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Sponsor/company:	sanofi-aventis	clinicaltrials.gov Identifier:	NCT00335465
		Study Code:	HOE901_4053
Generic drug name:	Insulin Glargine	Date:	03/Jul/2009

Title of the study:	PILOT STUDY FOR THE EVALUATION OF THE EFFECTS OF INSULIN TREATMENT ON MYOCARDIAL FUNCTION, PERFUSION, AND GLUCOSE METABOLISM IN PATIENTS WITH PRIMARY LEFT VENTRICULAR DYSFUNCTION AND TYPE 2 DIABETES (Study Code: HOE901/4053)		
Investigator(s):	Prof. Eleuterio Ferranini - Department of Internal Medicine – Institute of Clinical Physiology - University of Pisa - Italy		
Study center(s):	Single center study, in Italy		
Publications (reference):	N/A		
Study period: Date first patient enrolled: 28-Sep-2005 Date last patient completed: 09-Jun-2008		Phase of development: IV	
Objectives:	The primary objective of the present study was to assess changes of myocardial glucose uptake (MGU) during clamp studies using PET scanning in patients with type 2 diabetes and idiopathic LVD. The secondary objectives of the study were: assessment of changes of myocardial microcirculation at rest and during adenosine stimulation using PET; assessment of changes in myocardial structure and function evaluated by magnetic resonance imaging (MRI) and/or echocardiography (2D ECHO); assessment of glycaemic control by measurement of HbA1c, fasting blood glucose and insulin levels; assessment of safety (adverse event profile, laboratory data).		
Methodology:	Open label, single center, pilot study.		
Number of patients:	Planned: 15	Screened: 15	Treated: 12
Evaluated:	Intention-To-Treat (ITT) population: 12 Per-protocol (PP) population: 12		Safety: 12
	ITT population: all treated patients having taken at least one dose of study drug and with both the baseline and a final control visit done. PP population: all patients in the ITT population without major protocol violations. Safety population: all randomized patients known to have taken at least one dose of study drug		
Diagnosis and criteria for inclusion:	Male / female patients (18-75 years) with type 2 diabetes mellitus (either new or previous diagnosis), left ventricular (LV) systolic dysfunction (2D-Echo LVEF < 50%) with or without LV dilation (2D-Echo LV EDD ≥ 56 mm) or left ventricular end-diastolic diameter (LVEDD) > 55mm with or without LV dysfunction, angiographycally normal coronary arteries (< 50% vessel narrowing).		

Investigational product: Dose: Administration:	insulin glargine (3 ml cartridges containing 100 U/ml) Individualized, once daily, dose to reach mean fasting plasma glucose (FPG) between 80 mg/dl (4.44 mmol/l) and 100 mg/dl (5.56 mmol/l) in patients treated with oral antidiabetic drugs (OADs), or FPG < 150 mg/dl (mmol/l) in patients previously treated with insulin. subcutaneous
Duration of treatment: overall treatment duration of 6 months with insulin glargine, including a 2-week titration phase (visit 2 to visit 5) and a treatment phase (visit 6 to visit 8)	Duration of observation: 28-25 weeks: 4 weeks or 1 week run-in period + 6 months of treatment with study drug
Reference therapy:	N/A (open label study)
Criteria for evaluation:	
Efficacy:	Primary: assessment of changes of myocardial glucose uptake during clamp studies using PET in order to verify the relationship linking insulin resistance and hyperglycaemia with the pathogenesis and treatment of myocardial dysfunction, in the absence of coronary artery disease. Secondary: • Assessment of changes of myocardial microcirculation at rest and during adenosine stimulation and during clamp studies using PET; changes in liver and skeletal muscle blood flow during adenosine stimulation and glycaemic clamp using PET; • Assessment of changes of glucose uptake by liver, skeletal muscle and adipose tissue during clamp studies using PET and fat content in liver using MRI; • Assessment of changes in myocardial metabolism by MRI, myocardial structure, and systolic and diastolic myocardial function, evaluated by magnetic resonance imaging (MRI) and/or echocardiography (2D ECHO); • Assessment of glycaemic control by measurement of HbA1c, fasting blood glucose and insulin levels; daily glucose profile; lipid profile (total cholesterol and fractions; triglycerides); inflammatory indexes (CRP, ESR); norepinefrine dosage;

