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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00384215
		Study Code:	HOE901_4020
Generic drug name:	Insulin Glargine	**Date:**	29/Oct/2008

GCP non-compliance	Efficacy data from 36 randomized subjects at two (2) investigator sites were excluded due to GCP non-compliance/scientific misconduct in other clinical trials. Datasets with these 2 sites included and excluded were generated and the outputs examined to ensure that the results of the study were non-compromised. Results excluding data from these 36 subjects are provided in the main efficacy analysis sections, and results including data from these 36 subjects are provided in the additional efficacy analysis section. All randomized subjects were included in the safety analysis in the amended CSR.
Title of the study:	Insulin glargine [rDNA origin] injection (Lantus®) vs pioglitazone (Actos®) as add-on therapy in subjects failing monotherapy with sulfonylurea or metformin (Glucophage®): a randomized, open, parallel study
Investigator(s), Study center(s):	This was a multicenter study that was conducted at 59 US sites
Study dates: Date first patient enrolled: 27-Nov-2001 Date last patient completed: 16-Feb-2005	**Phase of development: :** Phase. IIIB
Objectives:	**The primary objective of the study was** to compare the effect of insulin glargine and pioglitazone add-on therapy (added to an existing treatment regimen of sulfonylurea or metformin), on glycemic control, as measured by hemoglobin A1c (A1c), in subjects who had previously failed monotherapy with a sulfonylurea (SU) or metformin. **The secondary objectives of this study were** to compare the effects of insulin glargine and pioglitazone add-on therapy on the following measures: (1) hypoglycemia, (2) weight, (3) fasting plasma glucose (FPG), (4) serum lipid profile, (5) percentage of subjects achieving A1c levels ≤ 7%, (6) time until an A1c ≤ 7% was achieved, (7) health-related quality of life (HRQoL), and (8) cost of glycemic contro1
Study Design:	This was a randomized (1:1), parallel-group, two-arm, open-label study. The study consisted of a screening phase that was up to 2 weeks in duration and a 48-week treatment phase. Randomization was stratified by previous treatment (sulfonylurea or metformin). Subjects were randomized on a 1:1 basis within each investigative center to receive either insulin glargine or pioglitazone, with continued sulfonylurea (SU) or metformin in both arms. The doses of SU or metformin in both arms were to remain at the doses subjects were receiving at randomization, throughout the treatment period.
Number of subjects planned:	320 subjects planned; 389 subjects enrolled in the study.

