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Sponsor/company:	Sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00297583
		Study Code:	HMR1964A_1501
Generic drug name:	Insulin glulisine	**Date:**	17 April 2007

STUDY SYNOPSIS

Study number HMR 1964A/1501

Title
A single-center, randomized, double-blind, 3-period cross-over trial to compare the effect of insulin glulisine, insulin lispro and unmodified human insulin on the endogenous glucose production in type 1 diabetic patients.

Investigator, study site
Thomas R. Pieber MD, Medical University Graz, Graz, Austria

Study duration and dates The first subject was enrolled on 14 April 2004. The last subject completed the study on 25 May 2004.

Phase I

Objectives
The primary objective of the study was to compare the effect of insulin glulisine, insulin lispro and unmodified human insulin on endogenous glucose production during euglycemic glucose clamps using stable labeled glucose in type 1 diabetic subjects.

The secondary objectives of the study were to assess:

- the effect of insulin glulisine, insulin lispro and unmodified human insulin on plasma nonesterified free fatty acids (NEFA) and glycerol levels
- the effect of insulin glulisine, insulin lispro and unmodified human insulin on plasma lactate levels
- the safety and tolerability of insulin glulisine in comparison to insulin lispro and unmodified human insulin.

Study design
This euglycemic glucose clamp trial followed a single-center, randomized, double-blind, 3-period cross-over, standard Latin-square design and comprised a screening visit to assess subject eligibility (Visit 1), 3 study (treatment) days (Visits 2-4), and a post-study visit (Visit 5). The three treatments were primed stepwise 3-hour intravenous infusions of

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insulin glulisine, insulin lispro or unmodified human insulin (infusion rates 0.33 mU/kg/min, 0.66 mU/kg/min, 1.00 mU/kg/min). Each study day lasted from the subject's arrival in the clinic at about 7:30 a.m. until approximately 10:00 p.m. Subjects who missed a dose were replaced.

At Visit 2, subjects fulfilling the inclusion criteria were randomized to receive insulin glulisine, insulin lispro and unmodified human insulin in a pre-determined sequence (only one treatment at each visit). Euglycemic clamps combined with a tracer dilution technique using D-[6,6-$^2H_2$]-labeled glucose were used to determine endogenous glucose production (EGP) and whole body glucose uptake (GU). The three treatment days were separated by a washout period of 5 to 21 days. The follow-up visit was performed up to 7 days after the last treatment visit.

Number of subjects planned
18

Inclusion criteria
Men or women aged 18-70 years with type 1 diabetes (as defined by the World Health Organization) for at least 2 years, HbA1c $\leq$ 10.0 %, fasting C-peptide < 0.05 nmol/L, treated with intensified insulin therapy (short acting insulin before meals (breakfast, lunch, dinner) with NPH (neutral protamine Hagedorn) insulin, or continuous subcutaneous insulin infusion (CSII) for at least 3 months, and a body mass index (BMI) $\leq$ 30 kg/m² were eligible for inclusion.

Treatments
Insulin glulisine, insulin lispro and unmodified human insulin administered as primed stepwise 3-hour intravenous infusions (infusion rates: 0.33 mU/kg/min, 0.66 mU/kg/min, 1.00 mU/kg/min).

Pharmacokinetic data
Sampling schedule during the clamp procedure was as follows: blood samples were collected at -240 min, at baseline (-40, -30, -20, -10 and 0 min), and after study drug administration at 20-30 min intervals except at steady state (terminal 40 min of each 3 h dosing interval), when samples were collected every 10 minutes (140-180 min; 320-360 min; 500-540 min).

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Serum insulin concentration time profiles were used to calculate the pharmacokinetic variables. Concentrations of serum insulin were analyzed using a radioimmunoassay with an insulin glulisine standard calibration curve for insulin glulisine samples and an unmodified human insulin standard calibration curve for either samples of insulin lispro or unmodified human insulin. The lower limit of quantification was 5.0 µU/mL for free insulin glulisine and 4.3 µU/mL for free immunoreactive insulin.

Pharmacodynamic data

The pharmacodynamic data collected were:

- Glucose infusion rates
- Blood glucose concentrations
- Plasma levels of non-esterified free fatty acids (NEFA)
- Plasma levels of lactate
- Plasma levels of glycerol

Sampling times for blood glucose were every 10 minutes from -240 min to +540 min.

Sampling times for NEFA, lactate, and glycerol were as described for pharmacokinetic data.

The primary derived PD variables were:

- Endogenous glucose production (EGP) – rate per minute standardized on body weight (kg at screening)
- Whole body glucose uptake (GU) – rate per minute standardized on body weight (kg at screening)

Safety data

Adverse events, hypoglycemic episodes, laboratory safety (hematology, biochemistry, urinalysis), physical examination, vital signs, electrocardiogram.

