These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi	**Study Identifiers:** NCT01121835, EudraCT 2009-018172-33, U1111-1116-9859
Drug substance(s): Insulin Glargine (HOE901)	**Study code:** LANTU_C_04589

Title of the study: A 24-week, open, multicenter, comparative study of 2 strategies (including insulin glargine versus premixed insulin) for the therapeutic management of patients with type 2 diabetes failing oral agents. (GALAPAGOS)

Study center(s): 91 active centers in 15 countries: Austria (4), Brazil (5), China (12), Colombia (5), Denmark (2), Greece (10), India (7), Italy (9), Korea (4), Kuwait (1), Mexico (5), Romania (3), Spain (9), Taiwan (8), Turkey (7).

Study period:

Date first patient enrolled: 17 June 2010

Date last patient completed: 15 March 2012

Phase of development: Phase IV

Objectives:

Primary Objective: To demonstrate the superiority of a strategy with insulin glargine (either in combination or not with one daily injection of insulin glulisine at the main meal), in comparison with a strategy including the premixed insulin in term of percentage of patients reaching hemoglobin A1c (HbA1c) below 7% at the end of the treatment period and who do not experience documented symptomatic hypoglycemia (confirmed by a plasma glucose [PG] ≤56 mg/dL [3.1 mmol/L]) over the treatment period, in type 2 diabetes patients failing lifestyle management and oral agents.

Main Secondary Objectives: To assess the effect of insulin glargine in comparison with premixed insulin on:

- Evolution of HbA1c level during the treatment period
- Percentage of patients who reach the target HbA1c <7% and who do not experience documented symptomatic hypoglycemia confirmed by a PG ≤70 mg/dL (3.9 mmol/L)
- Percentage of patients who reach the target HbA1c <6.5% and who do not experience documented symptomatic hypoglycemia confirmed by a PG ≤56 mg/dL (3.1 mmol/L)
- Percentage of patients who reach the target HbA1c <6.5% and who do not experience documented symptomatic hypoglycemia confirmed by a PG ≤70 mg/dL (3.9 mmol/L)
- Evolution of Fasting PG (FPG)
- Evolution of 7-point PG profiles
- Evolution of weight
- Hypoglycemia occurrence
- Dose of insulins
- Evolution of liver function and lipid parameters
- Patient Reported Outcomes (PRO): Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs) and Diabetes Treatment Satisfaction Questionnaire (change) (DTSQc)
- Overall safety

Methodology: This was a phase IV, multicenter, international, comparative, randomized (allocation ratio 1:1), open-label clinical study with 2 parallel groups.

At the end of a 2-week screening period during which current antidiabetic therapy was continued, eligible patients were randomized to receive either insulin glargine (once a day) or premixed insulin (once or twice a day) for a 24-week treatment period. A tight insulin titration based on PG values was implemented in both groups with a FPG target ≤100 mg/dL.

At the end of the first 12 weeks of treatment:

- Patients in the glargine group for whom HbA1c remained ≥7% with FPG <126 mg/dL received an additional injection per day of insulin glulisine at the main meal, until the end of the treatment period.
- Patients in the premixed insulin group continued the titration with the possibility to add a second injection in patients still treated once a day.

During the treatment period, patients continued the treatment with metformin. Current treatment with sulfonylureas, glinides or dipeptidyl peptidase IV-inhibitors were maintained in patients treated with one daily injection of insulin (insulin glargine alone or premixed once daily). These drugs were to be stopped as soon as patients received 2 daily insulin injections (insulin glargine+ insulin glulisine or 2 injections of premixed insulin).

Number of patients**:**

	Insulin glargine	Premixed insulin	All
Planned	435	435	870
Randomized population	466	468	934
Safety population	463	460	923
Modified Intent-to-Treat (mITT) population	462	461	923
Patients from mITT population evaluable for primary endpoint	455	446	901
Per Protocol (PP) population	424	412	836
Patient reported outcome(PRO) analysis population	454	454	908

Diagnosis and criteria for inclusion: Patients with type 2 diabetes diagnosed for at least one year, aged ≥35 years, insulin naïve, treated with oral antidiabetic drugs, at least metformin at the maximum tolerated dose (with a minimum dose of 1 g/day), for at least 3 months; and with an HbA1c ≥7% and ≤10.5% and a body mass index (BMI) ≤40kg/m² at study entry.