Safety:	Adverse events' profile, standard laboratory parameters, vital signs, electrocardiogram.
Statistical methods:	In the primary analysis, mean changes between Visit 0 (baseline) and Visit 8 with the relative 95% two-sided confidence interval were reported; differences were compared by way of the Paired Samples T-test. No interim analysis was performed Same statistical analysis was performed for variables considered for secondary efficacy. Correlations of changes between baseline and end of treatment were calculated for primary and secondary variables using Spearman correlation. Correlations taken into consideration were between changes within PET variables, between changes of PET variables and anthropometrics and biochemical variables, between changes of PET variables and biochemical variables related to euglycemic clamp, between changes of PET variables and 2D-ECHO variables, between changes of PET variables and others MRI variables, between changes of 2D-ECHO variables and anthropometrics and biochemical variables, between changes of 2D-ECHO variables and biochemical variables related to euglycemic clamp. Spearman correlation was also calculated for correlations between primary and secondary variables at baseline, such as: correlations between PET variables and MBF at baseline (at rest), between PET variables and MBF during i.v. adenosine, between PET variables and MBF reserve, between PET variables and FDG uptake, between PET variables and MBF during clamp, between PET variables and FDG extraction fraction, between PET variables and M-M/I value, between PET variables and MBF/Insulin (resting, perfusion, metabolic), between PET variables and anthropometrics and biochemical variables, between PET variables and biochemical variables related to euglycemic clamp, between PET variables and 2D-ECHO variables, between anthropometrics and biochemical variables and biochemical variables related to euglycemic clamp, between 2D-ECHO variables and anthropometrics and biochemical variables, between 2D-ECHO variables and biochemical variables related to euglycemic clamp. Changes in the safety laboratory data were analyzed at each time point with the relative 95% CI and reported with the corresponding p-value based on T-test for paired sample. The rate of patients with Treatment Emergent Adverse Events (TEAEs) was calculated.

Summary:

This pilot study recruited consecutive patients with T2DM and signs of left ventricular dysfunction with otherwise normal coronary arteries, for a 6-month treatment with insulin glargine, to evaluate the pathogenesis of myocardial dysfunction in relation to insulin resistance and hyperglycaemia. The primary objective was the assessment of the changes of myocardial glucose uptake during clamp studies using PET.

12 patients were evaluable for the study, out of 15 patients screened: 6 patients with newly diagnosed T2DM and 6 patients with previously diagnosed T2DM (same patients in the ITT, PP and safety population). Three screened patients were excluded because of elevated fasting glycaemia during run-in, occurrence of a new adverse event, poor compliance and diastolic blood pressure > 100 mmHg. No major protocol violations occurred.

Demographic characteristics and other clinical information are reported in the following table:

ITT / PP / safety population baseline characteristics	**Insulin Glargine (N=12)**
Male Female	12 (100.0%) 0
Mean age (years ± SD)	65.1 ± 5.0
Ethnic group: white	12 (100.0%)
BMI (kg/m^2 ± SD)	29.0 ± 4.1
mean SBP (mmHg ± SD) DBP (mmHg ± SD)	137.0 ± 14.6 78.8 ± 7.4
mean HR (b/min ± SD)	69.2 ± 8.9
mean LVEF (% ± SD)	41.5 ± 10.0
mean EDD (mm ± SD)	62.1 ± 7.89
Average calories in the diet (kcal ± SD)	2126.3 ± 209.3

All patients reported “congestive cardiomyopathy” in their medical history and all showed an abnormal electrocardiogram. 83.3 % of patients were taking carvedilol, 75 % ACE inhibitors, and 75 % diuretics (66.7% furosemide and 8.3% chlortalidone).

At baseline, one patient was on oral antidiabetic therapy (repaglinide) and two were taking insulin therapy.

The presence of “Dislipidemia” was reported in 7 patients and “Hypertension” in 4 patients.

