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

Sponsor / Company: Sanofi	**Study Identifiers:** NCT01122979
Drug substance(s): Insulin Glargine	**Study code:** LANTU_L_04737
Title of the study: National pilot phase IV, multicentric, randomized, open-label study, to obtain an estimation of the proportion of Type 2 Diabetes patients with moderate to severe renal failure, in use of insulin glargine associated to insulin glulisine or NPH insulin associated to regular insulin who achieve the target of HbA_{1c} level below 7% in the absence of confirmed symptomatic nocturnal hypoglycaemia (LANTU_L_04737).	
Study center(s): 11 active centers all in Brazil	
Study period: Date first patient enrolled: 06/Jul/2010 Date last patient completed: 18/Oct/2013	
Phase of development: Phase 4	

Objectives:

Primary:

- To estimate the proportion of diabetic patients with moderate to severe renal insufficiency reaching HbA_{1c} level below 7% in the absence of confirmed symptomatic nocturnal hypoglycaemia after 24 weeks of treatment with insulin glargine (Lantus®) associated with insulin glulisine (Apidra®), to obtain accurate data to be used in the sample size calculation for a larger clinical trial.

Secondary:

-To estimate glycaemic control in diabetic patients with moderate to severe renal insufficiency after 24 weeks of treatment with insulin glargine (Lantus®) associated with insulin glulisine (Apidra®) by the proportion of patients achieving HbA_{1c} less than 7%;

- To estimate the glycemic control in diabetic patient with moderate renal insufficiency after 24 weeks treatment with insulin glargine (Lantus®) associated with insulin glulisine (Apidra®) by the proportion of patients achieving fasting glucose level ≤100mg/dL;

- To evaluate the safety of 24 weeks treatment with insulin glargine (Lantus®) associated with insulin glulisine (Apidra®) in diabetic patients with moderate renal insufficiency in terms of the incidence of hypoglycaemia (symptomatic nocturnal, confirmed symptomatic, and severe symptomatic), incidence of adverse events (AEs), and weight and renal function change from baseline.

Methodology:

Randomized (1:1), open-label, parallel active control group with a 2 weeks screening period, 2 to 4 weeks run-in period, followed by 24 weeks treatment period. It was planned to randomize 72 patients (36 per treatment arm):

- Test Group (GLA+GLU): insulin glargine once a day (at bedtime) associated to insulin glulisine three times a day (at mealtime);

- Control Group (NPH+REG): insulin NPH twice a day (at morning and at night) associated to regular insulin three times a day (at mealtime);

The study comprised the visits described below:

Screening and run-in period:

- V_s: Enrollment visit (D -42 to D -28)

- V_{-1}: Run-in visit (D -28 to D -0)

Treatment Period:

- V_1: Randomization visit (Day 1)

- V_2 to V_{13}: Treatment Visits (V_2, V_4, V_6, V_8, V_9 and V_{12}: phone contacts)

(V_2: D7; V_3: D14; V_4: D21; V_5: D28; V_6: D35; V_7: D42; V_8: D56; V_9: D70; V_{10}: D84; V_{11}: D112; V_{12}: D140; V_{13}: D169 or end of treatment visit)

- Follow-up phone contact (one week after V_{13})

Number of patients**:**	Planned: 72 (36 per treatment arm)
	Randomized: 72
	Treated: 72
	Evaluated: 72
	Safety: 72

Diagnosis and criteria for inclusion:

Main inclusion criteria: Men and women (≥18 years) with Type 2 Diabetes Mellitus (T2DM); moderate to severe renal failure (severe: creatinine clearance ≥15 mL/min/1.73m^2 and <30 mL/min/1.73m^2; moderate: creatinine clearance ≥30 mL/min/1.73m^2 and <60 mL/min/1.73m^2); Albuminuria or microalbuminuria associated to diabetic retinopathy; HbA_{1c} ≥8%; in use of any oral anti-hyperglycemic agent associated to insulin therapy or insulin therapy alone.

Main exclusion criteria: History of diabetic ketoacidosis or positive Glutamic Acid Decarboxylase (GAD) antibodies; Severe hepatic disease or active hepatitis; Cardiac failure class III or IV (New York Heart Association); Patients on hemodialysis; Diagnosed cancer; Active infection.

