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Sponsor / Company: Sanofi **Drug substance(s):** Insulin Glargine (HOE901) Insulin Glulisine (HMR1964)	**Study Identifiers:** NCT01203111, U1111-1116-3517 **Study code:** LANTU_R_05048
Title of the study: Efficacy and safety of intensive insulin therapy with insulin glulisine in patients with type 2 diabetes inadequately controlled with basal insulin and oral glucose-lowering drugs (CHANGING)	
Study centers: Twenty-seven centers from 9 countries (Algeria, Brazil, Israel, Lebanon, Mexico, Peru, Saudi Arabia, United Arab Emirates, Venezuela).	
Study period: Date first patient enrolled: 20 December 2012 Date last patient completed: 16 July 2012	
Phase of development: Phase 4	

Objectives: The primary objective of the study was to evaluate the efficacy of an intensive insulin regimen with insulin glargine and insulin glulisine in terms of change in hemoglobin A1c (HbA1c) level from Week 12 (Visit 7) to Week 24 (Visit 10).

The secondary objectives (efficacy and safety) were the following:

- Percentage of patients with HbA1c < 7% at Week 24,
- Percentage of patients with HbA1c < 7% at Week 24 and no symptomatic nocturnal hypoglycemia event (between Week 0 and Week 24 for all patients and between Week 12 and Week 24 only for patients treated with insulin glulisine),
- Fasting plasma glucose(FPG) and 7-point self-monitoring of blood glucose (SMBG) at Week 0, Week 12 and Week 24,
- Doses of insulin glargine and insulin glulisine: the daily dose (U) and the daily dose per kg (U/kg) at Week 24,
- Systolic and diastolic blood pressure, heart rate, weight change at Week 0, Week 12 and Week 24,
- Number of patients suffering from hypoglycemias (asymptomatic, symptomatic, nocturnal symptomatic, severe and nocturnal severe) during the treatment period,
- Adverse events (AEs).

Methodology: This was an international, multicenter, non-comparative, open-label study. The study consisted in a 2-week run-in period followed by two 12-week treatment periods.

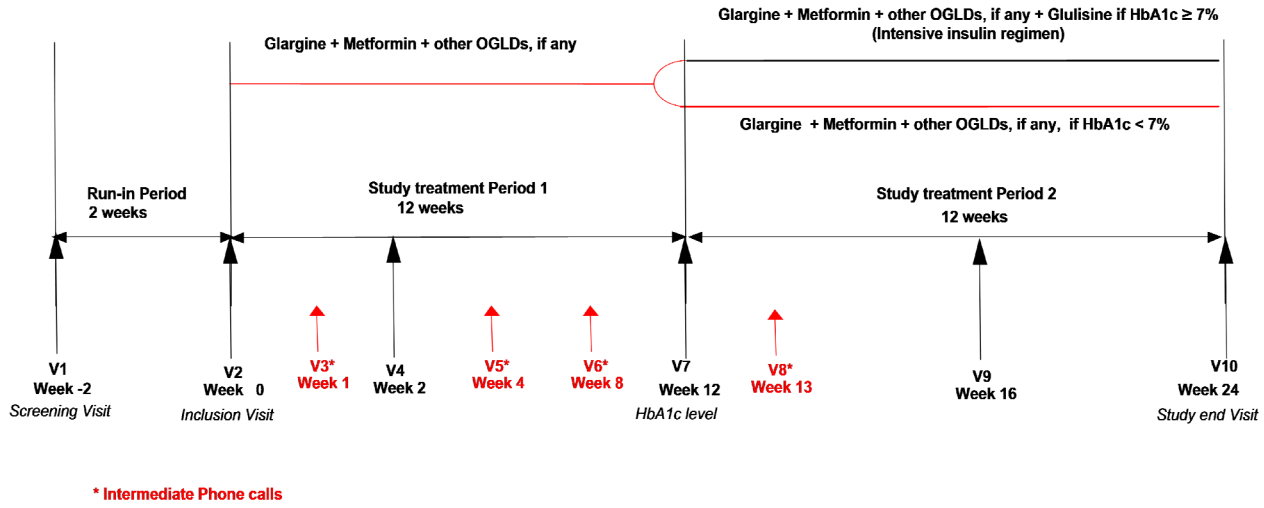
During the treatment period 1 (Week 0-Week 12), the patients were switched from their previous antidiabetic treatment to insulin glargine (1 daily injection in the evening) combined with metformin (MET) (at least 1 g) and other oral glucose-lowering drug (OGLD), if any (at treating investigator's discretion) at the same dosage as prior to study entry.

