during the study. There were no findings of laboratory tests, vital sign and weight measurements, physical examinations, and ECG recordings that were documented and reported as adverse events. There were no indications of study drug related changes in any of the safety variables.

Date of report

26 Jan 2006