Inclusion criteria:	Male and female subjects who were between 18 and 79 years-of-age (inclusive), who had a diagnosis of type 2 diabetes mellitus for at least six months and 8% ≥ A1c ≤ 12% at screening, and who had been on a stable doses of at least 1 g metformin or half-maximally labelled dose of SU for at least 3 months prior to screening.
Treatments:	Insulin glargine:10 IU/daily for the first seven days and then individually titrated to achieve glycemic targets (70 mg/dL ≥ fasting blood glucose ≤ 100 mg/dL through to week 24 and 70 mg/dL ≥ fasting blood glucose ≤ 94 mg/dL through to week 48), administered subcutaneously at bedtime for treatment duration of one year. Pioglitazone: 15 mg tablets started as one 15 mg tablet administered daily (single dose) and increased up to a maximum dose of 45 mg daily in order to reach glycemic targets for treatment duration of one year.
Population:	There were 3 populations analyzed in this study: ➢ Safety: All randomized subjects who received at least 1 dose of investigational product. ➢ Modified ITT (mITT): Randomized subjects who received at least 1 dose of investigational product and at least 1 post-baseline A1C measurement not more than 7 days after the last dose of study medication in addition to the baseline measurement. This population was referred to as ITT population in the protocol, but the naming has been changed here to more accurately reflect the modification from a traditional ITT definition. ➢ Completers: All randomized subjects who have a baseline HbA1c measurement (ie, prior to the start of study medication) and a final HbA1c measurement in the visit window for study week 48 with no major protocol violations. This is primary efficacy analysis population. Amendment 2 extended the study an additional 24 weeks in order to permit subjects' A1c values to reach equilibrium and to permit the use of a more aggressive dosing algorithm during the additional 24 weeks. Under Amendment 2, two major analysis populations became necessary for this study: the 24-week and 48-week analysis populations. The 24-week analysis population included all subjects who entered the study, ie, signed informed consent, whether or not they continued beyond the implementation of Amendment 2, but no data collected after study week 24. The 48-week analysis population included subjects who were randomized after the implementation of Amendment 2, or continued in the study for at least two visits after the implementation of Amendment 2. There was a complete set of analyses conducted for both the 24-week and 48-week analysis populations.
Efficacy Data	A1c at weeks 0, 2, 6, 12, 18, 24, 26, 30, 36, 42, and 48 FPG at 0, 2, 6, 12, 18, 24, 26, 30, 36, 42, and 48 weeks Serum lipids: total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TGs), and free fatty acids (FFAs) at 0, 6, 12, 18, 24, 30, 36, 42, and 48 weeks. Weight at weeks 0, 12, 24, 26, 36, and 48 and height at screening (height used only to calculate BMI)
Safety Data:	Hypoglycemic and severe hypoglycemic events throughout the study Adverse events throughout the study Laboratory tests (biochemistry at weeks 0, 6, 12, 18, 24, 30, 36, 42, and 48; hematology at weeks 0, 12, 24, 36, and 48; and urinalysis at weeks 0, 24, and 48) Physical examinations (weeks 24 and 48), vital signs (sitting blood pressure, oral body temperature, pulse, and respiratory rate assessed at weeks 0, 12, 24, 26, 36, and 48), ECGs (weeks 0, 24, and 48), and weight (weeks 0, 12, 24, 26, 36, and 48)

Statistical procedures:	Amendment 2 extended the study an additional 24 weeks, resulting in two major analysis populations, the 24-week analysis population (all subjects who entered the study, ie, signed informed consent, whether or not they continued beyond the implementation of Amendment 2) and the 48-week analysis population (all subjects who entered the study after the implementation of Amendment 2, or continued in the study for at least two visits after Amendment 2 was implemented). There was a complete set of analyses conducted for both analysis populations. The study was designed as a non-inferiority study with $\alpha = 0.05$ for a two-sided significance test. The insulin glargine arm was designated as the test treatment and pioglitazone as the comparator. Ninety-five percent confidence intervals were computed for the adjusted mean difference between the treatment groups from the ANCOVA model with treatment and stratification level as fixed effects and the corresponding baseline as covariate. Treatment by stratification and treatment by baseline interaction will be tested for. If one or both of the interaction term are not-significant they will be removed from the model. The non-inferiority of insulin glargine to the comparator was demonstrated if the upper boundary for the 95% CI for the difference in the adjusted mean changes from baseline to endpoint for A1c was $\leq$ 0.5%. A non-inferiority hypothesis was tested for both the completer's population and the mITT population for the 48-week population. If the inferiority hypothesis was rejected for both populations, then superiority was to be assessed in the 48-week mITT population. The same procedure was also conducted for the 24-week population (non-inferiority was to be first assessed in the 24-week completer population and the 24-week mITT population and superiority was to be subsequently assessed in the 24-week mITT populations) and the analysis of changes in A1c from study week 24 to the last on-therapy observation (non-inferiority was to be first assessed in the 48-week completer population and 48-week mITT population and superiority was to be subsequently assessed in the 48-week mITT population). The residuals from this primary ANCOVA model were assessed for normality. If the residuals were not normally distributed, the data was analyzed using rank analysis of variance and/or rank analysis of covariance. If the assumptions of parallel regression lines for ANCOVA was not satisfied for the endpoint analyses, additional analyses using alternative procedures was carried out to assess the robustness of the results from ANCOVA. The analysis of continuous variables (changes from baseline A1c, FPG, serum lipids, liver enzymes and weight) was conducted using analysis of covariance (ANCOVA) with treatment, and stratification level and center as main effects, and baseline value as covariate. The proportion of responders, the proportion of subjects with A1c $\leq$ 7% and $\leq$ 6.5% at week 48 (or the last on-therapy observation), and the incidence of hypoglycemia were compared using the Cochran-Mantel-Haenszel test stratifying by treatment center (pooled). The time to response was analyzed using the log-rank statistic. Adverse events and the results of laboratory assessments, physical examinations, and vital signs assessments were reviewed for clinically significant abnormalities. The 48-week efficacy analysis population included subjects enrolled in GCP compliant sites that were randomized after the implementation of Amendment 2, or continued in the study for at least two visits after the implementation of Amendment 2. The 24-week efficacy analysis population included all subjects enrolled in GCP compliant sites that entered the study, and signed informed consent. To ensure the results of the study are non-compromised, the Sponsor ran sensitivity analysis excluding and including the GCP non-compliant subjects, and compared results of the analysis. All randomized subjects who were dispensed study medication are included in the Safety analysis population.

