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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi Drug substance(s): insulin glargine	Study Identifiers: NCT01204593, U1111-1116-3450 Study code: LANTU_R_05033
Title of the study: Phase IV, multicenter, international, non-comparative, open label study of efficacy and safety of basal bolus therapy (insulin glargine + insulin glulisine) in patients with T1 diabetes previously uncontrolled on any insulin regimen. (LANTU_R_05033)	
Study center(s): Thirty-eight (38) centers have been initiated in 10 countries (Algeria, Argentina, Brazil, Columbia, Iran, Kuwait, Mexico, Saudi Arabia, South Africa, Tunisia); 36 centers recruited patients	
Study period: Date first patient enrolled: 09/Nov/2010 Date last patient completed: 31/Jan/2013	
Phase of development: Phase 4	
Objectives: The primary objective of the study was to evaluate the efficacy of the association insulin glargine (Lantus®) (once a day [o.d.]) + insulin glulisine (Apidra®) (thrice a day [t.i.d.]) in terms of change in hemoglobin A_{1c} (HbA_{1c}) from baseline to end of study (week 24), in patients with type 1 diabetes mellitus (T1DM). The secondary objectives were to evaluate: • The change of HbA_{1c} from baseline to week 12, • The percentage of patients with HbA_{1c} <7% at week 12 and week 24, • The fasting blood glucose (FBG) and the 7-point self-monitoring of blood glucose (7-point SMBG) at baseline, week 12 and week 24, • The daily dose for both insulin glulisine and insulin glargine at baseline, week 12 and week 24, • The incidence of symptomatic hypoglycemias, • Adverse events (AEs).	
Methodology: This was an international, multicenter, open label, non-comparative study. The study consisted in a 2-week run-in period followed by a 24-week treatment period. At the start of the study treatment period (week 0, Visit 2), the patients were switched from their current anti-diabetic treatment to insulin glargine (o.d.) and insulin glulisine (t.i.d.). During the study, patients were assessed at mandatory clinical visits: screening (week - 2), baseline (week 0) weeks 12 and 24. Mandatory phone calls were made at week 2, 4 and 8.	
Number of patients:	Planned: 200 Screened:295 Treated: 206
Evaluated:	Modified Intent to Treat (mITT): 193 patients with one HbA_{1c} measurement at week 0 and with at least one HbA_{1c} measurement post-baseline. Per Protocol (PP): 151 patients of the mITT population with one HbA_{1c} measurement at week 0 and at least one post baseline HbA_{1c} measurement, and with no major deviations. Safety: 206 screened patients who received at least one dose of study medication

Diagnosis and criteria for inclusion: Male or female patients from 18 to 60 years old inclusive with T1DM treated with any type of insulin regimen (except continuous subcutaneous insulin infusion (CSII) pump and/or insulin glargine) for at least 1 year and with HbA_{1c} level between 8% and 10% assessed over the past 6 months.

Inclusion criteria for entry in the treatment period: HbA_{1c} level between 8% 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 medicinal product(s): Lantus® (insulin glargine) and Apidra® (Insulin glulisine)

Formulation:

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

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

Route(s) of administration: Both products were administered subcutaneously.

Dose regimen:

Insulin glargine: once a day, at bedtime The dose of insulin glargine was individually titrated once a week to achieve FBG between 80 and 120 mg/dL (4.5-6.7 mmol/L).

Insulin glulisine: three times a day, preferably just before the meal. The dose of insulin glulisine was individually titrated once a week to achieve a 2-hour postprandial blood glucose (PBG) <180 mg/dL (<10 mmol/L) and ideally around 140 mg/dL.

Duration of treatment: 24 weeks

Duration of observation: 26 weeks, including a 2-week run-in period

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was the change in HbA_{1c} values (%) between baseline (week 0) and week 24. The secondary efficacy endpoints were:

- Change in HbA1c (%) from week 0 to week 12,
- Percentage of patients with HbA_{1c} <7% at week 12 and week 24,
- Change in FBG (mmol/L) and in 7-point SMBG (daily mean blood glucose [BG] and 7-point BG mean profile – mmol/L) between week 0 and week 12 and between week 0 and week 24,
- Doses of insulin glargine and insulin glulisine: daily dose (U) at first administration, weeks 2, 4, 8, 12 and 24 and daily dose per kilo (U/kg) at first administration, weeks 12 and 24.

