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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00347100
		Study Code:	LANTU_L_01051
Generic drug name:	Insulin Glargine	**Date:**	19 August 2009

Title of the study:	Treatment of early insulinization with Glargine in type 2 diabetes patients uncontrolled on sulfonylurea or metformin monotherapy.	
Investigator(s):	China Japan Friendship Hospital	Pr. Yang Wenying
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Study center(s):	12 centers in China	
Publications (reference):	None	
Study period: Date first patient/subject enrolled: 15-06-2006 Date last patient/subject completed: 26-05-2008		Phase of development: Phase IV

Objectives:	Primary: To compare the glycemic control, as measured by hemoglobin A1c (HbA1c), between insulin glargine or OAD add-on therapies(added to an existing treatment regimen of sulfonylurea or metformin) in subjects who had previously failed monotherapy with a sulfonylurea (SU) or metformin. Secondary: To compare the effects of insulin glargine and OAD add-on therapy on several parameters (occurrence of hypoglycemia; change in fasting plasma glucose [FPG];change in prandial plasma glucose [PPG]; change in body weight and C-peptide level.)		
Methodology:	This was a multicentre, randomized (1:1), 2-arm, parallel-group, open label study comparing insulin glargine or OAD add-on therapies. There was a screening period that was up to 2 weeks in duration followed by a 24-week treatment period. The study visits included: screening (-2 to 0 weeks), baseline (week 0), and treatment (week 12, 24).		
Number of patients/subjects:	Planned: 388	Randomized: 387	Completed treatment: 351
Evaluated:	Efficacy/Pharmacodynamics: NA	Safety: 375	Pharmacokinetics: NA
	Efficacy: Change from baseline in HbA1c, fasting plasma glucose (FPG), prandial plasma glucose (PPG), body weight, and lipids, C-peptide level and proportions of patients with HbA1c values ≤7% and ≤6.5%. Safety: Safety was assessed through adverse events(reported by the patients or noted by the investigator), hypoglycaemia, body weight, physical examinations, vital signs, standard hematology, blood chemistry and urinalysis.		
Diagnosis and criteria for inclusion:	Male and female subjects who were between 18 and 80 years-of-age (inclusive), had a diagnosis of type 2 diabetes mellitus for at least six months and were inadequately controlled (HbA1c between 7.5%≤ A1c ≤11% at screening), and who had been on a stable doses of SU or metformin for at least 1 months prior to screening.		
Investigational product: Dose: Administration:	Insulin glargine injection, 3 ml vial, 100 IU/ml The starting dose of insulin glargine was a single daily dose of 10 IU/day administered at bed time and increased by 2 IU/3day until the FPG was ≤ 5.6mmol/L through to week 24. No change(s) in the dosage(s) of the already prescribed OAD was permitted in the insulin glargine group. Subcutaneous injection		
Duration of treatment: 24 weeks		Duration of observation: 26 weeks (2 week screening phase plus 24 week treatment phase)	

Reference therapy: Dose: Administration:	SU (Glimepiride tablets, Glipizide tablets, Gliclazide tablets) and Metformin tablets The second OAD (SU or Metformin) administered daily and increased up to reach glycemic targets (fasting blood glucose ≤5.6 mmol/L) through to week 24. No increase(s) in the dosage(s) of the already prescribed OAD was permitted in the OAD group. Oral
Criteria for evaluation:	
Efficacy or Pharmacodynamics:	Efficacy: HbA1c, FPG, PPG, Body weight, BMI
Safety:	Safety was assessed through adverse events (reported by patients or noted by the investigator), hypoglycaemia, body weight, physical examinations, vital signs, standard haematology, blood chemistry and urinalysis.
Pharmacokinetics:	NA
Pharmacokinetic sampling times and bioanalytical methods:	NA
Statistical methods:	In this study, the primary efficacy analysis was to compare the mean change in A1c from baseline to study week 12 or week 24 between the insulin glargine group and OAD treatment group. Mean within-group and between-group changes in A1c from baseline were compared using paired t-test or rank sum test. Analysis of Covariance (ANCOVA) was also used, with treatment and study centers as factors, baseline as covariate. For categorical variables (e.g. proportions of patients with FPG＜5.6mmol/L), Pearson chi-square and/or Cochran-Mantel-Haenszel (CMH) test stratified by center were used to compare the two groups. The primary efficacy analysis was based on full analysis set population. The significance level was set at 0.05 for all statistical tests (two-sided).

