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

Sponsor / Company : sanofi-aventis **Drug Substance :** INSULIN GLARGINE	**Study Identifier :** NCT01081938 **Study Code :** LANTU_L_04572
Title of the study:	Open, randomized, multicentric, national, phase IV, comparative clinical trial to evaluate the efficacy and safety of insulin glargine plus glulisine versus insulin glulisine in hospitalized patients with diabetes mellitus type 2 under enteral nutrition
Study center(s):	10 sites in BRAZIL
Study period: Date first patient enrolled: 15-Feb-2010 Date last patient completed: 24-Feb-2011	**Phase of development:** Phase IV
Objectives:	Primary: To evaluate if the treatment with insulin glargine (Lantus®) plus insulin glulisine (Apidra®) produced a better glycemic control (measured by proportion of patients with mean daily blood glucose <140 mg/dL) than the treatment only with insulin glulisine in hospitalized patients diagnosed with type 2 diabetes mellitus and under enteral nutrition, in a period of at least 7 days. Secondary: To compare the two groups regarding: - hyperglycemia incidence (> 140 mg/dL) during the treatment period; - serious hyperglycemia incidence (> 400 mg/dL) during the treatment period; - hypoglycemia incidence (< 60 mg/dL) during the treatment period; - serious hypoglycemia incidence (< 40 mg/dL) during the treatment period; - total dose of insulin used during the treatment period; - total dose of insulin glulisine used during the treatment period; - control of the diabetes mellitus on the seventh day (V8); - comparison between the treatment groups regarding to the glycemic control (according to the mean daily blood glucose value). - frequency of adverse events related to the insulin;
Methodology:	This was a multicenter, randomized (1:1), open label, parallel-group, comparative study. The study consisted of: - Screening phase: 1- 4 days (Visit V-1); - Treatment phase: 7 days (Visits V1 to V7); - Treatment extension phase (optional): 1- 21 days; - End of Study: Visit V8 was the End of Study Visit in case the patient didn't remain in the extension phase, otherwise the visit was the first one of the extension phase and the End Of Study (EOS) visit was the last visit of the patient performed in the extension phase.

<table>
<tr><td>Methodology:</td><td colspan="3">The eligibility of a patient was defined in the randomization day (V1) and this was the first study treatment day. The registered data in V1 reflected the screening period, which was used as base reference pre-start of study medication.
The patients eligible for the study were randomized to either insulin glargine (once daily) plus sliding scale of insulin glulisine (every 6 hours) or only sliding scale of insulin glulisine (every 6 hours).
The study information was collected according to the acquisition period of it. For instance, the collected data in V2 referred to the previous 24 hours (between V2 and V1).
The completion of study participation for a patient was considered as the date of last patient visit.
The safety exam was collected in the screening phase and in the Visit V8 (and also in last visit of extension phase, for patients who was included on treatment extension optional phase).</td></tr>
<tr><td>Number of patients:</td><td>Planned: 110</td><td>Randomized: 15</td><td>Treated: 15</td></tr>
<tr><td rowspan="2">Evaluated:</td><td>Efficacy :15</td><td>Safety: 15</td><td>Pharmacokinetics: NA</td></tr>
<tr><td colspan="3">The study was prematurely terminated due to recruitment challenges.
Throughout the study, the protocol received three amendments – with no direct impact in the population to be analyzed, but with the intention to mitigate potential difficulties faced by the sites in the patients' recruitment.
However, over approximately one year, there were about 15 patients randomized from a total of 110 planned, so due to a business decision the study was stopped.</td></tr>
<tr><td>Diagnosis and criteria for inclusion:</td><td colspan="3">Hospitalized patients with diagnosis of type 2 diabetes mellitus for at least 6 months and/or HbA1c ≥ 6,5% (results of up to 90 days), capillary glycemia average <400 mg/dL (measured in the previous day to the randomization) and under enteral nutrition with carbohydrate in composition.</td></tr>
<tr><td>Investigational products:</td><td colspan="3"><u>Insulin glargine</u>: Lantus® (100 U/ml), pre-loaded pen SoloStar (3 mL).
<u>Dose regimen</u>:
1-The starting dose in insulin naïve patients should be 0, 2 units per kilogram of body weight per day when the admission and/or mean blood glucose concentration was between 140-200 mg/dL or 0, 25 units per kilogram of body weight per day when the admission and/or mean blood glucose concentration was between 140-200 mg/dL.
2-The starting dose of insulin glargine in patients on NPH will 80% of the total daily dose of NPH in use.
3-Patients who were on continuous insulin infusion (CII) during the previous 24 hours should receive 80% of the total regular insulin given during the previous 24 hours period. For patients with blood glucose>100 mg / dL and <200 mg / dL the initial dose of Glargine should be 60% of the total.
4-The daily dose of insulin glargine should be increased in 20% in case of more than two blood glucose measurements >140mg/dL during a period of 24 hours. In case of hypoglycemia (Blood Glucose < 60 mg/dL), the insulin glargine total daily dose should be decreased by 20%.