Safety:

- Symptomatic hypoglycemias (all, severe, nocturnal and nocturnal severe),
- AEs,
- Laboratory data (AST, ALT, serum creatinine),
- Clinical data (SBP, Diastolic Blood Pressure (DBP), Heart Rate (HR), weight).

Statistical methods: The primary analysis was based on the PP population and was performed by use of a mixed linear model for repeated measures with the changes in HbA_{1c} from baseline as the dependent variable and the baseline value and the visit (week 12, week 24) as fixed effect and with the subject as random effect. Adjusted means of changes were assessed with their 95% confidence interval (CI) at week 12 and week 24. The upper bound of the one-sided 95%CI had to be lower than 0 to conclude to significance at the 5% level. Sensitivity analyses were conducted in reproducing the same analyses using the mITT population and the complete patients of the mITT population with both data at baseline and at week 24.

Secondary efficacy FBG and BG variables were analyzed on the PP and on the mITT populations in the same way as for HbA1c. Other efficacy variables were analyzed by descriptive statistics, with the 95% CI of the mean for quantitative variables or of the percentage for qualitative variables when appropriate. Analyses of safety data were descriptive on the safety population.

Due to an outlier patient with multiple episodes of symptomatic hypoglycemia and an exclusion criterion confirmed after inclusion (brittle diabetes), a sensitivity analysis was conducted excluding this patient from the mITT population for efficacy parameters and from the Safety population for hypoglycemia. This patient was excluded from the PP population, since he presented with a major deviation (brittle diabetes).

Summary:

Population characteristics: Baseline characteristics were comparable for the safety, mITT and PP population. The safety population is described below.

Majority of the study patients were male (61%); mean age was 32 (±10) years, mean body mass index (BMI) was 24 (±4) kg/m^2. Overall, 58 patients (28%) had ongoing associated diseases: dyslipidemia (17%), hypertension (12%), hypothyroidism (6%), hyperthyroidism (1.5%).

Insulin therapy had been started at a median of 11 years ago (ranging from 9 months to 42 years), with a median duration of 3 years for current insulin therapy (ranging from less than one month to 42 years). The current insulin therapy consisted in the combination basal insulin + prandial insulin for 80% of the patients; basal insulin therapy only for 10%, premix insulin therapy for 7% and prandial + premix insulin therapy for 2%.

A total of 37 patients (18%) had at least one late diabetic complication, the most frequent being diabetic retinopathy (13%). At the time of the screening visit, 42% of the patients reported retrospectively hypoglycemia within the past month at a mean (±SD) frequency of 2 (±1) symptomatic hypoglycemic episodes per week. Severe hypoglycemic episodes were reported in 23% of the patients with hypoglycemic episodes.

Laboratory data at baseline are summarized in Table S1.

Table S1 - Laboratory data at baseline

	Safety population (N=206)	
	Mean (SD)	Median (range)
HbA_{1c} (%)	8.98 (0.58)	8.90 (7.3 ; 10.0)
FBG (mmol/L)	10.18 (5.28)	9.30 (0.1 ; 23.9)
Daily mean of 7-point BG (mmol/L)	10.07 (2.67)	9.64 (5.7 ; 20.5)
AST (U/L)	21.12 (8.70)	18.50 (10.0 ; 67.0)
ALT (U/L)	22.35 (13.65)	18.00 (6.0 ; 97.0)
Serum creatinine (µmol/L)	74.48 (16.37)	73.37 (36.2 ; 141.4)

On the 7-point BG profile, mean BG value before meal was 9.5 (±3.6) mmol/L before breakfast, 8.3 (±3.6) mmol/L before lunch and 10.5 (±4.3) mmol/L before dinner. After each meal, mean BG was between 10 and 11.5 mmol/L.

Efficacy results: The primary efficacy population was the PP population.

- Primary endpoint:

Mean (±SD) HbA_{1c} decreased from 9.0 (±0.6)% at baseline to 8.5 (±1.3)% at week 24. The adjusted mean (SE) change in HbA_{1c} was -0.5 (±0.1)% from baseline to week 24 (p<0.001).