Study treatments

Investigational medicinal product(s): Insulin glargine, premixed insulin, and insulin glulisine were provided by the Sponsor

Formulation: Insulin glargine, 100 Units (U)/mL solution for injection in a pre-filled SoloStar® pen (3 mL)

Route of administration: subcutaneous (SC) injection

Dose regimen: Insulin glargine was administered once a day in the evening, at the same time every day. The starting daily dose was 0.2 U/kg of body weight or 12 U, at the investigator's discretion. Patients were empowered to adjust their insulin doses, under strict investigator's supervision. The goal was to achieve, through a forced titration, 80 ≤FPG ≤100 mg/dL (4.4 ≤FPG ≤5.5 mmol/L). Patients used the last 3 FPG values to perform the titration every 3 days.

Formulation: Premixed insulin:

- 30% soluble insulin aspart (rapid acting) and 70% protamine-crystallized insulin aspart (long acting) in pre-filled Flexpen® for all countries except Mexico
- 25% insulin lispro solution and 75% insulin lispro protamine in cartridges for Humapen® Luxura® for Mexico only

Routes of administration: SC injection

Dose regimen: Premixed insulin was administered once a day (in the evening at dinner) or twice a day (in the morning before breakfast and in the evening at dinner). The starting daily dose was 6 U at breakfast and 6 U at dinner, if administered twice a day, or 12 U at dinner, if administered once a day. Patients were empowered to adjust their insulin doses, under strict investigator's supervision. The goal was to achieve, through a forced titration, 80 ≤pre-meal PG ≤100 mg/dL (4.4 ≤pre-meal PG ≤5.5 mmol/L). Patients used pre-meal PG values of the last 3 days to perform the titration every 3 days using pre-dinner PG values for breakfast dose adjustment and pre-breakfast PG values for dinner dose adjustment. When using once daily doses, it was recommended to move to twice daily doses once a dose of 30 U was reached by splitting the dose into equal breakfast and dinner doses.

Formulation: Insulin glulisine, 100 U/mL solution for injection in a pre-filled SoloStar® pen (3 mL)

Route of administration: SC injection

Dose regimen: For patients in the insulin glargine group requiring insulin glulisine at Week 12, insulin glulisine was administered once a day prior (0-15 minutes) to the main meal of the day, which was the meal with the highest Post-Prandial PG (PPPG) on the last 3 profiles performed before Week 12. The starting daily dose was 4 U. Patients were empowered to adjust their insulin doses, under strict investigator's supervision. The goal was to have a PPPG ≤140 mg/dL (7.8 mmol/L). Patients used the last 3 PPPG values measured 2 hours after the start of the main meal of the day to perform the titration every 3 days.

Noninvestigational medicinal product: Metformin was a background treatment, mandatory for each patient randomized in the study (at the minimum dose of 1 g/day). It was not supplied by the Sponsor.

Duration of treatment: 24 weeks of treatment period per patient

Duration of observation: 27 weeks per patient (2 weeks of screening, 24 weeks of treatment period, and 1 week of follow-up)

Criteria for evaluation:

Efficacy: The primary efficacy variable was the percentage of patients with an HbA1c <7% at the end of the treatment period, with no documented symptomatic hypoglycemia (confirmed by a PG ≤56 mg/dL) over the 24-week period.

Main secondary efficacy criteria were the following:

- the absolute change in HbA1c from baseline to the end of treatment (EOT) period
- the percentage of patients with HbA1c <7% or 6.5% at the EOT period
- the percentage of patients with HbA1c <6.5% at the EOT period with no documented symptomatic hypoglycemia (confirmed by a PG ≤56 mg/dL) over the 24 week treatment period
- the percentage of patients with HbA1c <7% or 6.5% at the EOT period with no documented symptomatic hypoglycemia (confirmed by a PG ≤70 mg/dL) over the 24 week treatment period
- the changes in 7-point PG-profiles, FPG and mean daily PG between baseline and EOT period
- the variability of FPG at the EOT period
- insulin doses

Safety:

- Adverse events
- Symptomatic hypoglycemia episodes
- Body weight, vital signs
- Liver and renal laboratory data
- Lipid profiles

Statistical methods:

Efficacy analyses:

The primary efficacy analysis compared the percentage of patients reaching primary criterion by a Pearson chi-square test at the significance level of alpha equal to 5%, in the mITT population (all randomized patients who received at least one dose of investigational product, and had at least one post-baseline assessment on-treatment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures).

Patients from the mITT population evaluable for primary criterion were patients who had:

- at least one post-baseline HbA1c measurement on-treatment as well as information on symptomatic hypoglycemia, or
- their last post-baseline HbA1c measurement on-treatment ≥7% and no information on symptomatic hypoglycemia, or
- no post-baseline HbA1c measurement on-treatment but at least one documented symptomatic hypoglycemia confirmed by a PG value ≤56 mg/dL during the treatment period.

Other cases were classified as missing values.