<u>Administration</u>:
Subcutaneous injection, once daily, at the same time everyday.</td></tr>
</table>

<table>
<tr><td>Investigational products:</td><td><u>Insulin glulisine</u>: Apidra® (100 U/ml), pre-loaded pen SoloStar (3 mL).
<u>Dose regimen</u>:
According to the plasmatic glycemia (mg/dL) (Table 1)

Table 1: Dose regimen for Insulin glulisine
<table><tr><th>Plasmatic glycemia (mg/dL)</th><th>Supplementary insulin glulisine dose</th></tr><tr><td>>141-180</td><td>2 UI</td></tr><tr><td>181-220</td><td>4 UI</td></tr><tr><td>221-260</td><td>6 UI</td></tr><tr><td>261- 300</td><td>8 UI</td></tr><tr><td>301-350</td><td>10 UI</td></tr><tr><td>351-400</td><td>12 UI</td></tr><tr><td>> 400</td><td>14 UI</td></tr></table>
<u>Administration</u>: Subcutaneous injection, every 6 (± 2) hours</td></tr>
<tr><td colspan="2">Duration of treatment:
7 days. The treatment could be maintained for an additional optional period lasting until 21 days, in case the patient remained hospitalized and with enteral nutrition indication.</td><td>Duration of observation:
Maximum of 32 days: 4 days in the screening phase, 7 days in the treatment phase and until 21 days in the extension.</td></tr>
<tr><td colspan="3">Criteria for evaluation:</td></tr>
<tr><td>Efficacy:</td><td colspan="2">- Proportion of patients with mean daily blood glucose <140mg/dL during the period of 7 days (primary endpoint).
- Hyperglycemia incidence (> 140 mg/dL) during the treatment period;
- Serious hyperglycemia incidence (> 400 mg/dL) during the treatment period;
- Hypoglycemia incidence (< 60 mg/dL) during the treatment period;
- Serious hypoglycemia incidence (< 40 mg/dL) during the treatment period;
- Total dose of insulin used during the treatment period;
- Total dose of insulin glulisine used during the treatment period;
- Control of the diabetes mellitus on the seventh day;
- Glycemic control according to the mean daily blood glucose value.</td></tr>
<tr><td>Safety:</td><td colspan="2">Adverse events reported by the patient or noted by the investigator.</td></tr>
<tr><td>Statistical methods:</td><td colspan="2">Due to premature end of study, only descriptive methods were used to analyze the efficacy and safety data.</td></tr>
</table>

Summary:

Fifteen patients were enrolled to the study, from 4 different sites, between 22-Feb-10 and 15-Feb-11, 7 patients were randomized for the treatment group that would get insulin glargine plus insulin glulisine and 8 patients for the group that would get only insulin glulisine. In this paper, these two groups will be called “GLA+GLU” and “GLU”, respectively.

All patients of group GLA+GLU were monitored during the entire treatment period of 7 days. In the group GLU, a total of 4 (50.0%) patients had premature termination of treatment/study: 2 (25.0%) due to adverse event (respiratory infection and pneumonia), 1 due to doubt about the stability of the study medication stored at the site and the other one due to hyperglycemia. Both patients with treatment interruption due to adverse event were evaluated until the visit V4 and the other two patients were evaluated until visit V6.