At the end of this first treatment period (Week 12):

- Patients whose HbA1c was ≥7% and FPG ≤100 mg/dL* (5.6 mmol/L) received an intensive insulin regimen with insulin glargine and insulin glulisine, combined with MET and other OGLD, if any, until Week 24. Insulin glulisine bolus was administered before the main meal defined as the meal with the highest postprandial glucose (PPG) value, average of 3 consecutive PPG measurements. Patients were instructed to eat the same amount of carbohydrate at each meal.
- Patients whose HbA1c was <7% continued the same therapy combining insulin glargine, MET and other OGLD, if any until Week 24.

** Investigators were instructed that patients with FPG value close to 100 mg/dL (up to 110 mg/dL) were also eligible when glucose value after the mean meal of the day was >180 mg/dL (7-point glucose profile at Week 12).*

Study design



Number of patients: Planned: 200
Screened: 252
Treated: 205

Evaluated:

After review of values of HbA1c, FPG and 7-point glucose profile at Week 12 for all patients, patients with FPG >100 mg/dL but ≤140 mg/dL and post-prandial glucose >180 mg/dL were considered as eligible for intensive insulin regimen in treatment period 2.

For efficacy:

- mITT population: 189 patients treated during the treatment period 2, with at least one post-baseline assessment under treatment.
- PP population (main population for efficacy analysis): 150 patients of the mITT population without major protocol deviations.

For safety:

- Safety population P1: 205 patients treated with at least 1 dose of insulin glargine during the treatment period 1.
- Safety population P2: 193 patients treated with at least 1 dose of insulin glulisine (for patients who received an intensive insulin regimen) or with at least 1 dose of insulin glargine (for patients who did not receive an intensive insulin regimen) during the treatment period 2.

In the post-hoc analysis, 5 groups were defined according to treatment received and values of HbA1c and FPG at Week 12.

Population	Group A: Insulin glargine + glulisine HbA1c ≥7% FPG ≤140 mg/dL	Group B: Insulin glargine alone HbA1c <7%	Group C: Insulin glargine alone HbA1c ≥7% FPG ≤140 mg/dL	Group D: Insulin glargine + glulisine HbA1c ≥7% FPG >140 mg/dL	Group E: Insulin glargine alone HbA1c ≥7% FPG >140 mg/dL	Total
Safety P1[a]						205 (81.3%)
Safety P2[b]	90	28	29	26	20	193 (94.1%)
mITT [c]	88 (97.8%)	28 (100%)	29 (100%)	24 (92.3%)	20 (100%)	189 (97.9%)
PP [c]	71 (80.7%)	26 (92.9%)	25 (86.2%)	9 (37.5%)	19 (95.0%)	150 (79.4%)

a Percentage calculated from screened patients
b Percentage calculated from Safety population P1
c Percentage calculated from Safety population P2

Diagnosis and criteria for inclusion: Male or female patients from 18 to 75 years old inclusive with uncontrolled type 2 diabetes mellitus (defined as HbA1c level between 7.5% and 10% assessed over the past 6 months), body mass index (BMI) between 25 and 40 kg/m^2, and currently treated with a basal insulin (NPH, insulin zinc or insulin detemir), plus at least 1 g MET daily, and other OGLD if any, for at least 3 months,

Inclusion criteria for entry in the treatment period: HbA1c level between 7.5% and 10% assessed between Week -2 and Week 0, serum creatinine ≤135 µmol/L in men and ≤110 µmol/L in women, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤3 times the upper limit of normal.

Study treatments

Investigational products:

Insulin glargine/ Lantus® SoloStar®: 100 U/mL (U-100), solution for injection, 3 ml cartridge system for Lantus® SoloStar®, pre filled disposable pen.