If superiority was not reached, switching to non-inferiority was considered and the comparison was made using a 95% confidence interval (CI) of the difference in percentages (glargine-premixed). The conclusion of non-inferiority was reached if the lower limit of the confidence interval was higher than or equal to the non-inferiority margin, defined as 25% of the percentage that was measured with premixed insulin. This result had to be confirmed in the Per Protocol population (patients from the mITT population evaluable for primary criterion with no important protocol deviations potentially impacting efficacy analysis).

For secondary efficacy variables, the difference between treatments was analyzed using a Chi-squared test for categorical data and an analysis of covariance (ANCOVA) for continuous data. Regarding insulin dose, only summary statistics were performed.

Safety analyses: all safety analyses were based on the safety population (all randomized and treated patients).

The number and percentage of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, possibly related TEAEs, TEAEs leading to treatment discontinuation and deaths were described.

Analyses were conducted on the frequency of patients with hypoglycemia using Pearson chi-square or Fisher's exact test and on the number of hypoglycemic episodes per patient-year of exposure, using a generalized linear model based on a Poisson or negative binomial distributions.

The measured changes in weight between baseline and end of treatment were compared between the 2 treatment groups by an ANCOVA.

Summary:

Population characteristics:

- A total of 1243 patients were screened, 934 were randomized and 923 were exposed to the study treatment; and 309 patients (24.9%) were screening failures. The main reason for screening failures was not meeting inclusion criteria (HbA1c out of required range in most of the cases).
- Out of the 923 patients who were treated with study medication, 860 (93.2%) completed the study (438 in the insulin glargine groups and 422 in the premixed insulin group).
- Patients from the mITT population were approximately half males (51.0 %), and females (49.0%), with a mean age of 56.3 (9.2) years. Mean body weight was 75.9 (13.7) kg and BMI was 28.4 (4.5) kg/m2. Median duration of diabetes was 7.8 years and mean baseline HbA1c was 8.7 (0.9)%.
- Among the 463 patients treated with insulin glargine, 197 (42.5%) patients received insulin glulisine in addition, at Week 12, as planned per protocol for patients insufficiently controlled. A total of 297 patients out of the 460 patients treated with premixed insulin started with 1 injection a day. Among them, 129 patients switched during the treatment period to 2 injections a day. Therefore, at the end of the treatment period, 292 (63.5%) were treated with premixed insulin twice daily.

Efficacy results:

- The superiority of the insulin glargine group compared to the premixed insulin group in terms of percentage of patients who reached an HbA1c <7% at end of treatment, with no documented symptomatic hypoglycemia (with PG ≤56 mg/dL) over the 24-week treatment period was not demonstrated. As planned in the protocol, the switch to non-inferiority testing was performed and the non-inferiority of insulin glargine group versus premixed insulin group was shown. The results were confirmed in the PP population.

Primary efficacy endpoint: HbA1c <7% at end of treatment with no documented symptomatic hypoglycemia (PG ≤56 mg/dL) (mITT population, N = 923)

	Insulin glargine		Premixed insulin	
	N = 462		N = 461	
HbA1c<7% at end of treatment, no documented symptomatic hypoglycemia (PG ≤56 mg/dL)				
N	455		446	
Success [n (%)]	151	(33.2)	140	(31.4)
Failure [n (%)]	304	(66.8)	306	(68.6)
Difference in success rate (%) (insulin glargine- premixed insulin)	1.8			
95% Confidence Interval (%)	(-4.32% to 7.91%)			
p-value	0.564			

Note: If superiority was not demonstrated, switching from superiority to non-inferiority was considered. Then non-inferiority was reached if the lower limit of the CI of the difference of percentage was ≥-7.848 (where ε=7.85 is 25% of rate measured with premixed insulin).

- The percentage of patients reaching the composite outcome was 33.2% and 31.4% respectively in the insulin glargine and premixed groups. The composite outcome was calculated using percentage of patients with HbA1c<7% (in favor of premixed insulin) and percentage of patients without symptomatic hypoglycemia confirmed by PG ≤56 mg/dL (in favor of insulin glargine, 77.6% versus 63.7% with premixed insulin).
- More patients met the primary efficacy criterion in both groups when treated with only 1 insulin injection (43.8% in the glargine group and 37.7% in the premixed group).
- The proportion of patients achieving HbA1c <7% at EOT was higher in the premixed group (52.6%) compared to insulin glargine (43.2%) (p = 0.005).
- The decrease from baseline to EOT in mean FPG was statistically significantly greater in the insulin glargine group (160.12 [36.70] mg/dL to 107.72 [20.66] mg/dL) than in the premixed insulin group (162.13 [42.43] mg/dL to 114.07 [24.93] mg/dL) , with a least squares mean difference from the premixed insulin group of -6.08 mg/dL (95%CI [-8.97; -3.18]), in favor of insulin glargine (p <0.001).
- Decrease in self monitoring PG was observed in both groups at each time point of the profile, more pronounced for insulin glargine group than for premixed insulin before breakfast and more pronounced for premixed insulin before lunch, after dinner and at bedtime.
- Mean daily dose increased up to the end of the treatment period in both groups, mainly in the first 12 weeks. The daily doses reached during the study were higher in the premixed insulin group (41.7 [29.9] U versus 27.1 [16.5] U in the insulin glargine group at Week 12, and 47.2 [35.8] U versus 30.3 [19.5] U at EOT). In the insulin glargine group, the mean starting daily dose of insulin glulisine at Week 12 was 4.2 (1.4) U and increased up to 13.6 (11.5) U at EOT.