Neither patient, for both groups, entered in the extension phase of the study.
In the group GLA+GLU, the most of patients was the gender female (5; 71.4%), the most belonged to ethnicity Caucasian (3; 42.9%) and black (2; 28.6%). The mean (±s.d.) age of the patients was 76.9±13.9 years, ranging from 50 to 91 years. Whereas in the group “GLU”, more than half of the patients was of gender male (5; 62.5%), the most belonged to ethnicity Caucasian (6; 75.0%) and mean (±s.d.) age of the patients was 77.9±7.8 years, ranging from 62 to 89 years.

The average time from diabetes mellitus diagnosis is 6.6 years (0.6-20 years) in Group GLA+GLU and 17 years (2-30 years) in Group GLU.

Clinical and surgical history:

Towards clinical and surgical history, all patients presented the occurrence of at least one event. The more frequent clinical histories are Hypertension (5 events in Group GLA+GLU and 7 events in Group GLU), Ischemic stroke (3 events in Group GLA+GLU and 9 events in Group GLU), Stroke (6 events in Group GLA+GLU and 4 events in Group GLU), Decubitus sores (2 events in Group GLA+GLU and 3 events in Group GLU) and Hemiparesis (2 events in Group GLA+GLU and 2 events in Group GLU).

Clinical examination:

According to the result thorough clinical examination done at the screening visit (Table 2), the most frequent clinically significant abnormalities observed in the patients of both groups was related to the neurological system.

Table 2. Clinically significant abnormalities by system.

System	**Group GLA + GLU** N (%)	**Group GLU** N (%)
Cardiovascular	-	-
Pulmonary	-	1 (12.5)
Abdominal	-	-
Musculoskeletal	3 (42.9)	3 (37.5)
Dermatological	-	2 (25.0)
Neurological	6 (85.7)	6 (75.0)

Summary:

Diet at screening visit (V-1):

Regarding diet, the most frequent administration via was nasoenteral for both groups: GLA+GLU (5; 71.4%) and GLU (7; 87.5%). The type of administration most frequent was continuous: 6 (85.7%) patients for Group GLA+GLU and 6 (75%) patients for Group GLU. The Total caloric load [mean(±s.d.)] was 1643 (±465) Kcal between the patients of Group GLA+GLU and 1606 (±657) Kcal between the patients of group GLU. Besides the diet administered by enteral via, one patient in each group had also diet administered by oral via (from visit V4 for the patient of Group GLA+GLU and from visit V2 for the patient of Group GLU).

Period previous to the study:

It was not observed a capillary blood glucose value below 60 mg/dL, however, one patient in Group GLU had a mean concentration above 400 mg/dL: 411 mg/dL.

The mean glucose serum concentration observed in the last 24 hours before the treatment was 215.7 mg/dL (154-348 mg/dL) in Group GLA+GLU and 209.3 mg/dL (111-411 mg/dL) in Group GLU.

Only one patient (Group GLU) did not use insulin in the 24 hours previous the first administration of the study treatment. The type of insulin used in the previous 24 hours is given in table 3 below:

Table 3. Type of Insulin used in the previous 24 hours.

Type of Insulin	Group GLA+GLU N=7	Group GLU N=8
NPH	5 (71.4%)	4 (50.0%)
mean±s.d.	32.2±16.8	23.0±18.8
min-max	15-50	4-46
Regular previous dose scaling	4 (57.1%)	6 (75, 0%)
mean±s.d.	13.0±10.1	13.0±10.3
min-max	4-26	2-30
Insulin Glargine	1 (14.3%)	-
mean±s.d.	16	-

Efficacy results:

The current report is an abbreviated report, and as such, the efficacy evaluation proposed by the protocol is being briefly summarized.

Neither patient included in the study presented the following signs and symptoms assessed during the treatment phase: profuse sweating, pallor, tachycardia and mental confusion. Only 2 (25%) patients of Group GLU had others symptoms, being one case of sleepiness (symptom identified in the visit V8) and another patient who presented hyponatremia (identified from visit V5 until visit V8).

Table 4 shows the measurements about capillary blood glucose, glycemic control, the occurrence of error in dose adjustment of any of two insulin (glargine and/or glulisine) and the dose of insulin administered during the treatment, for the patients of Group GLA+GLU at each visit.

