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| **Sponsor/company:** | Sanofi-aventis | **ClinialTrials.gov Identifier:** | NCT00311077 |
| | | **Study Code:** | HMR1964A_1502 |
| **Generic drug name:** | Insulin glulisine | **Date:** | 16 April 2007 |

# STUDY SYNOPSIS

## Study number

HMR1964A / 1502

## Title

Pharmacodynamic and Pharmacokinetic Properties of Insulin Glulisine (Apidra®) in Comparison to Insulin Lispro (Humalog®) in Healthy Lean and Obese Subjects

## Investigator(s), study site(s)

Principal investigator: Tim Heise, MD
Sub-investigators: Leszek Nosek, MD, Ulrike Hövelmann, MD, Christoph Kapitza, MD, Sibylle Dellweg, MD, Profil Institut für Stoffwechselforschung GmbH, D-41460 Neuss, Germany

| **Study duration and dates** | 13 April 2004 until 21 October 2004 | **Phase** | I |
|---|---|---|---|

## Objectives

Primary objective: To investigate pharmacodynamic and pharmacokinetic parameters after s.c. administration of two different doses (low dose, 0.2 IU/kg and high dose, 0.4 IU/kg) of insulin glulisine across healthy subjects in 4 different BMI-classes (lean, overweight, moderately obese, severely obese), using the euglycemic clamp technique with the Biostator™.

Secondary objective: To investigate the pharmacodynamic and pharmacokinetic properties after s.c. administration of insulin glulisine in comparison to insulin lispro and to investigate the safety and tolerability after s.c. administration of insulin glulisine in comparison to insulin lispro.

## Study design

The study was a single-center, randomized, double-blind, four-way cross-over trial.

Stratified into four different BMI groups, subjects were randomly assigned to one of the following treatment sequences:

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| **Stratum (BMI group)** | **Treatment Sequence** | **Treatment Sequence** | **Treatment Sequence** | **Treatment Sequence** |
|---|---|---|---|---|
| BMI<25 (lean) | A B C D | B D A C | C A D B | D C B A |
| 25≤BMI<30 (overweight) | A B C D | B D A C | C A D B | D C B A |
| 30≤BMI<35 (moderately obese) | A B C D | B D A C | C A D B | D C B A |
| BMI≥35 (severely obese) | A B C D | B D A C | C A D B | D C B A |

A = insulin glulisine, low dose (0.2 IU/kg)
B = insulin glulisine, high dose (0.4 IU/kg)
C = insulin lispro, low dose (0.2 IU/kg)
D = insulin lispro, high dose (0.4 IU/kg)

The study consisted of 6 trial periods: trial period 0 (screening visit), trial periods 1, 2, 3, 4, (treatment visits) and trial period 5 (follow-up visit).

## Number of subjects planned

80 subjects (20 in each BMI group) were planned to complete the study.

## Inclusion criteria

Healthy subjects of either gender between 18 and 65 years of age (inclusive), without any systemic concomitant medication and with normal $HbA_{1c}$ were eligible to participate in the study. Women had to either be postmenopausal, surgically sterilized, or not pregnant and using adequate contraception.

## Treatments

Insulin glulisine: two single doses of 0.2 IU/kg and 0.4 IU/kg injected subcutaneously in the periumbilical abdomen

Insulin lispro: two single doses of 0.2 IU/kg and 0.4 IU/kg injected subcutaneously in the periumbilical abdomen

## Pharmacodynamic data

Blood glucose, glucose infusion rate (GIR) and C-peptide were measured during an euglycemic clamp procedure. Characteristics of the GIR vs. time profiles were determined.

Primary pharmacodynamic variables were GIR-$t_{20\%}$ and GIR-AUC(0-1 h).