Insulin glulisine / Apidra® SoloStar®: 100 U/mL (U-100), solution for injection, 3 ml cartridge system for Apidra® SoloStar®, pre filled disposable pen.

Administration: Insulin glargine was administered subcutaneously, once daily in the evening at bedtime.

Insulin glulisine was administered subcutaneously, once daily, 0 to 15 minutes before the main meal, defined as the meal with the highest PPG value, average of 3 consecutive PPG measurements

Dose: The dose of insulin glargine was individually titrated every 3 days to achieve FPG ≤100 mg/dL (5.6 mmol/L).

The dose of insulin glulisine was individually titrated every 3 days to achieve a 2-hour PPG between 120 and 160 mg/dL.

Non investigational product: metformin administered orally at the same dosage (at least 1 g) as prior to study entry throughout the study.

Duration of treatment: 24 weeks.

Duration of observation: 26 weeks.

Criteria for evaluation:

Efficacy: The primary efficacy variable was the change in HbA1c level between Week 12 and the end of treatment period at Week 24 for patients with HbA1c ≥7% and FPG ≤140 mg/dL on intensive insulin therapy (addition of insulin glulisine at Week 12).

The secondary efficacy variables were:

- Percentage of patients with HbA1c <7% at Week 24,
- Percentage of patients with HbA1c level <7% at Week 24 and no symptomatic nocturnal hypoglycemia event (between Week 0 and Week 24 for all patients and between Week 12 and Week 24 only for patients treated with insulin glulisine),
- FPG (mmol/L) and 7-point SMBG (Daily mean PG and 7-point PG mean profile – mmol/L),
- Doses of insulin glargine and insulin glulisine: the daily dose (U) and the daily dose per kilo (U/kg),
- Weight change (kg).

Safety:

- Hypoglycemia (asymptomatic, symptomatic, nocturnal symptomatic, severe and nocturnal severe),
- AEs,
- Laboratory data (AST, ALT, serum creatinine analysed between Week-2 and Week 0),
- Clinical data: SBP, DBP, HR and weight at Week 0, Week 12 and Week 24.

Statistical methods:

The sample size calculation was based on a desired precision of ±3.2 in estimating the primary criterion. Considering a SD of 1.4 in the HbA1c change, 74 patients on intensive insulin regimen needed to be assessed at Week 24 to attain this precision with a two-sided 95%CI. Considering an expected rate of around 40% of patients not reaching the 7% at Week 12 and a drop-out rate of 8%, 200 patients needed to be recruited.

The primary efficacy analysis investigated the change in HbA1c between Week 12 and Week 24 for patients treated with intensive insulin regimen (patients with HbA1c ≥7% and FPG ≤140 mg/dL), and was based on the PP population (main population for efficacy analysis). 95% confidence interval (CI) of the mean of the change was assessed in addition to descriptive statistics. Descriptive statistics (raw value and change from baseline) were provided at baseline, Week 12 and Week 24 and by treatment group on the PP population. A sensitivity analysis was conducted in reproducing the same analysis on the mITT population. Descriptive statistics (raw value) were provided at baseline and Week 12 overall on the Safety population P1 and at baseline, Week 12 and Week 24 by treatment group and overall on the Safety population P2.

A descriptive analysis (with 95%CI of the proportion) was performed for patients with HbA1c < 7% at week 24 and patients with HbA1c < 7% at week 24 and no symptomatic nocturnal hypoglycemia (between week 0 and week 24 for all patients and between week 12 and week 24 for patients with only insulin glulisine) on the PP population and reproduced on the mITT population. The same analysis was performed for patients with HbA1c < 7% and no symptomatic nocturnal hypoglycemia at week 12.

For FPG, PG variables (daily mean PG and 7-point PG mean profile) and weight, a descriptive analysis (raw value and change from baseline) was performed at baseline, week 12 and week 24 and by treatment group on the PP and mITT populations. Descriptive statistics (raw value) were provided at baseline and week 12 overall on the Safety population P1 and at baseline, week 12 and week 24 by treatment group and overall on the Safety population P2.

Summary:

Population characteristics: The characteristics of the safety population P1 are presented in the following table. Similar results were observed for the Safety Population P2, the PP population and the mITT population. Baseline characteristics of patients included in Group A (main group of interest) were mostly similar to those of the overall safety population. They tended to be more often treated with other OGLD at screening and to have a longer duration of insulin therapy.