During the study, the patients received insulin glargine for an overall exposure of 226.8 (23.51) days. End-of-study plasma insulin concentration was 79.959 (22.833) µU/mL, with a significant increase reported at visit 5 (+17.97 µU/ml; p=0.029) and visit 6 (+10.36 µU/ml; p=0.022) compared to baseline.

Efficacy results:	Data reported for the ITT and PP populations are identical because of the absence of major protocol violations. Therefore, efficacy data are reported as single results for the two populations analyzed. Myocardial glucose (2-fluoro-2-deoxy-glucose - FDG) uptake: changes from baseline to end of treatment in average FDG uptake from 13 LV myocardial segments were not significant, as shown by the change in the coefficient of variation (-6.5936; 95% CI: -18.3673; 5.1802, p = 0.243). Average FDG uptake values of septal, inferior and anterior LV wall showed a reduction from baseline to the end of treatment, as well as the overall average value based on average septal wall, average inferior wall, average anterior wall and apical wall; however changes were not statistically significant, as shown in the next table:

FDG uptake	Δ (V0-V8) (µmol/min/g)	C.I.	p
average septal wall:	-0.0506	-0.1846; 0.0835	0.424
average inferior wall:	-0.0834	-0.2653; 0.0986	0.327
average anterior wall	-0.1053	-0.3133; 0.1027	0.289
overall average	-0.0555	-0.2176; 0.1065	0.467

Regional FDG extraction fraction in myocardium: the average FDG extraction fractions were non significantly reduced at the end of treatment, compared to baseline: septal wall −1.7705% (95% CI: −7.4146 ; 3.8737, p = 0.501); inferior wall −3.2950 % (95% CI: −11.6768 ; 5.0868, p = 0.397); anterior wall −2.790% (95% CI: −10.4045 ; 4.8227, p = 0.433); overall MBF −2.1008% (95% CI: −9.0864 ; 4.8849, p = 0.518)

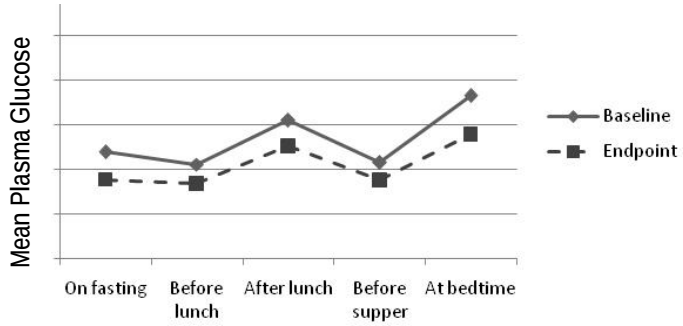
FDG uptake in liver, skeletal muscle and adipose tissue: FDG uptake non-significantly decreased in the liver at the end of treatment, compared to baseline (-0.0391 µmol/min/g; p = 0.191), in the skeletal muscle (- 0.0007 µmol/min/g; p = 0.940) and in the adipose tissue (-0.0005 µmol/min/g; p = 0.879).

Echocardiography: interventricular septal thickness (-0.778 mm), fractional shortening (-0.444%), cardiac output (-141.8 ml/min) and LVEF (-0.417 mm) showed a non statistically significant reduction between baseline and end of treatment. LV posterior wall thickness (0.444 mm), LV end−diastolic volume (17.125 ml), LV end−systolic volume (14 ml), LV mass (23.889 g), LV mass / body surface area (9.213 g/m2), LV remodeling index (0.005), stroke volume (3.6 ml), EDD (1.0 mm), and LV Stroke Work (47511.30) showed a non statistically significant increase between baseline and end of treatment.