Safety results:

- The proportion of patients experiencing at least one TEAE was similar in both groups. More patients presented with serious TEAEs, possibly related TEAEs and TEAEs leading to permanent treatment discontinuation in the premixed insulin group. Serious hypoglycemia occurred in 3 patients in the insulin glargine group and 5 patients in the premixed insulin group. One patient in the insulin glargine group died during treatment period, following pulmonary embolism.

Overview of adverse events: number (%) of patients (Safety population, N = 923)

	Insulin glargine		Premixed insulin	
	N = 463		N = 460	
Any TEAE	160	(34.6)	164	(35.7)
Any possibly related TEAE (to insulin glargine or premixed insulin)	12	(2.6)	31	(6.7)
Any possibly related TEAE (to insulin glulisine)	8	(1.7)	0	
Any possibly related TEAE (to metformin)	3	(0.6)	3	(0.7)
Any serious TEAE	12	(2.6)	23	(5.0)
Any TEAE leading to death	1	(0.2)	0	
Any TEAE leading to permanent discontinuation	3	(0.6)	11	(2.4)

Note: n (%) = number and percentage of patients with at least one adverse event.

- No relevant difference in the changes of body weight was observed between the two treatment groups (adjusted mean increase of 1.07 kg in the insulin glargine group and 1.41 kg in the premixed group).
- More patients experienced symptomatic hypoglycemia (all, confirmed, day-time and nocturnal) in the premixed insulin group compared to the insulin glargine group. Severe hypoglycemia was reported in few patients in both treatment groups.

Number (%) of patients with at least one episode of hypoglycemia (Safety population, N = 923)

	Insulin glargine		Premixed insulin		p-value Pearson (or Fisher)
	N=463		N=460		
All symptomatic	249	(53.8)	290	(63.0)	0.004 (a)
Symptomatic with PG ≤70 mg/dL	211	(45.6)	251	(54.6)	0.006 (a)
Symptomatic with PG ≤56 mg/dL	102	(22.0)	162	(35.2)	<0.001 (a)
Severe symptomatic	4	(0.9)	2	(0.4)	0.686 (b)
Nocturnal symptomatic	94	(20.3)	145	(31.5)	<0.001 (a)
Nocturnal symptomatic with PG ≤70 mg/dL	82	(17.7)	127	(27.6)	<0.001 (a)
Nocturnal symptomatic with PG ≤56 mg/dL	34	(7.3)	86	(18.7)	<0.001 (a)
Severe nocturnal symptomatic	1	(0.2)	1	(0.2)	1.000 (b)
Day-time symptomatic	230	(49.7)	275	(59.8)	0.002 (a)
Day-time symptomatic with PG ≤70 mg/dL	189	(40.8)	236	(51.3)	0.001 (a)
Day-time symptomatic with PG ≤56 mg/dL	88	(19.0)	131	(28.5)	<0.001 (a)
Severe day-time symptomatic	3	(0.6)	1	(0.2)	0.624 (b)

Note: Incidence of hypoglycemia compared between treatment arms by a Pearson's chi-square test (or Fisher's exact test).
(a) Pearson chi-square test, (b) Fisher's exact test

• The estimated rate of episodes of hypoglycemia per patient-year was lower in the insulin glargine group compared to the premixed insulin group for all types of hypoglycemia (except severe). The estimated rate (standard error [SE]) of symptomatic hypoglycemia per patient-year was 6.395 (0.52) and 11.257 (0.90) and the estimated rate (SE) of symptomatic hypoglycemia confirmed by a PG ≤56 mg/dL was 1.174 (0.14) and 2.93 (0.33), in the insulin glargine and in premixed insulin groups, respectively. • Overall, the safety profile was good and consistent with the expected safety profile of the investigational products.
Issue date: 27-Feb-2013