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Secondary PD variables were GIR-AUC(0-1.5 h), GIR-AUC(0-2 h), GIR-AUC(0-3 h), GIR-AUC(0-5 h), GIR-AUC(0-7 h), GIR-AUC(0-10 h), GIR-AUC(5-10 h), GIR-AUC(7-10 h), GIR-$t_{10\%}$, GIR-$t_{50\%}$, GIR-$t_{80\%}$, GIR-$t_{90\%}$, GIR-$t_{80\%}$ − GIR-$t_{20\%}$, $GIR_{max}$, GIR-$t_{max}$, GIR-$t_{50\%early}$, GIR-$t_{50\%late}$, GIR-$t_{50\%late}$ − GIR-$t_{50\%early}$, and ratio GIR-AUC(0-1 h) / GIR-AUC(0-10 h).

Blood glucose derived variables were $BG_{baseline}$ and BG-CV (individual coefficient of variation)

## Pharmacokinetic data

Concentrations of insulin glulisine and insulin lispro in serum during the euglycemic clamp procedure were determined by specific assays. Pharmacokinetic parameters were derived from the insulin vs. time profiles.

Primary pharmacokinetic variables were INS-$t_{20\%}$ and INS-AUC(0-1 h).

Secondary PK variables were INS-AUC(0-1.5 h), INS-AUC(0-2 h), INS-AUC(0-3 h), INS-AUC(0-5 h), INS-AUC(0-7 h), INS-AUC(0-10 h), INS-$t_{10\%}$, INS-$t_{50\%}$, INS-$t_{80\%}$, INS-$t_{90\%}$, $INS_{max}$, INS-$t_{max}$, INS-$t_{80\%}$ − INS-$t_{20\%}$, INS-MRT, and ratio INS-AUC(0-1 h) / INS-AUC(0-10 h).

## Anthropometric data

The thickness of the subcutaneous fat layer (skin thickness) at injection sites as determined by MRI, measurement of skin fold thickness at various sites, waist-to-hip ratio (WHR) and BMI.

## Safety data

Clinical laboratory (hematology, clinical chemistry, urinalysis), vital signs, 12-lead electrocardiogram (ECG), physical examination, injection site assessment, and adverse events.

## Statistical procedures

Descriptive statistical analyses were used for all variables. Statistical inferences for pharmacodynamic and pharmacokinetic variables relating to AUCs were based on a parametric ANOVA model. Estimation and inferences concerning time-parameters of the GIR- and insulin-profiles were based on non-parametric statistical procedures.

All PD variables pertaining to GIR-AUCs and $GIR_{max}$ were analyzed using analysis of variance (ANOVA) including the following main factors: insulin type, dose regimen, BMI-group, period, sequence and subject within sequence. The interactions between insulin type, dose regimen and BMI-group were also included in the model. All main effects were tested using F-tests derived

from the ANOVA-table. Based on the LS-means from this model, pairwise comparisons were made.

Analysis of the other PD variables was based on non-parametric statistical methods. 95% non-parametric confidence intervals for the respective median difference in treatment ("test-reference") were calculated for pairwise comparisons.

All PK variables pertaining to INS-AUCs and $INS_{max}$ were natural log-transformed and analyzed using a linear ANOVA model including the following main factors: insulin type, dose regimen, BMI-group, period, sequence and subject within sequence. The interactions between insulin type, dose regimen and BMI-group were also included in the model. All main effects were tested using F-tests derived from the ANOVA-table. Based on the LS-means from this model, mean parameter ratios were estimated (along with 95% confidence intervals) for comparisons.

Analysis of the other PK variables was based on non-parametric statistical methods. 95% non-parametric confidence intervals for the respective median difference in treatment ("test-reference") were calculated for pairwise comparisons.

