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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT01159353
		Study Code:	APIDR_C_01160
Generic drug name:	Insulin Glulisine	Date:	15/Jul/2010

Title of the study:	A randomized, double blind study to assess the pharmacodynamic and pharmacokinetic effects of insulin glulisine in obese subjects with type 2 diabetes after a standard meal in comparison to insulin aspart. Study Code APIDR_C_01160		
Coordinating investigator:	Pr G. BOLLI (Perugia, Italy)		
Study center(s):	This multinational study was conducted at 3 active sites in France (Nantes), Italy (Perugia), and in United Kingdom (Cardiff).		
Publications (reference):	None at the time of the report writing		
Study period: Date first subject enrolled: 17-Sep-2007 Date last subject completed: 07- Apr-2008		Phase of development: Phase I	
Objectives:	Primary: *Pharmacodynamic objective* The primary objective was to assess the effect of insulin glulisine on the post-prandial plasma glucose excursion during the first hour after a standard meal in comparison to insulin aspart. Secondary: *Pharmacodynamic objectives* • To assess the effect of insulin glulisine on the postprandial plasma glucose excursion during the 6 hours after a standard meal in comparison to insulin aspart *Pharmacokinetic objective* • To assess post-prandial plasma insulin excursion after a standard meal, in each treatment group. *Safety* • To assess safety of insulin glulisine in comparison to insulin aspart		
Methodology:	Randomized, double-blind, 2-period cross-over study performed in 3 centers.		
Number of subjects:	Planned: 36	Randomized: 37	Treated: 37
Evaluated:		Safety: 37	Pharmacodynamics / Pharmacokinetics: 30
Diagnosis and criteria for inclusion:	Men or women presenting with type 2 diabetes for at least one year, treated with oral antidiabetic agents (OADs) for at least 6 months, aged between 18 and 70 years, with baseline C-peptide ≥ 0.1 nmol/L and HbA1c < 8.5 % were eligible for the study.		

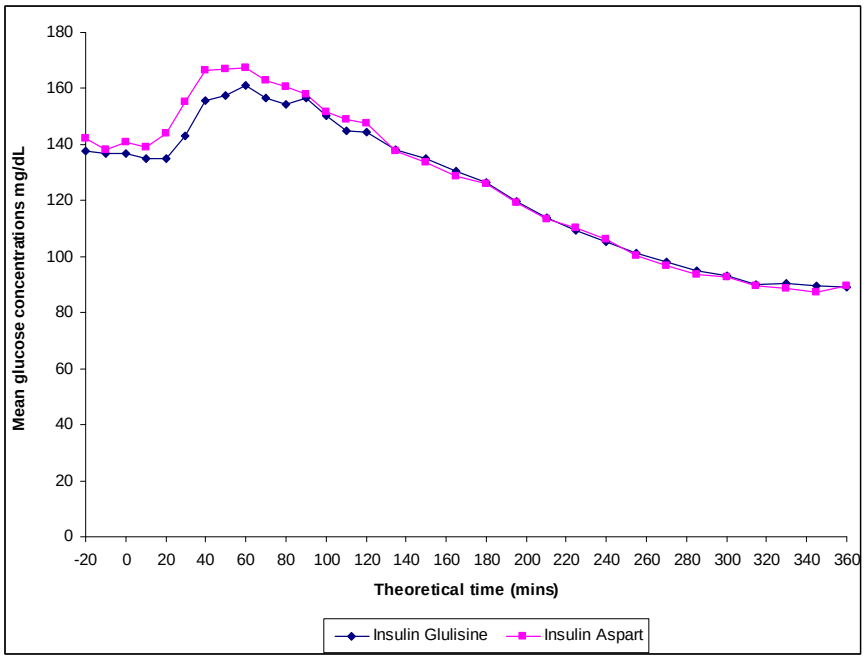
Investigational products: Dose: Administration:	• Insuline glulisine: Apidra® 100 U/mL, solution for injection in vial. • Insulin aspart: NovoRapid® 100 U/ml, solution for injection in vial. 0.2 U/Kg Single subcutaneous injection with syringe in the periumbilical abdomen within 2 min. before the standard meal.
Duration of treatment: Two study days separated by a 7-day wash-out period.	Duration of observation: The study comprised: • A screening period of 1-2 weeks : to access subject eligibility • Two study days (with a wash-out period of 7 days between the study days) • A follow-up visit (within 2 weeks after the end of the study treatment period)
Criteria for evaluation:	
Pharmacodynamics: Safety: Pharmacokinetics:	Primary analysis variable: Area under the curve of plasma glucose between 0 and 60 min ($AUC_{0\text{-}1h.}$) Secondary analysis variables: • Plasma glucose AUC_{0-2h} • Plasma glucose AUC_{0-4h} • Plasma glucose AUC_{0-6h} • Δ plasma glucose at 1 h after standard meal • Maximum Glucose concentration (GLU max) • Maximum Glucose excursion (Δ GLU max) • Time to Δ GLU max • Time to fraction of total glucose AUC (10%, 20%) Adverse events reported by the subject or noted by the investigator. Standard hematology and blood chemistry, vitals signs, physical examination, and inspection of site injection. • Plasma insulin AUC_{0-1h} • Plasma insulin AUC_{0-2h} • Plasma insulin AUC_{0-4h} • Plasma insulin AUC_{0-6h} • Maximum concentration (C_{max}) • Time to fraction of total insulin AUC (10%, 20%) • Time to C_{max}
Pharmacodynamics and Pharmacokinetic sampling times and bioanalytical methods:	Pharmacodynamics: Blood samples were taken at T_0-20, T_0-10, T_0 then every 10 minutes during the two first hours and then every 15 minutes until 360 minutes to measure plasma glucose. In all centres the assays were performed using the glucose oxidase method. Pharmacokinetic For the plasma insulin assay, Blood collection was done at T_0, T_0+10, T_0+20, T_0+40, T_0+60, then every 30 min until 120 min and then every 60 min until 360 min. Insulin aspart and insulin glulisine concentrations were determined centrally using a specific method: • Insulin glulisine concentration was determined using Linco method kits. • Insulin aspart concentration was determined using Capio Diagnostics kits.

