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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00358124
		Study Code:	HOE901_4014
Generic drug name:	Insulin Glargine	Date:	25/July/2008

Title of the study:	Insulin glargine® (insulin glargine) vs. Avandia® (rosiglitazone) as add-on therapy in subjects failing sulfonylurea and Glucophage® (metformin) combination treatment: a randomized, open, parallel study		
Coordinating Investigator:	Julio Rosenstock, MD Dallas Diabetes & Endocrine Center, 7777 Forest Lane, Suite C618, Dallas, TX 75230 USA		
Study center(s):	42 active study centers in the United States		
Publications (reference):	Rosenstock J, Sugimoto D, Strange P, et al. Triple Therapy in Type 2 Diabetes: Insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naïve patients. Diabetes Care 2006 Mar; 29(3):554-559. Vinik A, Zhang Q. Adding Insulin Glargine Versus Rosiglitazone: Health-related quality-oflife impact in type 2 diabetes. Diabetes Care 2007 Apr; 30(4):795-800 Errata. Vinik A, Zhang Q. Adding Insulin Glargine Versus Rosiglitazone: Health-related quality-of-life impact in type 2 diabetes Diabetes Care 2007 June; 30(6):1684.		
Study period: Date first patient enrolled: January 16th, 2001 Date last patient completed: June 24th, 2002	Phase of development: A post-marketing (Phase IV) study to investigate effects of adding either rosiglitazone or insulin glargine when combination of sulfonylurea and metformin no longer provided adequate glycemic control.		
Objectives:	Primary: To compare the glycemic control, as measured by hemoglobin A1C (HbA1C), between insulin glargine and rosiglitazone add-on therapies in patients who fail oral combination of a sulfonylurea and metformin. Secondary: To compare the following measures between patients who are randomized to insulin glargine versus rosiglitazone: occurrence of hypoglycemia; change in body weight; change in serum lipid profile; percentage of patients achieving HbA1C levels below or equal to 8% and the percentage with HbA1C levels below or equal to 7%; change in health-related quality of life; cost of therapy for hyperglycemia treatment.		
Methodology:	This was a randomized (1:1), parallel-group, two-arm, open-label study with 110 patients in each treatment arm. The study consisted of an up to 4-week screening and titration phase and a 24-week treatment phase. The study visits included: screening/titrating (–4 to 0 weeks), baseline (week 0), and treatment (weeks 2, 6, 12, 18, 24).		
Number of patients:	Planned: 220	Randomized: 219	Treated: 217 (insulin glargine: 105; rosiglitazone: 112)

Evaluated:

Analysis Populations.			
	All	**Insulin glargine**	**Rosiglitazone**
Safety Population (Randomized and Treated)	217	105	112
112 Intent-To-Treat (ITT) Population	216	104	112
Completers	176	89	87

Primary efficacy data: change in HbA1C from baseline to the final measurement in the intent-to-treat population.

Secondary efficacy data: change in HbA1C from baseline to each on-therapy visit at which it was measured; change in fasting plasma glucose (FPG) from baseline to each on-therapy visit at which it was measured; proportion of patients with final HbA1C $\leq$ 7%; proportion of patients with an HbA1C $\leq$ 8%; change in lipid values from baseline to each on-therapy visit at which they were measured; change in weight from baseline to each on-therapy visit at which they were measured.

The same secondary efficacy variables were analyzed for the completers population and the intent-to-treat population (ITT). For the ITT population, however, there was also an additional analysis of the change from baseline to the final on-therapy measurement for FPG and the lipid parameters (total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides (TG), free fatty acids (FFA)).

Safety: Safety was assessed through adverse events (reported by the patient or noted by the investigator), hypoglycemia, body weight, physical examinations, vital signs, standard hematology, blood chemistry, and urinalysis.