Interim analysis	There was no interim analysis performed for this study.

Results – Study subjects and conduct:

A total of 389 subjects were randomized, 190 subjects were randomized to glargine therapy and 199 subjects were randomized to pioglitazone therapy. Total of 76.8% (146/190) glargine treated subjects and 76.9% (153/199) pioglitazone treated subjects completed 24-week study duration; and 23.2% (44/190) glargine treated subjects and 23.1% (46/199) pioglitazone treated subjects were withdrawn prior to 25 week.

Of the 139 subjects randomized to glargine therapy and 140 subjects randomized to pioglitazone therapy 48-week analysis population, 107 glargine treated subjects and 97 pioglitazone treated subjects completed 48-week study duration. Fewer (22.3%, 31/190) glargine-treated subjects than that of pioglitazone-treated (30.0%, 42/199) subjects withdrew from the study. Randomized subjects who received at least 1 dose of investigational product were included in Safety population. A total of 184 subjects in the glargine group, and 198 subjects in pioglitazone group were included in Safety population. There were no differences between the two treatments groups in the baseline demography and disease states in the efficacy analysis population. There were no significant differences between treatments groups in study duration or patient year of treatment.

The following table provides a snapshot of the disposition of all randomized subjects.

	Glargine (N = 190)	Pioglitazone (N = 199)
24-Week Analysis Population [N]	190	199
Completed [n (%)][1]	146 (76.8)	153 (76.9)
Withdrawn Prior to 25 Weeks [n (%)] [1]	44 (23.2)	46 (23.1)
Reason for Withdrawal [n (%)]		
Adverse Event	2 (4.5)	12 (26.1)
Subject Died	0 (0.0)	0 (0.0)
Subject Did Not Meet Entry Criteria	0 (0.0)	0 (0.0)
Treatment Failure	0 (0.0)	9 (19.6)
Subject Did Not Wish to Continue	15 (34.1)	6 (13.0)
Protocol Violation	4 (9.1)	1 (2.2)
Subject Lost to Follow-up	9 (20.5)	10 (21.7)
Other Reason	14 (31.8)	8 (17.4)
48-Week Analysis Population [N]	139	140
Completed [n (%)][1]	107 (77.0)	97 (69.3)
Withdrawn Prior to Week 48 [n (%)] [1,2]	31 (22.3)	42 (30.0)
Reason for Withdrawal [n (%)]		
Adverse Event	2 (6.5)	15 (35.7)
Subject Died	1 (3.2)	0 (0.0)
Subject Did Not Meet Entry Criteria	0 (0.0)	0 (0.0)
Treatment Failure	0 (0.0)	9 (21.4)
Subject Did Not Wish to Continue	12 (38.7)	5 (11.9)
Protocol Violation	2 (6.5)	1 (2.4)
Subject Lost to Follow-up	7 (22.6)	10 (23.8)
Other Reason	7 (22.6)	2 (4.8)

[1] Percent based on number of subjects in analysis population.
[2] Patients 0072/00009 (Actos) and 0072/00027 (Lantus) did not complete 48-week study, but no withdrawal information was obtained.