Summary:

Patient population:

In the overall study, a total of 387 patients were randomized (193 patients were randomized to the Insulin glargine group and 194 patients were randomized to OAD group). Mean exposure to Insulin Glargine and optimized OAD therapy was 0.44 patient-years and 0.43 patient-years respectively.

The baseline demographics were comparable between two treatment groups with respect to age, disease state and T2DM duration. There were no significant differences between treatments groups in mean duration of treatment.

The baseline demographics(FAS):

Parameter	Insulin Glargine	OAD	p value
Sex (N, Male %)	186, 51.15	189, 47.1%	0.4402
Mean age (SD)	54.32(10.92)	53.85(10.46)	0.6702
Mean T2DM History/year (SD)	5.94(4.18)	4.92(4.02)	0.0093
Diabetic complications	14%	17.5%	0.3545
Mean weight/Kg(SD)	67.41(11.08)	66.17(11.95)	0.2136
Mean BMI (SD)	25.09(2.81)	25.09(3.14)	0.7143

The following table summarizes the deposition of patients in the all randomized population:

	Insulin Glargine	OAD
Randomized [N]	193	194
Completed [n(%)]	177 (91.7%)	174 (89.7%)
Discontinued [n (%)]	16 (8.2%)	20 (10.3%)
Reason For Discontinuing		
Adverse Event	1 (6.2%)	2 (10%)
Did Not Wish To Continue	5 (31.2%)	8 (40%)
Protocol Violation	2 (12.5%)	3 (15%)
Lost To Follow-Up	3 (18.7%)	2 (10%)
Patient Died	1 (6.2%)	0 (0.0)
Treatment Failure	1 (6.2%)	3 (15%)
Other	3 (18.7%)	2 (10%)

In the intent-to-treat population, the mean age was similar in the two groups: 54.3 years and 53.8 years, respectively, in the insulin glargine and OAD treatment groups. The mean duration of T2DM was 5.9 years in the insulin glargine treatment group and 4.9 years in the OAD group respectively. The unadjusted mean baseline HbA1C was 9.29% in the insulin glargine group and 9.06% in the OAD group (p= 0.1484).The unadjusted mean FPG was 10.21mmol/L and 9.6 mmol/L in the insulin glargine and OAD groups, respectively, and the unadjusted mean BMI was 25.09 kg/m2 and 25.09 kg/m2, respectively. The insulin glargine and OAD treatment groups were comparable at baseline with respect to diabetes variables (HbA1C, FPG, C-peptide, BMI, weight, metformin dose, SU dose), previous illnesses, and previous medications.

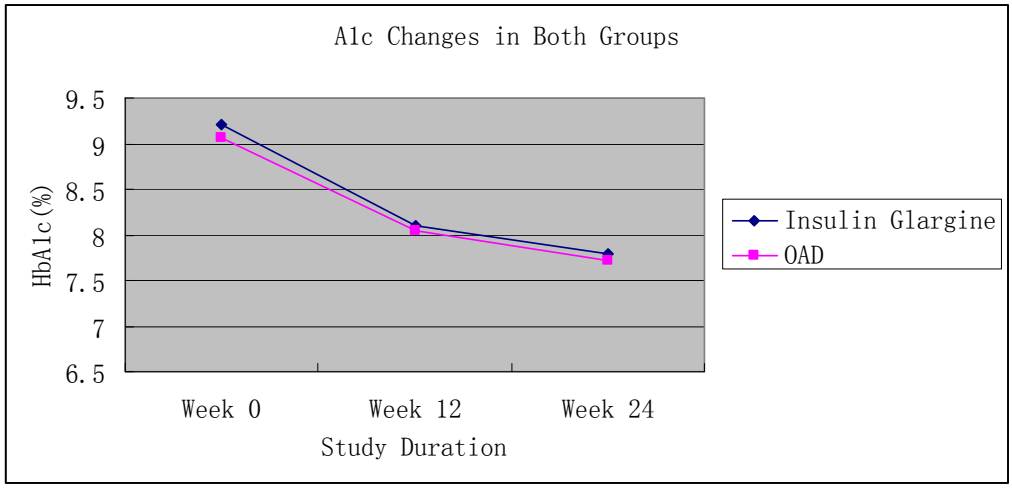
	Dosing: In the 24-week safety population, the overall mean baseline dose of Insulin glargine dosing was 10.0 IU, Gliclazide dosing was 72.7 mg, Glimepiride dosing was 1.52 mg, Glipizide dosing was 15.0 mg and Metformin was 1161.27 mg. In the 24-week safety population, the overall mean endpoint daily dose of Insulin glargine was 20.87 IU. Endpoint mean daily Gliclazide dosing was 90.7 mg, Glimepiride dosing was 4.85 mg, Glipizide dosing was 17.0 mg and Metformin was 1399.2 mg.