Health Outcomes: Health-related quality of life was assessed in terms of diabetes-related symptoms and symptom distress, emotional well being and general health perceptions. Cost of study drug (insulin glargine or rosiglitazone), sulfonylureas, and metformin, supplies for administration of insulin glargine, self-monitoring of blood glucose (strips, glucose meter) and laboratory testing per labeling.

Pharmacokinetics: Not applicable

Diagnosis and criteria for inclusion:	Male and female patients between 18 and 80 years of age, with type 2 diabetes mellitus, currently being treated with oral sulfonylurea and metformin, HBA1C ≥ 7.5 and ≤ 11 %, fasting C peptide concentration ≥ 0.27 mmol/L, and body mass index (BMI) of > 25 kg/m2.
Investigational product:	Insulin glargine injection, 10 mL vial, 100IU/mL
Dose:	The starting dose of insulin glargine was a single daily dose of 10 IU/day administered at bedtime for 7 days. After the first 7 days, the dose was adjusted (titrated) on a weekly basis according to FPG and self-monitored blood glucose (SMBG) meter levels to meet glycemic target levels (FPG values < 5.5 mmol/L (100 mg/dL))
Administration:	subcutaneous injection

Duration of treatment: 24 weeks	Duration of observation: 28 weeks (4 weeks screening/titration phase plus 24 weeks treatment phase)

Reference therapy:	Rosiglitazone (Avandia®), 100 tablets per bottle
Dose:	A single daily dose of 4 mg, with or without food. The dose could be increased to a maximum of 8 mg, administered once daily or 4 mg twice a day, after 6 weeks of therapy if there is insufficient reduction in FBG and/or FPG.
Administration:	oral
Aditional therapy:	Sulfonylurea and Metformin (Glucophage®)
Dose/ Administration:	Sulfonylurea: The dose of oral administration was left to the discretion of the investigator with the starting dose to be the same dose that the patient was taking at randomization. The dosages were to remain unchanged during the study. Metformin: Dose/Administration: The dose of oral administration was left to the discretion of the investigator with the dose titrated up to at least 2000 mg/day or the maximally tolerated dosage prior to randomization. The starting dose was the same dose at which the patient was taking at randomization. The dosage of metformin was to be unchanged after randomization.
Criteria for evaluation:	
Efficacy:	HbA1C, FPG, body weight, and serum lipids measurements
Safety:	Adverse events reported by the patient or noted by the investigator, hypoglycemic events, standard hematology, blood chemistry, urinalysis, 12- lead electrocardiogram, vital signs, and physical findings.
Pharmacokinetics:	Not Applicable

Pharmacokinetic sampling times and bioanalytical methods:	Not Applicable
Statistical methods:	Analysis of continuous efficacy variables, including the primary efficacy variable, change from baseline in HbA1C, was conducted using an analysis of covariance (ANCOVA) model that included baseline as the covariate and treatment and center as the main effects. Treatment differences were assessed based on the difference in the least mean squares. For dichotomous variables, such as the proportion of responders (i.e., patients with HbA1C $\leq$ 7% or the incidence of hypoglycemic episodes) the Cochran-Mantel-Hansen test was used to compare treatment groups. Stratification was by site. The treatment groups were compared with respect to demographic variables and baseline characteristics using t-tests for the continuous variables and chi-square (X2) tests for the discrete variables. The primary ANCOVA model was used to analyze change from baseline to endpoint for body weight, BMI, cholesterol, HDL, LDL, free fatty acids, and triglycerides Adverse events, routine laboratory assessments vital signs, and physical findings were assessed by incidence and frequency. Descriptive analyses were also conducted for both routine laboratories and vital signs.
Summary: Study Patients:	A total of 341 patients were screened for the study, 219 subjects were randomized and 217 subjects received study medication (insulin glargine: 105 subjects; rosiglitazone: 112 subjects).