The influence of the subcutaneous fat layer (skin thickness), as measured by the above mentioned methods, on the pharmacodynamics (as characterized by GIR-AUC(0-1 h), GIR-AUC(0-1.5 h), GIR-AUC(0-2 h), GIR-AUC(0-3 h), GIR-AUC(0-10 h), GIR-$t_{20\%}$, GIR-$t_{80\%}$, GIR-$t_{80\%}$ − GIR-$t_{20\%}$, $GIR_{max}$, GIR-$t_{max}$) and pharmacokinetics (as characterized by INS-AUC(0-1 h), INS-AUC(0-1.5 h), INS-AUC(0-2 h), INS-AUC(0-3 h), INS-AUC(0-10 h), INS-$t_{20\%}$, INS-$t_{80\%}$, $INS_{max}$, INS-$t_{max}$) of insulin glulisine and insulin lispro was analyzed by computing Pearson correlation coefficients with corresponding 95% confidence intervals.

For demographic and safety variables, summary statistics were presented. Where applicable, frequency tables were provided.

## Interim analysis

No interim analysis was performed for this study.

## Results - Study subjects and conduct

Eighty-three healthy subjects (43 males and 40 females), between 20.8 to 61.5 years of age and with BMI between 18.4 and 46.2 $kg/m^2$ were enrolled, randomized and exposed to the study medication (safety population). Three participants terminated the study prematurely prior to completion of all four treatment sessions. These three subjects were included in the safety analysis but not in the PK/PD analysis, and therefore the PK/PD population comprised 80 subjects, 20 in each BMI group. There were no further major protocol deviations.

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## Results - Pharmacodynamics and pharmacokinetics

**Primary PD variables and GIR-$t_{10\%}$ (arithmetic means ± Std.), PK/PD population, N=20 per BMI group**

| Variable | BMI group | Insulin glulisine 0.2 IU/kg | Insulin lispro 0.2 IU/kg | Insulin glulisine 0.4 IU/kg | Insulin lispro 0.4 IU/kg |
|---|---|---|---|---|---|
| GIR-AUC(0-1 h) (mg/kg) | Lean | 184.27 ± 82.07 | 166.02 ± 82.67 | 268.93 ± 94.50* | 190.32 ± 61.61 |
| | Overweight | 105.58 ± 40.21$^{+}$ | 76.71 ± 45.78 | 158.24 ± 62.52$^{+}$ | 125.28 ± 42.27 |
| | Moderately obese | 64.83 ± 41.24 | 54.20 ± 39.03 | 126.88 ± 73.03* | 73.02 ± 51.84 |
| | Severely obese | 54.31 ± 48.85 | 35.57 ± 32.16 | 77.77 ± 49.18 | 60.71 ± 39.17 |
| | Total | 102.25 ± 75.06$^{+}$ | 83.13 ± 72.78 | 157.95 ± 99.71* | 112.33 ± 70.75 |
| GIR-$t_{20\%}$ (h) | Lean | 1.58 ± 0.25 | 1.56 ± 0.30 | 1.67 ± 0.31 | 1.74 ± 0.25 |
| | Overweight | 1.94 ± 0.38 | 1.97 ± 0.46 | 2.06 ± 0.35 | 2.10 ± 0.27 |
| | Moderately obese | 2.17 ± 0.63 | 2.18 ± 0.47 | 2.21 ± 0.52 | 2.23 ± 0.41 |
| | Severely obese | 2.43 ± 0.63 | 2.44 ± 0.51 | 2.45 ± 0.33 | 2.43 ± 0.39 |
| | Total | 2.03 ± 0.58 | 2.04 ± 0.54 | 2.10 ± 0.48 | 2.12 ± 0.42 |
| GIR-$t_{10\%}$ (h) | Lean | 1.06 ± 0.22 | 1.12 ± 0.24 | 1.10 ± 0.21$^{+}$ | 1.20 ± 0.18 |
| | Overweight | 1.29 ± 0.26$^{+}$ | 1.41 ± 0.30 | 1.38 ± 0.24 | 1.44 ± 0.17 |
| | Moderately obese | 1.54 ± 0.50 | 1.55 ± 0.36 | 1.48 ± 0.35 | 1.58 ± 0.33 |
| | Severely obese | 1.63 ± 0.49 | 1.72 ± 0.40 | 1.69 ± 0.25 | 1.66 ± 0.28 |
| | Total | 1.38 ± 0.44$^{+}$ | 1.45 ± 0.39 | 1.41 ± 0.34$^{+}$ | 1.47 ± 0.30 |