	Myocardial Blood Flow (MBF): not significant reductions were observed at the end of treatment, compared to baseline, for MBF in the septal wall (-0.0084 ml/min/g; 95% CI: -0.0816; 0.0649, p = 0.806), anterior wall (−0.0265 ml/min/g; 95% CI: −0.1089 ; 0.0558, p = 0.493) and inferior wall (−0.0356 ml/min/g; 95% CI: −0.1011 ; 0.0299, p = 0.257), as well as overall (−0.0158 ml/min/g; 95% CI: −0.0796 ; 0.0480, p = 0.597). Changes of MBF during i.v. adenosine were also not significant at the end of treatment, compared to baseline: septal wall −0.1129 ml/min/g (95% CI: −0.2918 ; 0.0660, p = 0.190); inferior wall −0.0541 ml/min/g (95% CI: −0.2537 ; 0.1455, p = 0.559); anterior wall −0.1489 ml/min/g (95% CI: −0.3857 ; 0.0880, p = 0.192); overall −0.1012 ml/min/g (95% CI: −0.2915 ; 0.0892, p = 0.264). The MBF reserve was not significantly reduced at the end of treatment, compared to baseline: septal wall −0.2572 ml/min/g (95% CI: −0.6075 ; 0.0930, p = 0.133); inferior wall −0.0045 ml/min/g (95% CI: −0.4825 ; 0.4735, p = 0.984); anterior wall −0.2894 ml/min/g (95% CI: −0.6026 ; 0.0238, p = 0.067); overall −0.1969 ml/min/g (95% CI: −0.4845 ; 0.0908, p = 0.158). The average MBF during clamp non significantly increased at the end of treatment, compared to baseline: septal wall 0.0572 ml/min/g (95% CI: −0.1532 ; 0.2675, p = 0.558); inferior wall 0.0446 ml/min/g (95% CI: −0.1912 ; 0.2804, p = 0.679); anterior wall 0.0129 ml/min/g (95% CI: −0.1727 ; 0.1985, p = 0.880); overall MBF 0.0382 ml/min/g (95% CI: −0.1359 ; 0.2124, p = 0.635). Skeletal muscle Blood Flow (SBF): a non significant increase was observed for SBF at the end of treatment, compared to baseline (0.0045 ml/min/g; 95% CI: −0.0552 ; 0.0642, p = 0.871). Also SBF during clamp non significantly increased at the end of treatment, compared to baseline (0.0048 ml/min/g; 95% CI: −0.0596 ; 0.0692, p = 0.872). Hepatic Blood Flow (HBF): a non significant increase was observed for HBF at the end of treatment, compared to baseline (0.0644 ml/min/g; 95% CI: −0.0312 ; 0.1600, p = 0.164). A statistically significant reduction was found for HBF during i.v. adenosine at the end of treatment, compared to baseline (−0.3647 ml/min/g; 95% CI: −0.5511 ; −0.1784, p = 0.001). Also HBF during clamp non significantly increased at the end of treatment, compared to baseline (0.0799 ml/min/g; 95% CI: −0.0693 ; 0.2291, p = 0.260). Free Fatty Acids (FFA): FFA showed reduction between baseline and end of treatment (−0.2055 mmol/l; 95% CI: −0.6033 ; 0.1924, p = 0.277). FFA showed increase during metabolic study (0.0150 mmol/l; 95% CI: −0.0912 ; 0.1212, p = 0.762). Glycaemia: plasma glucose showed a reduction of −20.0 mg/dl (95% CI: −45.2002 ; 5.2002, p = 0.108) from baseline (142.91 mg/dl) to the end of treatment (122.91 mg/dl). The change was −14.1667 mg/dl during perfusion (p = 0.271) and −13.0833 mg/dl during the metabolic study (p = 0.247).