Statistical procedures

Three study populations were defined: the **evaluable population** comprised all subjects who received study medication and completed the study without major protocol violations and for whom the PD data from Visits 2 to 4 were considered evaluable by the sponsor; the **population for PK/PD (pharmacokinetic/pharmacodynamic) analyses**,

which comprised all subjects from the evaluable population and for whom PK data from visits 2 to 4 were considered evaluable by the sponsor; the **safety population**, which was defined as those subjects who received any amount of study medication, according to the treatment received rather than according to the randomized treatment.

Statistical tests were performed as two-sided tests with a nominal type I error level of alpha=0.05. Tests were performed separately for each insulin infusion rate (dose) where applicable. Due to the explorative character of the trial, no adjustment of the error levels due to multiple testing was performed.

Pharmacokinetics: Descriptive statistics of insulin concentrations during steady states were prepared. Summary statistics for ratios of individual geometric means (generated with the highest infusion rate (dose) as the reference dosage) were presented.

Pharmacodynamics: The primary analysis variable was the suppression of endogenous glucose production (SEGP), which was calculated as the absolute change in EGP from basal steady state (from -40 to 0 min before start of study drug administration) to the EGP during each of the three later steady state levels.

An ANOVA (analysis of variance) model was used to examine the null hypothesis of no difference in suppression of EGP between the three treatment groups in the evaluable population. The model included fixed effects for insulin, period, sequence and subject within sequence. From this ANOVA model, p-values for pair-wise-contrasts for insulin glulisine versus unmodified human insulin and versus insulin lispro were generated, as well as 95% two-sided confidence limits for treatment effects. Corresponding linear models for the secondary PD parameters were also performed.

In addition, ANCOVA (analysis of covariance) models including the corresponding baseline value of the various individual PD variable as a covariate (model I) were used to examine the null hypothesis of no difference in the corresponding PD-variable.

Performance of clamp: Clamp performance was assessed with descriptive parameters of individual blood glucose profiles.

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PK/PD: ANCOVA models adjusting for the individual geometric mean insulin concentration at each steady state (model II) were used to analyze %SEGP and %IGU (% increase in GU) per infusion rate (dose).

Safety: Safety parameters were listed individually and analyzed descriptively**.**

Interim analysis

There was no interim analysis.

Results - Study subjects and conduct

In total, 26 subjects with type 1 diabetes mellitus were screened; 18 subjects were randomized. All subjects were treated with insulin and evaluable for safety. One subject, with incomplete PD data, was not evaluable for PK or PD analyses. All subjects completed the study. There were no major protocol violations.

The safety population (n=18, 72% male subjects; 100% white subjects) had a mean age of 36.9 years (range: 23-54 years) and a mean BMI of 23.56 kg/m2 (range: 19.1-29.0 kg/m2). Mean HbA1c was 7.35% (range: 5.6-8.8%). Demographics of the evaluable population were similar. All subjects had been diagnosed with type 1 diabetes mellitus for at least 3 years.

It should be noted that the PK/PD population and the evaluable population turned out to be identical for this study.

Results - Pharmacokinetics and pharmacodynamics

Pharmacokinetics: Individual geometric mean serum insulin concentrations at steady state were comparable between treatments for each of the three infusion rates (doses). The geometric means for insulin glulisine, insulin lispro and unmodified human insulin were as follows: 0.33 mU/kg/min: 24.3, 24.6, 25.2 µU/mL; 0.66 mU/kg/min: 48.5, 43.2, 46.1 µU/mL; 1.0 mU/kg/min: 71.7, 63.5, 70.6 µU/mL. The ratios of concentrations for dosage steps (low/high and middle/high) were also comparable between treatment groups and were for each treatment close to the 1/3 and 2/3 fractions of the 1.0 mU/kg/min respectively, indicating dose proportionality.

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Pharmacodynamics: Insulin glulisine suppressed EGP at all dosages in subjects with type 1 diabetes mellitus (tabulated below). The insulin dose-increase to 1.0 mU/kg/min (high dose) did not suppress EGP much further than was already observed at 0.66 mU/kg/min (medium dose) for either insulin. EGP was not completely suppressible with any dose or insulin. The low variability in EGP accounted for statistically significant differences which were considered clinically-not-relevant.

In the primary analysis, the level of absolute SEGP documented for insulin glulisine was significantly lower than that of insulin lispro at all dosage levels (p=0.010, 0.030, and 0.008 for the low, medium and high dosage levels, respectively) and significantly lower than the SEGP documented for unmodified human insulin at the lowest dosage level only (p=0.038). The absolute maximum difference in the mean SEGP between insulin treatments was approximately 0.4 mg/kg/min (insulin glulisine versus insulin lispro at high dose), a difference without clinical relevance.