Baseline Characteristics		Safety population P1 (N=205)	Safety population P2 – Group A Insulin glargine + glulisine HbA1c ≥7% FPG ≤140 mg/dL (N=90)
Age (years)	Mean (SD)	57.9 (9.1)	58.9 (8.8)
Female Gender	n (%)	128 (62.4%)	59 (65.6%)
BMI (kg/m²)	Mean (SD)	30.6 (4.2)	30.1 (3.9)
Duration of type 2 diabetes (years)	Median (range)	11.0 (0.0 ; 35.0)	11.0 (0.0 ; 35.0)
Duration of basal insulin therapy (months)	Median (range)	13.9 (0.8 ; 140.6)	16.1 (1.1 ; 140.6)
Duration of metformin therapy (months)	Median (range)	47.7 (1.1 ; 317.6)	31.3 (2.6 ; 240.0)
Patients treated with other OGLD	n(%)	107 (52.2%)	53 (58.9%)
Duration of treatment with other OGLD (months)	Median (range)	27.1 (0.5 ; 349.4)	26.2 (0.5 ; 194.5)
At least one late diabetic complication	n(%)	81 (39.5%)	32 (35.6%)
Any targeted concomitant disease	n(%)	176 (85.9%)	75 (83.3%)
Hypertension	n(%)	140 (68.3%)	58 (64.4%)
Dyslipidemia	n(%)	126 (61.5%)	53 (58.9%)
Hba1c (%)	Mean (SD)	8.7 (0.7)	8.7 (0.7)
FPG (mmol/L)	Mean (SD)	8.7 (3.1)	8.5 (3.0)
Daily mean PG (mmol/L)	Mean (SD)	10.2 (2.2)	10.2 (2.2)

Efficacy results:

Results are presented below for Group A on the PP population. Similar results were obtained on the mITT population.

PP Population – Patients with HbA1c ≥7% and FPG ≤140 mg/dL at Week 12, treated with insulin glargine + glulisine from Week 12 to Week 24 (N= 71) – Summary of results

	Baseline	Week 12	Change from baseline to Week 12	Week 24	Change from Week 12 to Week 24	Change from baseline to Week 24
HbA1c (%)						
Mean [95%CI]	8.7 [8.6;8.9]	8.1 [7.9;8.3]	-0.7 [-0.9;-0.4]	7.4 [7.2;7.7]	-0.6 [-0.8;-0.5]	-1.3 [-1.5;-1.0]
Median (range)	8.7 (7.5; 10.0)	8.0 (7.0; 10.6)	-0.6 (-2.5; 1.7)	7.3 (6.4; 11.7)	-0.5 (-2.7; 1.6)	-1.3 (-3.2; 3.3)
n (%) patients with HbA1c <7% at Week 24				23 (32.4%)		
FPG (mmol/L)						
Mean [95%CI]	8.3 [7.6;9.0]	5.4 [5.1;5.7]	-2.9 [-3.7;-2.2]	6.3 [5.8;6.7]	0.9 (2.1)	-2.18 [-2.8;-1.3]
Median (range)	7.5 (2.8; 18.5)	5.2 (3.6; 7.7)	-2.4 (-13.1; 4.8)	6.2 (2.0; 12.3)	0.7 (-3.9; 7.3)	-1.4 (-12.1; 4.0)
Missing data	*0*	*0*	*0*	*1*	*1*	*1*
Daily mean PG (mmol/L)						
Mean [95%CI]	10.0 [9.5;10.6]	8.8 [8.4;9.2]	-1.3 [-1.9;-0.7]	8.6 [8.1;9.1]	-0.3 [-0.8;0.1]	-1.6 [-2.2;-1.0]
Median (range)	9.7 (6.8; 16.4)	8.9 (5.5; 13.0)	-0.7 (-8.8; 3.6)	8.1 (5.7; 14.7)	-0.5 (-4.3; 5.9)	-1.4 (-8.6; 5.4)
Missing data	*3*	*2*	*5*	*2*	*4*	*5*
Weight (kg)						
Mean [95%CI]	76.9 [74.0;79.9]	77.4 [74.4;80.4]	0.5 [0.0;1.0]	78.1 [75.0;81.1]	0.7 [0.2;1.1]	1.1 [0.5;1.8]
Median (range)	74.0 (56.0; 110.0)	74.5 (56.5; 110.0)	0.4 (-4.0; 6.5)	75.0 (57.0; 110.0)	0.5 (-3.0; 6.2)	0.6 (-4.3; 11.0)