	Insulinemia: basal plasma insulin (at rest) showed a reduction of −1.157 µU/ml (95% CI: −55.046 ; 52.732, p = 0.960) from baseline (31.271 µU/ml) to the end of treatment (30.114 µU/ml). The change was −18.760 µU/ml (95% CI: −88.303 ; 50.783, p = 0.557) during perfusion and −0.060 µU/ml (95% CI: −39.225 ; 39.105, p = 0.997) during the metabolic study. An additional analysis was performed after excluding two patients with very high and very low values. In this setting, the difference between baseline and end of treatment became positive, and insulin increased of 5.763 µU/ml (95% CI: −16.555 ; 28.080) however the change was not statistically significant (p = 0.561). Metabolic rate: change of metabolic rate at the end of treatment, compared to baseline, was −1.033 µmol/min/kg. Change of metabolic rate adjusted by mean insulin was -0.005 (µmol /min/kg)/(µUl/ml) Both variables did not show a statistically significant change (p = 0.509 and p = 0.895, respectively). MRI: the change between baseline and end of treatment in the functional parameters was negative for left atrial diameter (-1.0 mm; p = 0.240), right ventricular end−diastolic diameter (−0.375 mm; p = 0.349), left ventricular ejection fraction (-1.0%; p = 0.568), left ventricular mass (−2.125 g; p = 0.793) and left ventricular mass / body surface area (−1.25 g/m2; p = 0.755) whereas it was positive for other functional parameters considered. None of the functional parameters considered showed statistically significant changes. The change for HARP analysis calculated for E1 and E2 values of 16 LV myocardial segments showed statistical significant changes only for E1 Anterior Lateral Basal (p = 0.043); E1 Inferior Middle (p = 0.031); E1 Anterior Apical (p = 0.038); E1 Lateral Apical (p = 0.035) Fasting plasma glucose (FPG): compared to baseline, FPG significantly decreased during the treatment phase, as shown in the following table: visits v.5 v.6 v.7 v.8 Δ (mg/dl) -36.36 -28.83 -29.83 -14.08 p 0.007 0.006 0.001 0.007 HbA1c: a non significant decreasing trend was found during treatment, as also detected with the Random Coefficient Models (RCM: -0.06, p = 0.067) Insulin: a statistically significant increase was found between baseline and visit 5 (+17.97 µU/ml; p = 0.029) and visit 6 (+10.36 µU/ml; p = 0.022).

	Homeostasis Model Assessment (HOMA): mean values of HOMA showed a non significant increase between baseline and visits 5, 6, 7, and 8 (+66.14, +34.41, +54.96, +99.89, respectively). Such an increase was confirmed by the calculated trend showing an estimated average slope of 10.39 (p = 0.123). Cholesterol and triglycerides: the mean value of total cholesterol showed an increase during the study (statistically significant change only between baseline and visit 6: + 17.17 mg/dl; p = 0.023). The same increasing trend over time was found for HDL and LDL cholesterol. Also triglycerides showed a non statistically significant increase during the study. C-reactive protein: no significant changes were detected during the study. Autonomic function parameters – Norepinephrine: no significant changes were detected during the study. However, an increasing trend was found for the mean values using the Random Coefficient Models (change from baseline value: +20.32; p = 0.236) Spearman correlations of changes between baseline (visit 0) and end of treatment (visit 8): Various significant correlations of changes between baseline (visit 0) and end of treatment were found for primary and secondary variables, as reported in the following table:. - correlation of changes of average value of MBF (during clamp) and changes of average FDG uptake rho -0.6727 p=0.033 changes of FDG extraction fraction rho -0.7696 p=0.009 changes of average MBF reserve rho -0.6606 p=0.037 average MBF insulin reserve rho 0.8727 p=0.0004 - correlation of changes of average FDG uptake and Left ventricular remodelling index rho -0.8116 p=0.049 Left ventricular volume end-systolic rho 0.7142 p=0.046 Other correlations became evident at baseline, such as the correlation of average FDG uptake and MBF reserve rho -0.7212 p=0.018 M value rho 0.6848 p=0.028 MBF metabolic adjusted by insulin at rest rho 0.7166 p=0.029 average MBF metabolic adjusted by insulin at perfusion rho 0.7666 p=0.015 EDD value rho -0.7454 p=0.013 Left ventricular mass / body surface area rho -0.7416 p=0.014 Left ventricular mass rho -0.6363 p=0.047 Stimulation studies at baseline: changes in plasma glucose, plasma insulin, RPP and FFA were evaluated before and during the clamp technique, at visit 0. Plasma glucose showed a reduction (-17.6 mg/dl; p = 0.010), plasma insulin increased (+58.6111 µU/ml; p = 0.016), FFA significantly decreased (from 0.8827 mmol/l to 0.3336 mmol/l; p<.001), RPP increased (+283.3333 mmHg x beats/min; p = 0.541). During clamp, regional MBF non significantly increased in the average values of the septal, inferior, anterior and apical LV walls.