There were no differences between the two treatments groups in the baseline demography and disease states in all randomized population.

Results – Study subjects and conduct: (continued)	When Sites 71 (15 randomized subjects) and 72 (21 randomized subjects) were excluded from the study analysis, the randomized study population comprised of 353 subjects, 171 subjects in glargine arm and 182 subjects in pioglitazone arm. No differences in the two treatments groups in study duration or patient year of treatment were observed in all subjects randomized excluding data from Sites 71 and 72 summary analyses. The following table provides a snapshot of the disposition of randomized subjects excluding data from sites 71 and 72.

	Glargine (N = 171)	Pioglitazone (N = 182)
	171	182
24-Week Analysis Population [N]		
Completed [n (%)][1]	137 (80.1)	142 (78.0)
Withdrawn Prior to 25 Weeks [n (%)] [1]	34 (19.9)	40 (22.0)
Reason for Withdrawal [n (%)]		
Adverse Event	2 (5.9)	12 (30.0)
Subject Died	0 (0.0)	0 (0.0)
Subject Did Not Meet Entry Criteria	0 (0.0)	0 (0.0)
Treatment Failure	0 (0.0)	9 (22.5)
Subject Did Not Wish to Continue	13 (38.2)	4 (10.0)
Protocol Violation	3 (8.8)	1 (2.5)
Subject Lost to Follow-up	9 (26.5)	10 (25.0)
Other Reason	7 (20.6)	4 (10.0)
48-Week Analysis Population [N]	129	130
Completed [n (%)][1]	101 (78.3)	90 (69.2)
Withdrawn Prior to Week 48 [n (%)] [1]	28 (21.7)	40 (30.8)
Reason for Withdrawal [n (%)]		
Adverse Event	2 (7.1)	15 (37.5)
Subject Died	1 (3.6)	0 (0.0)
Subject Did Not Meet Entry Criteria	0 (0.0)	0 (0.0)
Treatment Failure	0 (0.0)	9 (22.5)
Subject Did Not Wish to Continue	11 (39.3)	3 (7.5)
Protocol Violation	2 (7.1)	1 (2.5)
Subject Lost to Follow-up	7 (25.0)	10 (25.0)
Other Reason	5 (17.9)	2 (5.0)

[1] Percent based on number of subjects in analysis population.

Results Pharmacokinetics and pharmacodynamics:	No bioanalytical variable analysis and pharmacokinetic–pharmacodynamics (PK-PD) analysis were performed in this study