No missing data unless otherwise stated

Primary efficacy endpoint:

In the group of 71 patients with HbA1c ≥7% and FPG ≤140 mg/dL, treated with insulin glargine + insulin gliulisine (Group A), the mean (±SD) value of HbA1c decreased from 8.7 (±0.8)% at baseline to 8.1 (±0.8)% at Week 12 after treatment with insulin glargine alone and to 7.4 (±0.9)% at Week 24 after treatment with insulin glargine combined with insulin glulisine. The mean [95%CI] change from Week 12 to Week 24 was -0.6% [-0.8;-0.5].

Secondary efficacy endpoints

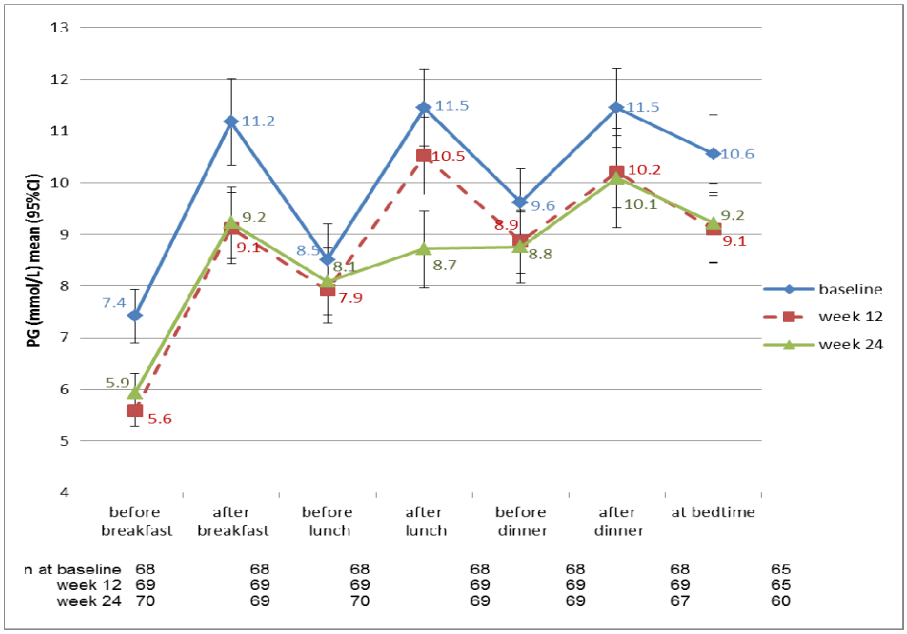
In Group A, 23 patients (32%) had an HbA1c value <7% at Week 24. Among these patients, 14 did not experience symptomatic nocturnal hypoglycemia between Week 12 and Week 24 and 11 did not experience symptomatic nocturnal hypoglycemia during the whole treatment period (between Week 0 and Week 24).

The mean (±SD) FPG value decreased from 8.3 (±3.0) mmol/L at baseline to 5.4 (±1.2) mmol/L at Week 12, with a mean [95%CI] change of -2.9 mmol/L [-3.7; -2.2]). At Week 24, the mean FPG value was 6.3 (±1.9) mmol/L, with a mean [95%CI] increase from Week 12 of 0.9 mmol/L [0.4; 1.4].

The mean (±SD) of the daily mean PG was 10.0 (±2.2) mmol/L at baseline, 8.8 (±1.7) mmol/L at Week 12 and 8.6 (±2.2) mmol/L at Week 24. Mean decrease was -0.3 mmol/L [95%CI: -0.8; 0.1] between Week 12 and Week 24 and -1.6 mmol/L [95%CI: -2.2; -1.0] between baseline and Week 24.