Pairwise comparisons vs. same doses and same BMI groups of insulin lispro: $^{+}$ $p<0.05$; *$p<0.0001$

GIR-AUC(0-1 h) was highest in lean subjects and decreased in the order lean, overweight, moderately obese, and severely obese. GIR-$t_{20\%}$ was lowest in lean subjects and increased in the order lean, overweight, moderately obese, and severely obese. With a few exceptions, the

differences between the BMI groups within the treatments were statistically significant. Differences between lean and obese subjects (moderately or severely) were significant in all cases.

For GIR-AUC(0-1 h), ANOVA revealed global statistically significant effects ($p<0.0001$) regarding insulin type, dose and BMI group.

Early metabolic action (GIR-AUC (0-1 h)) was in all BMI-groups consistently greater with insulin glulisine than with insulin lispro at equal dose levels (statistical significant effects flagged in table above).

The comparison for GIR-$t_{20\%}$ revealed no differences between lispro and glulisine. The comparison of GIR-$t_{10\%}$ as an additional marker of onset of metabolic action demonstrated differences in favor of insulin glulisine.

The results found for the other secondary variables generally corresponded to those obtained for the primary variables.

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**Primary PK variables and INS-$t_{10\%}$ (geometric means / geom. Std.), PK/PD population, N=20 per BMI group**

| Variable | BMI group | Insulin glulisine 0.2 IU/kg | Insulin lispro 0.2 IU/kg | Insulin glulisine 0.4 IU/kg | Insulin lispro 0.4 IU/kg |
|---|---|---|---|---|---|
| INS-AUC(0-1 h) (h*µIU/mL) | Lean | 81.71 / 1.27* | 57.51 / 1.49 | 169.96 / 1.37* | 105.18 / 1.34 |
| | Overweight | 71.29 / 1.40* | 46.82 / 1.55 | 136.82 / 1.46* | 79.15 / 1.46 |
| | Moderately obese | 56.89 / 1.51* | 36.74 / 1.54 | 98.68 / 1.57* | 61.30 / 1.67 |
| | Severely obese | 56.65 / 1.40* | 29.59 / 1.75 | 100.42 / 1.40* | 65.73 / 1.63 |
| | Total | 65.82 / 1.44* | 41.36 / 1.68 | 123.21 / 1.54* | 76.11 / 1.60 |
| INS-$t_{20\%}$ (h) | Lean | 0.84 / 1.20 | 0.85 / 1.22 | 0.88 / 1.25$^{+}$ | 0.95 / 1.19 |
| | Overweight | 1.04 / 1.21 | 1.11 / 1.21 | 1.13 / 1.20$^{+}$ | 1.25 / 1.16 |
| | Moderately obese | 1.21 / 1.26 | 1.23 / 1.21 | 1.37 / 1.26 | 1.38 / 1.23 |
| | Severely obese | 1.34 / 1.20 | 1.39 / 1.27 | 1.50 / 1.19 | 1.43 / 1.23 |
| | Total | 1.09 / 1.30 | 1.13 / 1.31 | 1.19 / 1.33 | 1.24 / 1.27 |
| INS-$t_{10\%}$ (h) | Lean | 0.55 / 1.21$^{+}$ | 0.62 / 1.23 | 0.58 / 1.25* | 0.68 / 1.19 |
| | Overweight | 0.68 / 1.22* | 0.79 / 1.21 | 0.74 / 1.21* | 0.89 / 1.14 |
| | Moderately obese | 0.79 / 1.25$^{+}$ | 0.87 / 1.21 | 0.89 / 1.27$^{+}$ | 0.97 / 1.23 |
| | Severely obese | 0.86 / 1.18$^{+}$ | 0.99 / 1.26 | 0.97 / 1.19 | 0.99 / 1.23 |
| | Total | 0.71 / 1.29* | 0.81 / 1.30 | 0.78 / 1.33* | 0.87 / 1.26 |