Results – Efficacy:	This study was designed to compare the effect of glycemic control with insulin glargine and pioglitazone as add-on therapy in subjects whose existing monotherapy therapy with oral agents (primarily sulfonylureas or metformin) has failed. Results of the study excluding data from site 71 and 72 are briefly summarized below: ➢ Glargine showed superior glycemic control than pioglitazone by demonstrating a greater reduction in A1c values at the study endpoint [(mITT population: -2.48 ± 0.116 vs. –1.86 ± 0.112; GLAR vs. PIO; adjusted mean difference = -0.62, 95% CI: -0.93, 0.31, p = 0.0001) and [(Completers population: -2.58 ± 0.098 vs. –2.29 ± 0.105; GLAR vs. PIO; adjusted mean difference = -0.29, 95% CI: -0.57, -0.01, p = 0.0427)] ➢ Glargine treatment group, both in 48-week completers' (n= 91) and mITT population (n = 121), displayed a significant improvement in glycemic control by change in HbA1c values at the study endpoint from baseline compared with the pioglitazone treatment group (completers, n = 82; mITT, n = 126) ➢ In the mITT population at endpoint, the mean A1c values decreased to 6.9% and 7.6% for the glargine and pioglitazone therapy arms respectively, while in the completers population the A1c value at endpoint in the glargine arm was 6.7% whereas it was 7.0% in the pioglitazone arm ➢ In the mITT population, glargine therapy produced a numerically better response-rate than that of pioglitazone therapy in reducing A1c ≤ 7% (glargine vs pioglitazone: 65.3% vs 47.6%, p= 0.0228) ➢ Glargine-treated subjects in the 48-week mITT population therapy took less time in reducing A1c value ≤ 7% than that of pioglitazone therapy (median time: glargine vs pioglitazone: 171 vs 253 days, p=0.0368). ➢ After 48 weeks of treatment, both treatment arms were significantly (p< 0.0001) effective in reducing FPG from baseline to endpoint for mITT and completer subjects [(mITT population: -99.1 ± 4.72 vs. –64.2 ± 4.58; GLAR vs. PIO; adjusted mean difference = -34.9, 95% CI: -47.6, -22.2, p < 0.0001) and [(Completers population: -101.0 ± 4.43 vs. -73.3 ± 4.72; GLAR vs. PIO; adjusted mean difference = -27.7, 95% CI: -40.4, -15.1, p < 0.0001). Overall, the add-on therapy with glargine was more effective in bringing the FPG down than the add-on therapy with pioglitazone ➢ Throughout the study pioglitazone-treated subjects gained numerically more weight than glargine-treated subjects, although this difference was not statistically significant. ➢ Although pioglitazone treatment showed a better result in elevating HDL cholesterol-values than that of glargine treatment, glargine therapy produced better results in controlling total cholesterol, LDL, and FFA than that of pioglitazone therapy. ➢ In the mITT subjects, the mean overall average daily dose of study drug glargine was 51.59 IU/daily (range: 7.1-140.5 IU/daily) and that of pioglitazone was 33.53 mg daily (range: 12.0-42.5 mg daily). At week 24, the mean dose of study drug glargine was 37.45 IU/daily (range: 7.1 – 89.3 IU/daily) and that of pioglitazone was 29.14 mg daily (range: 12.0 - 40.3 mg daily). ➢ Treatment differences between glargine and pioglitazone groups were consistent from MET stratum to SU stratum throughout the 48-week study duration. Similar efficacy results were observed in analysis of subjects including data from site 71 and 72.

Results – Efficacy: (continued)

The following table provides a change from baseline to endpoint for the clinically relevant modelled efficacy variables in the 48-week mITT population. HbA1c and FPG results are reported for 48-week mITT population excluding sites 71 and 72, whereas lipid profile, BMI and weight results are reported for 48-week safety population.

Variable	Glargine		Pioglitazone		Glargine-Pioglitazone
	Mean	Adjusted Mean	Mean	Adjusted Mean	
	Baseline	Change from baseline to endpoint	Baseline	Change from baseline to endpoint	Prob
HbA1c	9.32 ± 0.122	-2.48 ± 0.116	9.43 ± 0.118	-1.86 ± 0.112	0.0001
FPG (mg/dL)	223.6 ± 5.97	-99.1 ± 4.72	223.6 ± 5.78	-64.2 ± 4.58	<0.0001
TC (mmol/L)	5.290 ± 0.1146	-0.250 ± 0.0775	5.318 ± 0.1129	0.103 ± 0.0764	0.0010
HDL mmol/L)	1.194 ± 0.0250	0.057± 0.0218	1.183 ± 0.0247	0.194 ± 0.0214	<0.0001
LDL (mmol/L)	2.884 ± 0.0951	-0.034 ± 0.0674	3.002 ± 0.0948	0.081± 0.0672	0.2211
TG (mmol/L)	3.257 ± 0.3302	-0.888± 0.1061	2.928 ± 0.3254	-0.893 ± 0.1053	0.9683
FFA[1] (mmol/L)	0.64 ± 0.027	-0.20 ± 0.018	0.60 ± 0.027	-0.15 ± 0.018	0.0902
BMI (kg/m^2)	33.36 ± 0.651	1.35 ± 0.300	33.69 ± 0.652	1.65 ± 0.301	0.4760
Weight (kg)	95.43 ± 2.033	3.85 ± 0.910	97.02 ± 2.039	4.74 ± 0.912	0.4808