Comparison of basal EGP values showed statistically significant differences between insulin treatments overall (p=0.015) and for the comparisons between insulin glulisine and insulin lispro (p=0.011) and between insulin glulisine and unmodified human insulin (p=0.012). A highly significant effect of the covariate “basal EGP” on the outcome (SEGP) could be observed from the corresponding ANCOVA analysis (model I). When adjusted for basal EGP, there were differences in SEGP between the insulin treatments.

There was no effect of the covariate “individual insulin level” on the outcome (%SEGP) in the corresponding ANCOVA analysis (model II). Nevertheless, when adjusted for individual insulin levels, there was no statistically significant or clinically relevant difference in %SEGP between the insulin treatments.

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Variable	Infusion rate (dose)	ls mean			Glulisine vs. Lispro		Glulisine vs. Unmodified human insulin	
(unit)	(mU/kg/min)	Glulisine	Lispro	Unmodified human insulin	Treatment effect	95% CI	Treatment effect	95% CI
EGP [a] (mg/kg/min)	Basal	1.88	2.12	2.12	-	-	-	-
ANOVA								
SEGP (mg/kg/min)	0.33	-1.08	-1.34	-1.29	0.258	0.066, 0.451	0.205	0.013, 0.398
	0.66	-1.36	-1.64	-1.56	0.284	0.029, 0.540	0.196	-0.059, 0.451
	1.00	-1.30	-1.70	-1.49	0.400	0.115, 0.685	0.189	-0.096, 0.474
%SEGP (%)	0.33	-57.78	-63.21	-61.00	5.421	-0.658, 11.500	3.213	-2.866, 9.292
	0.66	-72.58	-77.60	-72.08	5.020	-3.727, 13.768	-0.506	-9.254, 8.242
	1.00	-68.61	-79.93	-69.32	11.325	0.890, 21.759	0.705	-9.729, 11.140
Max SEGP (mg/kg/min)	Overall	-1.45	-1.81	-1.65	0.362	0.104, 0.621	0.200	-0.059, 0.458
ANCOVA model I (adjusted for basal EGP values)								
SEGP (mg/kg/min)	0.33	-1.21	-1.28	-1.23	0.066	-0.079, 0.211	0.017	-0.127, 0.161
	0.66	-1.54	-1.56	-1.47	0.018	-0.162, 0.198	-0.065	-0.244, 0.114
	1.00	-1.48	-1.62	-1.41	0.134	-0.097, 0.365	-0.071	-0.301, 0.158

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Variable	Infusion rate (dose)	ls mean			Glulisine vs. Lispro		Glulisine vs. Unmodified human insulin	
(unit)	(mU/kg/min)	Glulisine	Lispro	Unmodified human insulin	Treatment effect	95% CI	Treatment effect	95% CI
SEGP (%)	0.33	-59.21	-62.52	-60.35	3.314	-3.357, 9.985	1.149	-5.495, 7.793
	0.66	-75.13	-76.36	-70.91	1.234	-8.168, 10.635	-4.215	-13.579, 5.149
	1.00	-71.74	-78.41	-67.89	6.674	-4.500, 17.848	-3.851	-14.980, 7.279
Max SEGP (mg/kg/min)	Overall	-1.64	-1.72	-1.56	0.080	-0.087, 0.248	-0.076	-0.243, 0.090

[a] Comparison of basal EGP values showed significant differences between treatments and overall (overall p=0.015; insulin glulisine vs. insulin lispro p=0.011; insulin glulisine vs. unmodified human insulin p=0.012).

For the secondary pharmacodynamic variable, IGU, there was a step-wise increase in GU with the increasing insulin infusion rates (doses) of the three insulin treatments. The greatest increase was achieved with insulin glulisine at all insulin infusion rates. The differences between the insulin treatments were neither statistically significant nor clinically relevant at any dosage level.

For the secondary pharmacodynamic variables reduction in NEFA and increase in plasma lactate following adjustment of basal values, there were statistically significant differences between insulin glulisine and insulin lispro at 0.66 mU/kg/min (p=0.046) and 1.0 mU/kg/min (p=0.031). None of the differences were clinically relevant. There were no statistically significant or clinically relevant differences between insulin glulisine and unmodified human insulin at any dosage level.

The change in plasma levels of glycerol (baseline adjusted) showed neither statistically significant nor clinically relevant differences between the insulin treatments.

Results - Safety

There were no serious adverse events.

In total 17 AEs were reported of which 15 were treatment emergent adverse events (TEAEs). The incidence of TEAEs was lower with insulin glulisine (16.7%) than with insulin lispro (38.9%) or unmodified human insulin (27.8%). The incidence of possibly-related TEAEs also was lower with insulin glulisine. There was only one case of hypoglycemia (subject treated with unmodified human insulin).

There were no clinically relevant abnormalities in hematology, blood chemistry, urinalysis, vital signs, physical examination, electrocardiogram or body temperature.

Date of the report: 24 February 2005