Pairwise comparison vs. same doses and same BMI groups of insulin lispro: $^{+}$ $p<0.05$; *$p\leq0.0001$

INS-AUC(0-1 h) was highest in lean subjects and decreased in the order lean, overweight, moderately obese/severely obese. INS-$t_{20\%}$ was lowest in lean subjects and increased in the order lean, overweight, moderately obese, and severely obese. With a few exceptions, the differences between the BMI groups within the treatments were statistically significant. Differences between lean and obese subjects (moderately or severely) were significant in all cases.

For INS-AUC(0-1 h), ANOVA revealed global statistically significant effects ($p<0.0001$) regarding insulin type, dose and BMI group.

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Early insulin exposure ( INS-$t_{20\%}$ and INS-$t_{10\%}$ ) revealed consistently faster appearance of insulin glulisine versus insulin lispro at the same dose level. This effect was more pronounced for INS-$t_{10\%}$.

The results found for the other secondary variables generally corresponded to those obtained for the primary variables.

Anthropometric parameters (BMI, WHR etc.) were in general well correlated with the primary pharmacodynamic and pharmacokinetic variables. Correlations with GIR-AUC(0-1 h) and INS-AUC(0-1 h) were negative, with GIR-$t_{20\%}$ and INS-$t_{20\%}$ positive. Correlation coefficients ranged from -0.3186 to -0.6899 (GIR-AUC(0-1 h)), -0.0633 to -0.5968 (INS-AUC(0-1 h)), 0.1014 to 0.6338 (GIR-$t_{20\%}$), and 0.1801 to 0.7071 (INS-$t_{20\%}$), and in their vast majority they were significantly different from zero. Overall, BMI and WHR showed the most pronounced correlation with the primary pharmacodynamic and pharmacokinetic parameters while correlations of biceps and triceps skinfold thickness were the weakest.

Correlation of the anthropometric parameters with the secondary variables generally corresponded to the results obtained for the primary variables.

## Results – Safety

Eighty-three subjects were included in the safety analysis. All 4 treatments were considered to be safe and well tolerated. No serious adverse events were reported during the study. A total of 63 adverse events occurred in 33/83 subjects (39.8%). After insulin glulisine 0.2 IU/kg 7/80 subjects (9%) reported a treatment-emergent adverse event (TEAE), after insulin glulisine 0.4 IU/kg 9/82 (11%), after insulin lispro 0.2 IU/kg 9/81 (11%), and after insulin lispro 0.4 IU/kg 10/81 (12%).

Mild to moderate headache was the most common adverse event, reported by 5 subjects (6%) after 0.2 IU/kg insulin glulisine, by 5 subjects (6%) after 0.4 IU/kg insulin glulisine, by 5 subjects (6%) after 0.2 IU/kg insulin lispro, and by 8 subjects (10%) after 0.4 IU/kg insulin lispro.

Subject 150 (female) was withdrawn from the study after trial period 1 (with 0.4 IU/kg insulin glulisine) due to adverse events (severe eyelid and peripheral edema), “possibly associated” with the study medication and occurring within 24 hours post-dose.

While after dosing with insulin glulisine no hypoglycemic episodes were reported, a few cases of hypoglycemia occurred after insulin lispro administration (one after 0.2 and two after 0.4 IU/kg). In none of these cases, the criteria for “severe hypoglycemia” were fulfilled.

Injection site assessment revealed in 4 cases a hardly perceptible erythema: 10 hours after insulin glulisine 0.2 IU/kg (1 subject), 15 minutes after insulin glulisine 0.4 IU/kg (1 subject), and 10 hours after insulin lispro 0.4 IU/kg (2 subjects). There was no case of reported pain sensation.

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There were no findings of laboratory tests, vital sign measurements, physical examinations, injection site assessments and ECG recordings which were documented and reported as adverse events.

Report date: 10 May 2005