[1] FFA = Non-esterified free fatty acids

Results – Safety:

- Both treatments were safe and tolerable. There was no treatment related death reported for this study, and no difference between treatments in the overall reported incidence of adverse events.
- A total of 67.4% (124/184) subjects in the glargine group reported at least 1 TEAE and 12.0% (22/184) of glargine-treated subjects reported TEAE to be possibly related to treatment. Similarly in the pioglitazone treatment-group, 70.2% (139/198) subjects reported at least 1 TEAE and 20.7% (41/198) subjects reported TEAE to be possibly related to add-on pioglitazone therapy. Peripheral oedema was the biggest contributor of possibly related TEAE in the pioglitazone treatment-group and for the glargine group TEAE was upper respiratory tract infection. About 7.1% (14/198) of pioglitazone treated subjects reported at least 1 serious TEAE, as opposed to 10.3% (19/184) of the glargine-treated subjects.
- Four times more pioglitazone treated subjects 18/198 (9.1%) subjects in the pioglitazone group were discontinued from the study due to adverse event as compared with glargine treated 4/184 (2.2%) subjects.
- There was 1 death reported in the study, subject was hit by a car while crossing the street, and was killed instantly. There was no treatment related death reported for this study, and no difference between treatments in the overall reported incidence of adverse events.

Results – Safety: (continued)

The following table summarizes the TEAEs during the study duration in the all-safety population.

All Safety Population	Glargine (N=184)		Pioglitazone (N=198)	
	TEAE	Possibly Related TEAE	TEAE	Possibly Related TEAE
Reported at Least One TEAE [n (%)]	124 (67.4)	22 (12.0)	139 (70.2)	41 (20.7)
Reported at Least One Serious TEAE [n (%)]	19 (10.3)	3 (1.6)	14 (7.1)	1 (0.5)
Subjects Discontinued Due to a TEAE [n (%)]	4 (2.2)	2 (1.1)	18 (9.1)	12 (6.1)
Subjects Who Died During the Study [n (%)]	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

TEAE: Treatment-emergent adverse events;

Irrespective of the time of day, glargine-treated subjects experienced a statistically significantly greater number of hypoglycemic events than the pioglitazone-treated subjects.

The following table summarizes the hypoglycemic events in the all safety population.

		Glargine (N=184)		Pioglitazone (N=198)		
Type of Hypoglycemia		N	%	N	%	Prob
All Types	Subjects With >= 1 Episode	81	44.0	41	20.7	<0.0001
	Episodes Reported	756		174		
Confirmed Clinically Relevant	Subjects With >= 1 Episode	74	40.2	36	18.2	<0.0001
	Episodes Reported	631		135		
Moderate to Severe	Subjects With >= 1 Episode	27	14.7	13	6.6	0.0098
	Episodes Reported	52		22		
Severe	Subjects With >= 1 Episode	7	3.8	1	0.5	0.0254
	Episodes Reported	9		1		
Unconfirmed Non-severe	Subjects With >= 1 Episode	34	18.5	15	7.6	0.0014
	Episodes Reported	125		39		
Nocturnal	Subjects With >= 1 Episode	42	22.8	15	7.6	<0.0001
	Episodes Reported	99		35		
Symptomatic	Subjects With >= 1 Episode	66	35.9	29	14.6	<0.0001
	Episodes Reported	423		119		
Asymptomatic	Subjects With >= 1 Episode	47	25.5	22	11.1	0.0002
	Episodes Reported	333		55		

Results – Safety: (continued)	The rate of hypoglycemia due to drug exposure during the 48 weeks of treatment duration was estimated for both treatment groups. In all categories reported glargine-treated subjects displayed significantly more hypoglycemic event rates compared with the pioglitazone-treated subjects
Date of report:	20-October-2008