	Lantus	Avandia
Randomized [N]	105	112
Discontinued [n (%)]	8 (7.6)	21 (18.8)
Reason for Discontinuing [n (%)]		
Adverse Event	2 (1.9)	9 (8.0)
Did Not Wish To Continue	1 (1.0)	3 (2.7)
Protocol violation	3 (2.9)	2 (1.8)
Lost To Follow-Up	1 (1.0)	7 (6.3)
Other	1 (1.0)	0 (0.0)

Significantly more rosiglitazone than insulin glargine-treated patients who discontinued prematurely from the study (insulin glargine: 8 subjects; rosiglitazone: 21 subjects; p = 0.0047). Major protocol violations occurred in 3/105 insulin glargine patients and in 2/112 rosiglitazone patients.

The mean daily dose at study endpoint and mean duration of insulin glargine treatment was 38.5 IU (SD=26.5) and 163.6 days in the ITT population, respectively. The mean daily dose at study endpoint and mean duration of rosiglitazone treatment were 7.1mg (SD=1.65) and 155.9 days in the ITT population, respectively. The mean duration of treatment was not significantly different between the two treatment groups in the ITT population (p = 0.0855).

The baseline demographics were comparable between the insulin glargine and rosiglitazone treatment groups with respect to age, race, age of type 2 diabetes mellitus (T2DM) at onset and T2DM duration. There was a trend towards more females in the insulin glargine group and more males being in the rosiglitazone group (p = 0.0646). In the intent-to-treat population, the mean age was similar in the two groups: 55.9 years and 55.3 years, respectively, in the insulin glargine and rosiglitazone treatment groups. The majority of patients were white in both treatment groups with 70.2% in the insulin glargine group and 76.8% in the rosiglitazone group. The mean duration of T2DM was 8.5 years in the insulin glargine treatment group and 8.1 years in the rosiglitazone, with a mean age of onset of diabetes in the insulin glargine and rosiglitazone treatment groups of 48.0 years and 47.9 years, respectively. The unadjusted mean baseline HbA1C was 8.80% in the insulin glargine group and 8.70% in the rosiglitazone group. The unadjusted mean FPG was 10.4 mmol/L (187.3 mg/dL) and 10.6 mmol/L ((190.9 mg/dL) in the insulin glargine and rosiglitazone groups, respectively, and the unadjusted mean BMI was 34.62 kg/m2 and 33.64 kg/m2, respectively. The insulin glargine and rosiglitazone treatment groups were comparable at baseline with respect to diabetes variables (HbA1C, FPG, C-peptide, BMI, weight, calorie need, metformin dose, titration of metformin during screening, use of sulfonylurea agents, glipizide dose, glimepiride dose), previous illnesses, and previous medications. The difference in the baseline dosage of glyburide was statistically significant between the treatment groups but this difference is not clinically relevant. The treatment groups were comparable at baseline with respect to concomitant illnesses and concomitant medications.

Summary:

Efficacy results:

The mean change in HbA1C, FPG, and serum lipids from baseline to endpoint within and between the insulin glargine treatment group and the rosiglitazone treatment group in the ITT population.

Summary of Hb_{A1C}, FPG, and Serum Lipids: Change from Baseline to Endpoint – ITT Population

	Adjusted Mean Change from Baseline within Treatment Group (% Change from Baseline)		Difference of Adjusted Mean Change from Baseline between Treatment Groups (Difference in % Change from Baseline between Treatment Groups)	p-value for Difference between Treatment Group (Change from Baseline)
Variable (unit)	Insulin glargine	Rosiglitazone	Insulin glargine - Rosiglitazone	
Primary Efficacy Variable				
Hb_{A1C} (%)	-1.66*	-1.51*	-0.15	0.1446
Secondary Efficacy Variables				
FPG (mmol/L)	-3.60*	-2.57*	-1.03	0.0010†
FPG (mg/dL)	-64.9*	-46.3*	-18.6	0.0010†
Weight (kg)	1.65*	3.00*	-1.35	0.0196†
BMI (kg/m^2)	0.53*	1.03*	-0.50	0.0190†
Total Cholesterol (mmol/L)	-0.222 (-4)*	0.510 (11)*	-0.732 (15)	0.0001†
HDL Cholesterol (mmol/L)	0.004 (0)	0.047 (5)*	-0.043 (5)	0.0407†
Calculated LDL Cholesterol (mmol/L)	-0.043 (-2)	0.360 (17)*	-0.403 (19)	0.0004†
Calculated LDL Cholesterol/HDL Cholesterol Ratio (mmol/L)	-0.031 (-1)	0.338 (13)*	-0.369 (14)	0.0030†
Triglycerides (mmol/L)	-0.466 (-15)*	0.126 (6)	-0.592 (21)	0.0011†
Free Fatty Acids (mmol/L)	-0.140 (-20)*	-0.113 (-17)*	-0.027 (3)	0.4374