Study treatments

Investigational medicinal product: Lantus® (Insulin Glargine)

Formulation: Injectable aqueous solution at concentration of 100 unit/mL in pre-filled SoloStar® pen (3 mL)

Route(s) of administration: Subcutaneous

Dose regimen: Dose adjusted according to glycaemic level*

Investigational medicinal product: Apidra® (Insulin Glulisine)

Formulation: Injectable aqueous solution at concentration of 100 unit/mL in pre-filled Solostar® pen (3 mL)

Route(s) of administration: Subcutaneous

Dose regimen: Dose adjusted according to glycaemic level *

Active comparator: Humulin NPH® (Human isophane Insulin)

Formulation: Injectable suspension at concentration of 100 unit/mL (3 mL refill) and a HumanPen® pen for application

Route(s) of administration: Subcutaneous

Dose regimen: Dose adjusted according to glycaemic level*

Active comparator: Humulin Regular® (Regular Insulin)

Formulation: Injectable solution at concentration of 100 unit/mL (3 mL refill) and a HumanPen® pen for application

Route(s) of administration: Subcutaneous

Dose regimen: Dose adjusted according to glycaemic level*

*Insulin glargine

1- The starting dose of insulin glargine had to be 80% of the total NPH dose in use, at bedtime, once daily.
2- The goal was to achieve a fasting plasma glucose (FPG) of ≤100 mg/dL
3- Patients had to measure the FPG every morning (with a glucometer) and increase the insulin dose by 1 IU if FPG was >100 mg/dL and by 2 IU if the FPG was above 180 mg/dL.
4- The insulin dose had to be decreased in 10% or 4 IU if an episode of confirmed hypoglycaemia occurred (<70 mg/dL).
5- Insulin dose had to be maintained when the FPG stabilizes at ≤100 mg/dL.

*Insulin glulisine/ Insulin Regular

1- Had to be given at mealtime, 3 times a day, according to the dose defined at the end of run-in period.
2- Patients had to measure the preprandial glycaemia (with a glucometer) and increase the insulin dose by 1 IU for each 50 mg/dL above the FPG value of 100 mg/dL.
3- The dose could be modified by investigator at the randomization visits and/or at another on site visits according to the level of variable dose replacement in the preceding period.
4- In case of a preprandial glycaemia <70 mg/dL, the insulin glulisine had not to be taken at the meal.

*NPH insulin

1- The starting dose of NPH had to be the last one given at the run in phase, administered in two doses (at morning and at night).
2- Patients had to measure the FPG every morning (with a glucometer) and increase the insulin dose by 1 IU/day until FPG =100 mg/dL.
3- The dose adjustments should occur only at the nocturnal dose.

Duration of treatment: 24 weeks

Duration of observation: About 31 weeks (2 weeks of screening period, 2 to 4 weeks of run-in period, 24 weeks of treatment, one week follow-up by phone contact).

Criteria for evaluation:

Efficacy: The primary efficacy endpoint consisted of proportion of patients who reached the target of HbA_{1c} <7% in the absence of confirmed symptomatic nocturnal hypoglycaemia*.

*Defined as the occurrence of clinical symptoms considered resultant from hypoglycaemia, confirmed by a plasma glucose measure ≤70 mg/dL and associated with a rapid recovery after oral administration of carbohydrate, which occurred while the subject is asleep after lying down (after insulin injection) and before waking (before the morning measurement of fasting plasma glucose).

The secondary efficacy endpoints were:

- The proportion of patients who reached the target of HbA_{1c} <7%.

- The proportion of patients who reached the target of fasting blood glucose less than or equal to 100 mg/dL.

Safety: The proportion of patients with at least one episode of symptomatic nocturnal hypoglycaemia** during the treatment period.

**Defined as symptomatic hypoglycaemia that occurs while the patient is asleep after lying down (after insulin injection) and before waking up (before the morning measurement of fasting plasma glucose).

- The proportion of patients with at least one episode of confirmed symptomatic hypoglycaemia during the treatment period.

§Defined as the occurrence of clinical symptoms resulting from hypoglycaemia, confirmed by plasma glucose ≤70 mg/dL and associated to a quick recovery after administration of oral carbohydrates.

- The proportion of patients with at least one episode of severe symptomatic hypoglycaemia§§ during the treatment period.

§§Defined as the occurrence of clinical symptoms resulting from hypoglycaemia that required assistance from another person due to patient's inability because of acute neurological impairment resulting from hypoglycaemia, associated to plasma glucose <36 mg/dL or to a quick recovery after administration of oral carbohydrates, IV glucose, or glucagons.

- Incidence of AEs during treatment period.

- Weight change between baseline and end of treatment.

- Renal function change from baseline and end of treatment according to the clearance of creatinine.