It is considered as an error of dose adjustment for insulin glargine: when the dose of insulin was increased and there were not at least 3 measures of capillary blood glucose ≥ 140 mg/dL in the previous 24 hours or when the insulin dose was maintained although at least 3 measures of capillary blood glucose had values ≥ 140 mg/dL.

It is considered as an error of dose adjustment of insulin glulisine when the scaling method (Table 1) was not followed.

It's possible to note an indication of decreasing in the mean capillary blood glucose along the visits. Moreover, it appears that the mean dose of insulin glargine plus glulisine administered for each patient increases along the visits, while the mean of insulin glulisine dose administered in each visit decreases.

Table 4. Capillary blood glucose values, patients under glycemic control, error in dose adjustment and insulin dose administered by visit - Group GLA+GLU.

Group GLA+GLU	V2 (N=7)	V3 (N=7)	V4 (N=7)	V5 (N=7)	V6 (N=7)	V7 (N=7)	V8 (N=7)
Capillary blood glucose (mg/dL)							
mean±s.d.	207±42	179±55	175±32	163±37	161±21	146±40	128±29
min - max	146-271	107-250	129-229	117-227	132-196	101-200	96-165
Glycemic control : Nº patients (%)							
	-	2 (28.6)	1 (14.3)	2 (28.6)	2 (28.6)	3 (42.9)	4 (57.1)
Error in dose adjustement: N° patients (%)							
Error [1]	-	1	1	1	-	1	-
Error [2]	2	1	1	-	1	2	1
Dose of Insulin glargine + Insuline Glulisine daily per patient (UI):							
Mean ± s.d.	37.4 ± 17.1	39.6 ± 19.4	41.9 ± 16.2	46.3 ± 20.9	47.0 ± 23.2	49.7 ± 25.5	49.3 ± 29.3
Min - max	19 - 64	14 - 74	21 - 69	20 - 78	25 - 89	23 - 97	19 - 97
Dose of Insuline Glulisine daily per patient (UI):							
Mean ± s.d.	15.7 ± 8.7	11.4 ± 9.2	11.3 ± 6.4	10.0 ± 6.2	8.0 ± 5.5	13.0 ± 2.0	9.3 ± 3.1
Min - max	4 - 28	2 - 26	4 - 22	2 - 22	2 - 16	12 - 16	6 - 12

[1] Patients under Glycemic control.

[2] Patients not under Glycemic control.

Efficacy results:

Table 5 shows the measurements about capillary blood glucose, glycemic control, the occurrence of error in dose adjustment of insulin glulisine and the dose of insulin administered during the treatment, for the patients of Group GLU at each visit. It is considered as an error of dose adjustment of insulin glulisine when the scaling method (Table 1) was not followed.

There is an indication that the mean capillary blood glucose values and the mean doses of insulin glulisine administered almost are not differing along the visits.

Table 5. Capillary blood glucose values, patients under glycemic control, error in dose adjustment and insulin dose administered by visit - Group GLU.

Group GLU	V2 (N=8)	V3 (N=8)	V4 (N=8)	V5 (N=6)	V6 (N=6)	V7 (N=4)	V8 (N=4)
Capillary blood glucose (mg/dL)							
mean±s.d	207±86	222±68	231±52	222±53	218±64	205±58	195±62
min - max	115-374	115-319	141-303	139-285	131-296	144-281	137-269
Glycemic control: Nº patients (%)							
	2 (25.0)	1 (12.5)	-	1 (16.7)	1 (16.7)	-	1 (25.0)
Error in dose adjustement: N° patients (%)							
Error [1]	-	1	-	-	-	-	-
Error [2]	1	2	2	1	1	-	-
Dose of Insuline Glulisine daily per patient (UI):							
Mean ± s.d.	20.0 ± 15.1	23.4 ± 12.8	20.5 ± 10.2	17.7 ± 9.8	18.0 ± 13.1	17.0 ± 12.7	14.5 ± 11.5
Min - max	2 - 48	4 - 38	4 - 34	4 - 32	2 - 34	4 - 34	4 - 28

[1] Patients under Glycemic control.