There was a significant country effect indicating differences in HbA_{1c} results between countries, which should be interpreted with caution due to small sample size in some countries.

- Secondary endpoints:

Mean (±SD) HbA_{1c} decreased from 9.0 (±0.6)% at baseline to 8.3 (±1.2)% at week 12. The adjusted mean (SE) change in HbA_{1c} was -0.7 (±0.1)% from baseline to week 12 (p<0.001). There was a significant country effect indicating differences in HbA_{1c} results between countries, which should be interpreted with caution due to small sample size in some countries.

An HbA_{1c} value <7% was obtained for 18 patients (12%, [95%CI: 7.8% ; 18.3%]) at week 12 and 14 patients (10%, [95%CI: 5.7% ; 15.3%]) at week 24.

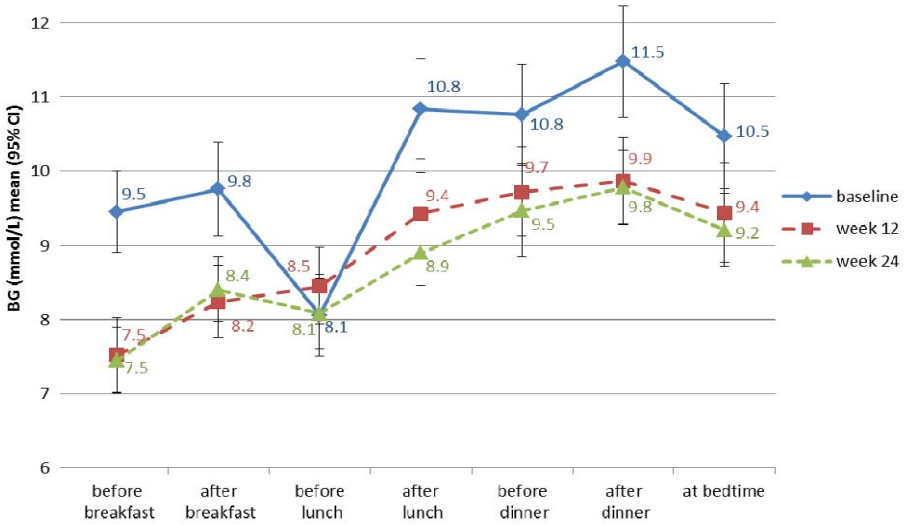
Improvement in FBG and daily mean BG was also observed at week 12 and week 24. Results are summarized in Table S2. A significant country effect was also observed for FBG results.

Table S2 – Summary of Efficacy results

		Mixed linear model for repeated measures		
	Mean (SD) value at timepoint	Adjusted mean (SE) change from baseline	Upper limit of 95% CI	p value
HbA_{1c} (%)				
Baseline	8.97 (0.56)			
Week 12	8.27 (1.15)	-0.70 (0.09)	-0.52	<0.001
Week 24	8.52 (1.29)	-0.45 (0.10)	-0.24	<0.001
FBG (mmol/L)				
Baseline	10.34 (5.56)			
Week 12	8.33 (4.36)	-1.97 (0.36)	-1.26	<0.001
Week 24	8.27 (4.41)	-2.03 (0.36)	-1.32	<0.001
Daily mean BG (mmol/L)				
Baseline	10.12 (2.77)			
Week 12	8.95 (2.29)	-1.22 (0.19)	-0.85	<0.001
Week 24	8.70 (1.78)	-1.42 (0.15)	-1.12	<0.001

The 7-point BG mean profile improved between baseline and week 12, with a mean decrease in BG between -1.9 and -1.1 mmol/L observed at all timepoints except before lunch when mean BG increased of 0.4 (±4.3) mmol/L. This decrease was statistically significant except at bedtime. The 7-point BG profile at week 24 was mostly similar to the profile at week 12, with a statistically significant decrease in BG from baseline at all timepoints except before lunch

Figure S1 – Evolution of 7-point BG profile



Efficacy results were similar in the mITT and in the sensitivity mITT populations.

Daily dose of insulin glargine and insulin glulisine: In the safety population, during the first 8 weeks of treatment, the median daily dose of insulin glargine was 28 U at first administration and at week 2, 26 U at week 4 and week 8. The median daily dose of insulin glulisine increased from 20 U at first administration to 21 U at week 2, 23 U at week 4 and 24 U at week 8. The daily dose at week 12 and week 24 is presented in Table S3 for the Safety population. Similar results were observed for the PP population.