Statistical methods:	Pharmacodynamics The AUCs, GLUmax and ΔGLUmax of uncorrected blood glucose concentrations as well as of baseline corrected concentrations were analyzed by ANOVA, with subject, treatment, sequence group and period effect. Two-sided 90% CIs were provided for the respective mean differences and mean ratios (Fieller's Theorem). The Wilcoxon signed rank sum test was applied to time to ΔGLUmax and time to fraction of total glucose AUC (10%, 20%). Hodges-Lehman 90% CIs were provided for median difference for time to ΔGLU max and time to fraction of total glucose AUC (10%, 20%). Superiority testing was done at the 5% significance level. For all variables other than time measurements: in case of non significant difference, if the two-sided 90% CIs for the ratios of the means were within the conventional equivalence range (80% ; 125%), bioequivalence was concluded. Pharmacokinetics The AUCs and Cmax for insulin were analyzed by ANOVA, with subject, treatment, sequence group and period effect. If necessary, natural log transformation was applied on data before analysis. Two-sided 90% CIs were provided for the respective mean differences and mean ratios. The Wilcoxon signed rank sum test was applied to Tmax and time to fraction of total glucose AUC (10%, 20%). Hodges-Lehman 90% CIs were provided for median difference for Tmax and time to fraction of total insulin AUC (10%, 20%). Superiority testing was done at the 5% significance level. For all variables other than time measurements: in case of non significant difference, if the two-sided 90% CIs for the ratios of the means were within the conventional equivalence range (80% ; 125%), bioequivalence was concluded.
Summary:	Overall, 43 subjects were screened and 37 were randomized in the study. All the 37 randomized subjects were evaluated for safety. Thirty (30) subjects (81.1%) were included in the PD and PK analyses. Six subjects had at least one major protocol deviations. Two out of these 6 subjects were excluded after the database lock, following the Steering Committee recommendation: the first due to Aspart plasma levels very low, incompatible with aspart administration, the second due to meal duration superior to 1 H. One subject was withdrawn after the first administration from the study at his own request. Thirty six (36) subjects received both treatments and one (1) subject only insulin aspart.

Pharmacodynamic results:

Mean glucose plasma concentrations-time profiles after insulin glulisine and insulin aspart injections are displayed thereafter:

Mean glucose concentration over time – PD population



Mean values (median values for Tmax) of main PD parameters were calculated. ANOVA results are presented in the following table.

Glucose concentration Results of ANOVA – PD population:

Parameter	Estimated Sample mean (n=30)		p-value	Fieller's estimate and 90%CI for mean ratios (Glulisine/Aspart)#
	Insulin Glulisine	Insulin Aspart		
AUC (0-1h) (mg.h/dL)	148.52	158.26	0.0455	93.84%[89.97;99.41]
AUC (0-2h)(mg.h/dL)	300.33	315.28	0.1247	95.26%[91.24;100.90]
AUC (0-4h)(mg.h/dL)	548.89	564.07	0.3622	97.31%[93.46;102.92]
AUC (0-6h)(mg.h/dL)	737.74	750.19	0.5382	98.34%[94.82;103.53]
Δ GLUmax (mg/dL)	32.70	40.48	0.0634	80.78%[69.57;100.20]
Δ plasma glucose at 1 h (mg/dL)	23.43	26.62	0.5473	88.04%[69.78;134.57]
GLUmax (mg/dL)	169.97	181.03	0.0337	93.89%[90.09;98.86]
Time to DeltaGLUmax (min)	60.0*	59.5*	0.3328	-5.2[-20.0;4.5]###

#Point estimate and 90%CI for the ratio of treatment means according to Fieller's Theorem, based on untransformed data

###Point estimate and 90%CI for the difference of treatment medians (glulisine-aspart) from non-parametric analysis (Hodges and Lehmann method), based on untransformed data