[2] Patients not under Glycemic control.

Safety results:

All patients included, with exception of one (Group GLU) have reported some adverse event (AE) during the study period. Some of these events occurred at the screening phase: 9 events in Group GLA+GLU, one of them classified as serious (hyperglycemia) and 9 events were reported by patients of the Group GLU, all of them classified as non-serious.

Regarding the treatment phase (Table 6), 7 patients of the Group GLA+GLU have reported a total of 15 events. The most frequent AE was diarrhea, reported by 2 (28.6%) patients. None of the events was considered as serious and neither related to the study medication. In the Group GLU, 7 patients have reported a total of 24 adverse events. The most frequent AEs were fever (3 patients, 37.5%; 7 events), tachypnea (2 patients, 25.0%; 2 events) and dehydration (2 patients, 25.0%; 2 events). One event was considered as serious (pneumonia) and two of them (pneumonia and respiratory infection) leading to patients withdrawal from the study/treatment. None of the events was considered as related to the study medication.

Safety results:

Table 6. Patients reporting any Adverse Event

Adverse Event	Group GLA+GLU		Group GLU	
	Patients N=7 (%)	Nº of Events	Patients N=8 (%)	Nº of Events
Any	7 (100)	15	7 (87.5)	24
Related to study medication	-	-	-	-
Serious	-	-	1 (12.5)	1
Serious and related	-	-	-	-
Causing death	-	-	-	-
Related and causing death	-	-	-	-
Leading to treatment/study withdrawal	-	-	2 (25.0)	2
Related and leading to treatment/study withdrawal	-	-	-	-

Serious Adverse Event:

One patient of each group (14.3% in group GLA+GLU and 12.5% in group GLU) had serious adverse event.

The patient of group GLA+GLU had hyperglycemia of moderate intensity during screening phase. The event occurred at Visit V-1 and became serious in the next day. The event recovered occurred before the beginning of the treatment phase (Visit V1).

The patient of group 2 had pneumonia of moderate intensity, at Visit V4, which is also considered unrelated to the insulin glargine or glulisine, but leading to the patient discontinuation of study. In the clinical historical of the patient, it was reported an event of pneumonia in the previous month of the patient's study enrollment.

Hyperglicemia:

Group GLA+GLU:

All 7 patients of this group had at least one event of hyperglycemia during the first 5 days of the treatment. Two patients didn't had hyperglycemia in the last two days of the treatment and one patient did not have this condition only in the seventh day of the treatment.

One patient presented an event of severe hyperglycemia at Visit V2 and this same patient had hypoglycemia at Visit V8. It is important to note that there was an error in dose adjustment, for this patient, at visit V7: the dose of insulin glargine administered was increased, although there were less than 3 measures of capillary blood glucose over 140 mg/dL.

Group GLU:

All the patients presented at least one event of hyperglycemia during the study. One patient had severe hyperglycemia at visits V2 and V3. There was not observed any error in dose adjustment for this patient.

Safety results:	Hypoglycemia: Two (28.6%) patients had clinical symptoms of hypoglycemia, both in the Group GLA+GLU. One of them had nocturnal capillary glycemia of 58 mg/dL. According to the CRF information, it was administered 500 mL of EV hypertonic 50% glucose at the same time of hypoglycemia verification. The event was associated to clinical symptoms, but not to loss of consciousness, to coma or to convulsions occurrence. In the previous measurement, performed in the previous day, the patient had capillary glycemia of 182 mg/dL and it was administered 4 UI of insulin glulisine. The other patient had capillary glycemia of 59 mg/dL, not nocturnal. It was administered 16 mL of EV hypertonic 50% glucose. The event was also associated to clinical symptoms, but not to loss of consciousness, to coma or to convulsions occurrence. About 30 minutes after, a new measurement of glycemia was made and the value obtained was 44 mg/dL, when it was administered additional 23 mL of EV hypertonic 50% glucose. In the previous measurement occurred about one hour and half before this event, the value of capillary glycemia was of 118 mg/dL and at that moment it was not administered insulin glulisine to the patient. No patient, in any of the groups had severe hypoglycemia (capillary glycemia < 40 mg/dL).
Issue date:	24 April 2012