Table S3 – Daily dose of insulin glargine and insulin glulisine

	Insulin glargine		Insulin glulisine	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)
Daily dose (U)				
at first administration	29.00 (13.51)	28.00 (6.0 ; 86.0)	22.74 (13.60)	20.00 (3.0 ; 108.0)
at week 12	29.64 (12.80)	26.00 (8.0 ; 86.0)	27.85 (15.91)	24.00 (3.0 ; 110.0)
at week 24	30.52 (13.61)	27.50 (0.0 ; 90.0)	28.71 (17.52)	24.00 (0.0 ; 110.0)
Daily dose (U/kg)				
at first administration	0.43 (0.19)	0.41 (0.1 ; 1.1)	0.33 (0.19)	0.30 (0.0 ; 1.1)
at week 12	0.43 (0.17)	0.39 (0.1 ; 1.1)	0.41 (0.22)	0.36 (0.0 ; 1.5)
at week 24	0.44 (0.18)	0.41 (0.0 ; 1.2)	0.41 (0.24)	0.37 (0.0 ; 1.6)

Safety results:

Symptomatic hypoglycemia

Before treatment, 45% of the patients had experienced episodes of symptomatic hypoglycemia, 2% severe symptomatic hypoglycemia, 15% nocturnal symptomatic episodes, and 1% severe nocturnal symptomatic hypoglycemia. During the treatment period, the percentages were 68%; 12%, 35% and 5%, respectively in the safety population.

When considering hypoglycemia confirmed by BG value <36 mg/dL (2.0 mol/L), 10% of the patients had at least one episode of symptomatic hypoglycemia, 5% at least one episode of severe symptomatic hypoglycemia, 3% at least one episode of nocturnal symptomatic hypoglycemia and 2% at least one episode of nocturnal severe symptomatic hypoglycemia during the treatment period.

Treatment Emergent Adverse Events (TEAEs) other than hypoglycemia

During the treatment period, 64 patients (31%) experienced at least one TEAE. TEAEs were mainly reported in the system organ class (SOC) “Infections and Infestations” (15.5%), “Investigations” (5.8%) and “Nervous system disorders” (5.3%). The most frequently reported non-serious TEAEs were influenza (8.3%), weight increase (2.4%), weight decrease (2.4%), sinusitis (1.9%) and headache (1.9%).

No overdose and no pregnancy were reported.

Treatment Emergent Serious adverse events (SAEs)

Treatment emergent SAEs were reported for 13 patients (6%): 8 (4%) experienced treatment emergent SAEs possibly related to insulin glargine and insulin glulisine. Treatment emergent SAEs related to insulin glargine and/or insulin glulisine were hypoglycemic seizures and hypoglycemic unconsciousness, each reported for three patients and hypoglycemia, reported for two patients.

No deaths were reported during the study.

TEAEs leading to permanent discontinuation

One treatment emergent SAE (hypoglycemic seizure) possibly related to insulin glargine and insulin glulisine led to permanent discontinuation of the study treatment.

No non-serious TEAE led to permanent discontinuation of the study treatment.

TEAEs related to study treatment

TEAEs possibly related to insulin glargine were reported for 11 patients (with five non-serious TEAEs and 10 SAEs). Non-serious TEAEs possibly related to insulin glargine were headache, inadequate control of diabetes mellitus, weight fluctuation (one patient each) and weight increase (two patients). TEAEs possibly related to insulin glulisine were reported for 10 patients (with three non-serious TEAEs and nine SAEs). These TEAEs were the same as those considered possibly related to insulin glargine except for one case of weight increase and the inadequate control of diabetes mellitus.

Overall, serum creatinine remained stable with a median change of 0 µmol/L, but changes ranged from a decrease of -44 µmol/L to an increase of 30 µmol/L.

Vital Signs

Blood pressure and heart rate remained stable during the study. Weight and BMI slightly increased with a mean (±SD) change of 0.73 (±3.00) kg and 0.27 (±1.10) kg/m², respectively. Similar results were observed for weight and BMI in the PP population

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