*Indicates difference from baseline statistically significant ($p < 0.05$) within treatment group. †Indicates difference from baseline statistically significant ($p < 0.05$) between treatment groups.

There was no significant difference in the change from baseline in HbA1c, however, there were significant differences in the changes from baseline in FPG, total cholesterol, triglycerides HDL cholesterol, calculated LDL cholesterol, and calculated LDL cholesterol/HDL cholesterol ratio all favouring insulin glargine. The difference in the mean change of weight from baseline to endpoint was significantly greater in the rosiglitazone patients than in the insulin glargine patients ($p = 0.0196$). Rosiglitazone had a significantly greater effect on the mean changes in BMI from baseline than insulin glargine ($p = 0.0190$). There was no difference between treatment groups in the change from baseline for free fatty acids. In the ITT population, there were 92.3% and 48.1% of insulin glargine patients achieved an HbA1C≤ 8% and HbA1C≤ 7%, respectively, versus 83.0% and 49.1% of rosiglitazone patients.

Safety results	The number of patients with TEAEs was not different between the insulin glargine group (79/105 patients, 75.2%) and the rosiglitazone group (88/112 patients, 78.6%). The types of adverse events observed in the treatment groups were comparable with the exception of peripheral edema and increased weight, which occurred more frequently in the rosiglitazone group than in the insulin glargine group. There were 4 times more rosiglitazone patients than insulin glargine patients with possibly related TEAEs (insulin glargine: 7/105, 6.2%; rosiglitazone: 32/112, 28.4%). TEAEs leading to discontinuation of study medication were reported in 2 (1.9%) patients receiving insulin glargine and 9 (8.0%) patients receiving rosiglitazone. Five patients (4.8%) in the insulin glargine group and 11 patients (9.8%) in the rosiglitazone group reported serious treatment emergent adverse events (TEAEs) during the study. The 5 serious TEAEs in the insulin glargine group were not considered related to the study medication. Of the 11 rosiglitazone patients with serious TEAEs, 3 were considered possibly related to rosiglitazone. There were no deaths in the study. The frequency of all hypoglycemic events reported was not significantly different between the insulin glargine and rosiglitazone treatment groups (insulin glargine: 67/105 patients, 63.8%; rosiglitazone: 64/112 patients, 57.1%; p = 0.2530). The treatment groups had comparable numbers of patients with unconfirmed symptoms of hypoglycemia, confirmed symptomatic hypoglycemia, and severe hypoglycemia. Insulin glargine patients had numerically more episodes of confirmed hypoglycemia than rosiglitazone patients, which did not achieve statistical significance (p=0.0528). Significantly more patients in the insulin glargine group had nocturnal hypoglycemia than in the rosiglitazone group (p=0.0084). The insulin glargine treatment group had a significantly higher median rate of confirmed hypoglycemia observed from the second month to the end of treatment than the rosiglitazone treatment group (insulin glargine: 2.48/365 days (0.0, 99.9); rosiglitazone: 0.00/365 days (0.0, 46.6); p = 0.0073).There were no differences between the treatment groups in the mean and median changes in clinical laboratory data for any laboratory analyte or the number of patients with clinically noteworthy abnormal laboratory values. There were few shifts outside the normal range for the majority of laboratory variables. A greater number of rosiglitazone patients had a shift outside from the normal range to low hemoglobin (insulin glargine: 6; rosiglitazone: 16) and high uric acid (insulin glargine: 7; rosiglitazone: 12) compared to insulin. The number of patients with a shift from normal physical examination findings at baseline was not different between the insulin glargine and rosiglitazone treatment groups, with the exception of peripheral edema, which was observed more frequently in the rosiglitazone patients than in the insulin glargine patients, 16 versus 5 patients, respectively. There were no significant differences in the change in vital signs from baseline between the insulin glargine and rosiglitazone treatment groups.