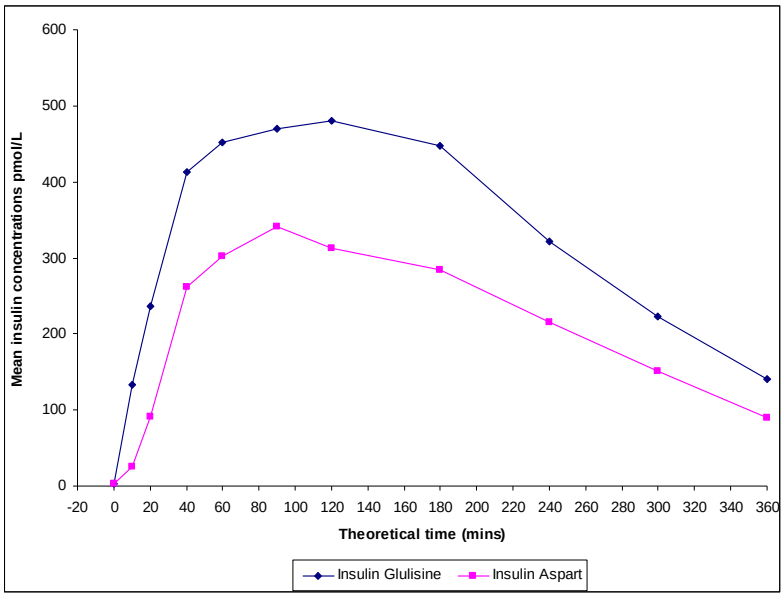
* Median values

Safety results:	During the first hour post insulin injection, plasma glucose concentration was significantly lower after insulin glulisine than after insulin aspart administration (p=0.0455). Peak of glucose was also lower after glulisine administration as compared to insulin aspart one (p=0.0337). These results revealed a better glucose control for insulin glulisine during this phase. When regarding the global assessment period (6 hours), glucose bioavailability calculated using baseline corrected and uncorrected glucose plasma levels and glucose excursions were similar between the 2 treatments and so glucose control could be considered as equivalent between both insulins. No SAE occurred during the study and no TEAE led to study discontinuation. Overall, 5 TEAEs were reported in 4 subjects (10.8%) respectively during the study. Two TEAEs were reported in 2 subjects (5.6%) under insulin glulisine versus 3 TEAE in 3 subjects (8.1%) under insulin aspart. All subjects recovered from TEAE at the end of the study. TEAEs and possibly related TEAEs were similar in terms of type, incidences and intensity between treatments. TEAEs described during the study were in accordance with the known safety profiles of the administered treatments. No clinically significant changes in laboratory value and vital signs were reported during the study. Episodes of hypoglycemia defined as glucose level < 70 mg/dL with or without symptom were described in 13 (36.1%) and in 16 (43.2%) subjects after insulin glulisine and insulin aspart injections respectively. Incidences of symptomatic hypoglycemia and of pain at injection site were similar between treatments. Overall, study treatments were well-tolerated during the study.

Pharmacokinetic results

Mean insulin plasma concentrations-time profiles after insulin glulisine and insulin aspart injections are displayed thereafter:

Mean Insulin Concentration over time – PK population



Insulin plasma levels were higher after glulisine injection in comparison to insulin aspart injection and remained higher throughout the assessment period (from 0 to 6 h post injection).

Insulin Concentration Results of ANOVA – PK population:

	Estimated Sample Geometric mean (Arithmetic mean) (n=30)			Fieller's estimate and 90%CI for mean ratios (Glulisine/Aspart) #
Parameter	Insulin Glulisine	Insulin Aspart	p-value	
AUC (0-1h) (pmol.h/L)	271.80(296.79)	137.91(166.59)	<.0001	197.08%[156.93;247.50]
AUC (0-2h) (pmol.h/L)	717.24(781.33)	450.23(490.05)	<.0001	159.31%[137.64;184.39]
AUC (0-4h) (pmol.h/L)	1552.57(1628.14)	987.73(1037.96)	<.0001	157.19%[141.44;174.68]
AUC (0-6h) (pmol.h/L)	2001.98(2077.38)	1288.95(1333.34)	<.0001	155.32%[141.05;171.03]
Cmax (pmol/L)	533.86(570.13)	362.95(385.08)	<.0001	147.09%[132.54;163.24]
Tmax (min)	120.0*	93.0*	0.5133	16.5[-9.5;37.0]###

Point estimates and 90% CI for the ratio of treatment means, based on ln-transformed data.
###Point estimate and 90%CI for the difference of treatment medians (glulisine-aspart) from non-parametric analysis (Hodges and Lehmann method), based on untransformed data
* Median values

Significant higher values for the peak of insulin (Cmax) were obtained with insulin glulisine as compared to insulin aspart: +47% (p<0.0001).
Plasma exposures to insulin assessed by AUCs calculated over 1 to 6 hours were at least 1.5 higher after insulin glulisine sc injection in comparison to insulin aspart.
No significant difference was shown between treatments for rate of absorption.

Date of report:	Final version dated 9-Feb-2009