Mean (±SD) weight at baseline was 77 (±13) kg at baseline. A mean increase of 0.5 kg [95%CI: 0.0; 1.0] was observed between baseline and Week 12 and of 0.7 kg [95%CI: 0.2; 1.1] between Week 12 and Week 24.

The 7-point PG mean profile improved between baseline and week 12 with mean values of PG decreased at all timepoints. Mean decrease from baseline in PG level was around 2 mmol/L before and after breakfast, between -0.6 and -1.6 for the other timepoints. The 7-point PG profile at Week 24 was similar to the profile at Week 12, except for lower mean PG after lunch (mean decrease of -2.0 mmol/L [95%CI: -2.9; -1.0] between Week 12 and Week 24).



Safety results:

Doses of insulin glargine and insulin glulisine

Overall, in the Safety Population P2, the median daily dose of insulin glargine was 28 U at baseline, 32 U at Week 2, 38 U at Week 12, 39 U at Week 16 and 42 U at Week 24. The median daily dose per kg was 0.34, 0.39, 0.50, 0.51 and 0.53 U/kg respectively.

Patients in Group A were treated with a median first daily dose of 28 U of insulin glargine and, at Week 12, 6 U of insulin glulisine. The treatment increased throughout the study up to a median dose of 39 U and 9 U, respectively, at Week 24.

Hypoglycemia

During treatment period 1, 66 patients of the Safety population P1 (32%) experienced at least one episode of asymptomatic hypoglycemia, 498 patients (48%) at least one episode of symptomatic hypoglycemia, 31 patients (15%) at least one episode of nocturnal symptomatic hypoglycemia. Only one patient experienced severe hypoglycemia during the day.

During treatment period 2, 80 patients of the Safety population P2 (42%) experienced at least one episode of asymptomatic hypoglycemia, 111 patients (58%) at least one episode of symptomatic hypoglycemia, 43 patients (22%) at least one episode of nocturnal symptomatic hypoglycemia. Only one case of severe hypoglycemia was reported in one patient in Group A. In this group of patients of main interest, 44 patients (49%) had at least one asymptomatic episode, 62 patients (69%) at least one symptomatic episode and nocturnal symptomatic episodes were reported for 23 patients (26%).

Three cases of hypoglycemia were reported as serious adverse events during treatment period 2: 1 severe symptomatic hypoglycemia in Group A that was considered possibly related to insulin glargine and 2 cases (1 in Group A and 1 in Group D) of hypoglycemia due to overdose of insulin glulisine. All resolved within 2 days.

Adverse events other than hypoglycemia

During treatment period 1, when all patients were receiving insulin glargine, 54 patients (26%) experienced at least one TEAE. The most frequently reported non-serious TEAEs were influenza (4%), headache (3%) and dizziness (2%).

During treatment period 2, overall 65 patients (34%) experienced at least one TEAE. The most frequent non-serious TEAEs were headache and dizziness, reported in 7% of the patients in Group A and 4% of the patients overall.

Overall 14 patients experienced SAEs during the treatment periods: 3 patients (2%) during the treatment period 1 and 11 patients (6%) during the treatment period 2 (5 in Group A, 2 in Group B, C and D and none in Group E). Except for the cases of hypoglycemia described above, none of the SAEs was considered related to insulin glargine or insulin glulisine. At the end of the study, all SAEs had resolved, except one (carpal tunnel syndrome) that was recovering.

No deaths were reported during the study.

Adverse events possibly related to insulin glargine were reported for 6 patients during the treatment period 1 and 4 patients (3 in Group A and 1 in Group C) during the treatment period 2. The most frequent were dizziness, headache, tremor and hyperhidrosis, none reported for more than 3 patients. Adverse events considered possibly related to insulin glulisine were reported for 13 patients in Group A and 1 in Group D during the treatment period 2. The most frequent were dizziness (4 patients), headache and asthenia (2 patients each). Most events related to IPs were of mild intensity and resolved within 1 day.

Three patients, all in Group A, had to permanently discontinue the study treatment because of TEAEs, all considered related to IPs: malaise and somnolence for the same patient, diarrhea and headache.

Vital signs

No clinically significant changes in SBP, DBP and heart rate were identified during treatment period 1 and treatment period 2 with median changes from baseline close to 0.

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