Health Outcomes – Quality of Life	A total of 214 patients (104 insulin glargine patients, 110 rosiglitazone patients) completed baseline health-related quality-of-life (HRQL) questionnaires. The number of patients with missing scale scores at baseline was no more than 5 percent. Among those who completed baseline, the number of missing scale scores were ≤ 7% for all baseline scale scores (except for general health perception: 13%) and ranged from 14% to 21% at weeks 6, 12, 18, and 24 (week 24: 17% missing observations). Patients randomized to insulin glargine had nominally worse scores at the baseline assessment for most HRQL measures than patients randomized to rosiglitazone (higher mean scale scores for symptoms and symptom-distress measures as well as lower mean scale scores for emotional well-being and general health perceptions). For most follow-up assessments, the change from baseline in HRQL measures was generally better among patients randomized to insulin glargine versus those receiving rosiglitazone; at the week 24 assessment, nominal differences in change scores favouring insulin glargine were noted for 18 of the 20 HRQL measures. In multivariate analyses examining mean HRQL scores at week 24 controlling for differences in HRQL at baseline, patients randomized to insulin glargine in general were generally found to have nominally better HRQL; these differences were statistically significant ($p < 0.05$) for symptoms of hypoglycemia and ophthalmologic symptoms. In repeated-measures analysis examining the contrast between the baseline and all follow-up assessments, statistically significant differences ($p < 0.05$) favouring insulin glargine were noted for hypoglycemia symptoms, ophthalmologic symptoms, ophthalmologic distress, and emotional well-being.

Health Outcomes – Health economics	A total of 216 patients (104 insulin glargine patients, 112 rosiglitazone patients) were included in the ITT population. Baseline clinical and demographic characteristics were comparable in the two treatment arms. In the ITT population, the mean (±SD) total use of study medication over 24 weeks was 4588 IU (±2753 IU) in the insulin glargine group (mean daily dose: 28.7 IU) and 929 mg (±341 mg) in the rosiglitazone group (mean daily dose: 6.3mg). The mean usages of metformin, sulfonylureas, lancets and test strips were higher in the insulin glargine group compared with the rosiglitazone group. Among the ITT population, the mean cost of study therapy was $348 lower among patients randomized to insulin glargine versus rosiglitazone (insulin glargine: $216; rosiglitazone: $564). However, the cost of other anti-hyperglycemic medications and other resources were slightly higher in the insulin glargine group (insulin glargine: $1152; rosiglitazone: $1039). The mean cost of test strips and lancets dispensed was higher in the insulin glargine group ($331 for 419 tests strips and lancets) than in the rosiglitazone group ($291 for 368 test strips and lancets). On an overall basis, estimated mean total cost of modalities to monitor and improve glycemic control over 24 weeks was $235 lower among patients randomized to insulin glargine versus patients randomized to rosiglitazone (insulin glargine: $1368; rosiglitazone: $1603), despite a longer duration of treatment in the former group. The estimated mean total cost of health-care resources for glycemic control over the last 6-week period ending at week 24 was $345±75.5/6weeks for the insulin glargine group and $441±52.7/6 weeks for the rosiglitazone group of the ITT population. Pharmacokinetic results: Not applicable
Pharmacokinetic results	Not applicable
Date of Report:	13-June-2008