	i.v. adenosine stimulation studies showed a significant increase of regional MBF. The increase was 0.3919 ml/min/g for septal wall ($p < 0.001$), 0.2967 ml/min/g for inferior wall ($p < 0.001$), 0.3850 ml/min/g for anterior wall ($p < 0.001$) and 0.3114 ml/min/g for apical wall ($p < 0.001$). The overall average of MBF increased of 0.3462 ml/min/g. ($p < 0.001$). Insulin stimulation determined a significantly increase of HBF (+0.0871 ml/min/g; $p = 0.036$) whereas no significant change for SBF ($p = 0.810$). Adenosine stimulation determined a significantly increase of HBF (+0.2620 ml/min/g; $p = 0.007$) and a non significant change for SBF ($p = 0.452$). <u>Stimulation studies at endpoint:</u> same tests as at baseline were performed at visit 8. The effect of the acute insulin stimulation during the euglycaemic clamp was to reduce plasma glucose (-11.75 mg/dl; $p = 0.027$), to increase plasma insulin (+54.11 µU/ml; $p<0.001$), to reduce FFA (from 0.6950 µg/l before stimulation to 0.3325 µg/l after stimulation; $p = 0.003$). RPP showed a non significant increase (+137.6 mmHg x beats/min; $p = 0.843$). During clamp, regional MBF significantly increased in the average values of the septal, inferior, anterior LV walls (non significant increase for apical wall). i.v. adenosine stimulation studies showed a significant increase of regional MBF. The increase was 0.2668 ml/min/g for septal wall, 0.2684 ml/min/g for inferior wall, 0.2414 ml/min/g for anterior wall and 0.1948 ml/min/g for apical wall. The overall average of MBF increased of 0.2428 ml/min/g. ($p = 0.002$). Insulin stimulation determined a non significant increase of HBF (+0.1014 ml/min/g; $p = 0.187$) and no significant change for SBF ($p = 0.747$). Adenosine stimulation determined a significantly decrease of HBF from 0.2763 ml/min/g to 0.0951 ml/min/g ($p = 0.002$). <u>Changes [%] of stimulation test between baseline and end of treatment:</u> T-test for paired samples comparing changes detected at baseline vs changes at the end of treatment. No comparisons showed significant differences except for HBF under adenosine stimulation ($p<.001$). <u>Blood glucose profiles (5-points):</u> blood glucose profile (5-points) at baseline (visit 0) was compared with endpoint (visit 8), showing a highly significant reduction of values at all time points ($p=0.002$), as shown in the following figure: 

	Spearman correlation between variables grouping LV segments and patients: a statistically significant negative correlation was found at visit 0 between increase of FDG uptake and MBF reserve (rho -0.36253; p<.0001). Conversely, no significant results were found at visit 8 for the same variables (rho -0.05408; p = 0.5168). A statistically significant negative correlation between variables was shown at visit 0 between FDG extraction fraction and MBF reserve (rho -0.36872, p<.0001). Conversely, no significant results were found at visit 8 for the same variables (rho 0.08102; p = 0.3361) Summary of changes between MBF clamp vs MBF grouping LV segments and patients: the change between MBF clamp vs. MBF at visit 0 was calculated grouping all 13 LV segments and the ITT patients as belonging to a unique group. A statistically significant change (0.1427 ml/min/g; p<.0001) was found with the T-test for paired sample as for MBF during clamp at visit 0 (0.6515 + 0.3280 ml/min/g) and MBF before clamp (0.5088 + 0.1208 ml/min/g).
Safety results:	Treatment Emergent Adverse Events (TEAEs) were reported in two patients as nephrolithiasis or thyroid disorder. No patients experienced serious, treatment related TEAEs, or TEAEs leading to withdrawal or resulting in death. No episodes of symptomatic hypoglycemia occurred. Body weight, BMI, heart rate and blood pressure did not show statistically significant changes during the study. Standard hematology, biochemistry (liver and renal function) and urinalysis showed no relevant changes during the study, except for AST showing a statistically significant decrease.
Date of report:	03-JUN-2009