Efficacy results:

or

Pharmacodynamic results:

The mean change in HbA1C, FPG, PPG and C-Peptide level from baseline to endpoint within and between the insulin glargine treatment group and the OAD treatment group in the ITT population.



Summary of HbA1c, FPG, PPG and C-Peptide : Change from Baseline to Endpoint –ITT Population

	Mean Change from Baseline within Treatment Group(Change from Baseline)		p-value for differences between Treatment Group (Change from Baseline)
Variable	Insulin Glargine	OAD	
HbA1c (%)±SD 0-12Wks	-1.19±1.27	-1.20±1.17	0.7271
HbA1c(%)±SD 0-24Wks	-1.51±1.29	-1.30±1.27	0.1641
FPG(mmol/L) ±SD 0-24 Wks	-3.90±3.00	-2.08±3.04	<0.0001
Mean FPG(mmol/l) ± SD 24wks	6.80±2.03	8.07±2.37	<0.0001
Subjects Reached A1c <7%, N (%)	52(27.96%)	61(32.28%)	0.3622
Subjects Reached A1c<6.5%, N(%)	18(9.68%)	22(11.64%)	0.5381
Subjects Reached FPG (＜5.6mmol/L) Target(%), N(%)	52(27.96%)	30(15.87%)	0.0046
PPG[2h after standard meal(mmol/L)]±SD 0-24 Wks	-3.92±4.24	-2.30±3.78	0.0003
Mean PPG[2h after standard meal(mmol/L)] ±SD 24Wks	12.72±3.49	13.76±3.88	0.0096
C-peptide level [2h after standard meal(ng/ml)] ±SD 0-24 Wks	-0.27±3.07	0.74±3.73	0.0020
Weight (kg)±SD 24Wks	68.37±11.40	66.50±12.25	0.0960
BMI(kg/m²) ±SD 24Wk	25.43±2.84	25.18±3.12	0.2457

There was no significant difference in the change from baseline in HbA1c, however, there were significant differences in the changes from baseline in FPG, Prandial Plasma Glucose and C-peptide level after a standard meal, all favoring insulin glargine. There was no significant difference between treatment groups in the change from baseline for weight and BMI. In the ITT population, there were27.96% and 9.68% of insulin glargine patients achieved an HbA1C ≤ 7% and HbA1C ≤ 6.5%, respectively, versus 32.28% and 11.64% of OAD patients.

Safety results:

Safety results:

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 incidences.

The percentage of patients with overall TEAEs was significantly different between the insulin glargine group 25.81% and the OAD group 36.51% (p=0.0253).TEAEs leading to discontinuation of study medication were reported in 1(0.52%) patients receiving insulin glargine and 2 (1.06%) patients receiving OAD. Four patients (2.25%) in the insulin glargine group and 2 patients (1.14%) in the OAD group reported serious treatment emergent adverse events (TEAEs) during the study.

There were 2 patients in Insulin Glargine group and one patient in OAD group reported severe headache. Another patient in glargine group complained serious pain in lower extremities. One patient in each group reported severe diarrhoea.

	Insulin Glargine(186 patients)		OAD(189 Patients)		p-value
	Case	Percentage	Patient (Case)	Percentage	
All TEAEs	48(73)	25.81(45.34)	69(88)	36.51(54.66)	0.0253
Patients discontinued due to a TEAE	1(1)	0.54(0.62)	2(2)	1.06(1.24)	0.8730
Serious TEAE	4(4)	2.25(2.48)	2(2)	1.14(1.24)	0.8886

Hypoglycaemic Events:

There were no statistically significant differences between the two groups in the percentage of patients with hypoglycaemic events, all types (29.0% for the Insulin glargine group and 21.6% for the OAD group), however OAD group produced significantly less nocturnal hypoglycaemic events compared with Insulin glargine group.

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

	Insulin Glargine			OAD			p-value
	Number of Incidents	Patient Number	Percentage (%)	Number of Incidents	Patient Number	Percentage (%)	
All Types	88	54	29.03	66	41	21.69	0.1023
Symptomatic	77	49	26.4	63	40	21.16	0.2385
Severe	0	0	0.0	1	1	0.53	0.5040
GI＜56mg/dl	27	16	30.7	36	16	54.5	0.003
Nocturnal	20	15	8.06	4	3	1.59	0.0034

Pharmacokinetic results:	NA
Date of report:	04-August-2009