Statistical methods:

Patients who signed the informed consent form (ICF) were considered as screened and patients who signed the ICF and for whom a treatment was assigned according to the randomization process, independently if the treatment was administered were considered as randomized.

All randomized patients who had used at least one dose of any study treatment were considered in the Intent-to-treat (ITT) population. The Modified Intent-to-Treat (m-ITT) population was composed of the patients from the ITT population with at least one available HbA_{1c} measure after Visit V_1.

For primary efficacy endpoint if the HbA_{1c} value at Visit V_{13} was not available (due to a premature study discontinuation), the HbA_{1c} value was replaced by the last value available after Visit V_1 (method of last observation carried forward [LOCF]).

The safety analyses were conducted based on the ITT population and the efficacy analysis based on the m-ITT population.

The initial plan was to randomize 72 patients (36 per treatment arm), assuming a drop-out rate of 15%, to obtain a sample size of at least 30 randomized patients per study group.

Summary:

Patients enrollment

Between 06-Jul-2010 (first patient in [FPI]) and 27-Mar-2013 (last patient in [LPI]), 198 patients were enrolled in the study. From this total, 72 patients were randomized: 33 (45.8%) to the Test Group and 39 (54.2%) to the Control Group. The main reason for non-randomization was that patients did not meet the inclusion/exclusion criteria defined by the study protocol (Table 1).

Table 1. Reasons for non-randomization (multiple answers were possible)

Reasons for non-randomization	**Total 198 (100%)**
Didn't meet inclusion/exclusion criteria	114 (57.6%)
Consent withdrawal	5 (2.5%)
Lost to follow-up	1 (0.5%)
Adverse event	4 (2.0%)
Non-adherence to the run-in treatment	3 (1.5%)
Patients randomized	**72 (36.4%)**

Demographic data

From the 72 randomized patients, the age of the patients at time of inclusion ranged overall from 45 to 78 years, with a mean age of 60.6 years (SD=7.9) for the Test Group and 62.5 years (SD=6.2) for the Control Group. In the Test Group most patients were female: 18 (54.6%). On the other hand, in the Control Group, most patients were male: 22 (56.4%). Majority of patients were Caucasian in both groups: 15 patients (45.4%) in the Test Group and 22 patients (56.4%) in the Control group (Table 2).

Table 2. Demographic

Characteristics	**Test Group N=33 (100%)**	**Control Group N=39 (100%)**
Age (years)		
Median	60	62
Mean ± S.D	60.6 ± 7.9	62.5 ± 6.2
Min - Max	45 - 77	48 - 78
Gender		
Male	15 (45.4%)	22 (56.4%)
Female	18 (54.6%)	17 (43.6%)
Ethnicity		
Caucasian	15 (45.4%)	22 (56.4%)
Mixed	10 (34.3%)	8 (20.5%)
Spanish	3 (9.1%)	5 (12.9%)
Black	3 (9.1%)	4 (10.3%)
Oriental	2 (6.1%)	0

Baseline characteristics

From all randomized patients, the mean time of T2DM diagnosis was 19.6 years (SD=7.7) in the Test Group and 22.7 years (SD=9.4) in the Control Group. Patient's mean weight at inclusion was 86.4 kg (SD=16.5) for Test Group and 84.2 kg (SD=14.6) for Control Group. The HbA_{1c} values at Visit V_S ranged between 8.0% and 19.2%. The median HbA_{1c} was 9.7% in the Test Group and 10.0% in the Control Group. The FBG values at V_{-1} ranged from 55 mg/dL to 359 mg/dL. The median of FBG was 205.5 mg/dL in the Test Group and 180.0 mg/dL in the Control Group (Table 3).

Table 3. Baseline characteristics

Characteristics	Test Group N=33 (100%)	Control Group N=39 (100%)
T2DM Time of diagnosis (years)		
Mean ± S.D	19.6 ± 7.7	22.7 ± 9.4
Median	18	23
Min – Max	3 - 41	4 – 39
Weight (Kg)		
Mean ± S.D	86.4 ± 16.5	84.2 ± 14.6
Min – Max	66.5 – 143.0	58.5 – 115.3
HbA_{1c} (%)		
Median	9.7	10.0
Min – Max	8.0 – 14.1	8.0 – 19.2
≥ 8% and <10%	21 (63.6%)	19 (48.7%)
≥ 10% and <12%	8 (24.2%)	14 (35.9%)
≥ 12%	4 (12.1%)	6 (15.4%)
FBG (mg/dL)		
Median	205.5	180.0
Min – Max	90 – 359	55 – 359
Missing	1	1

Study completion

From all patients randomized to the Test Group, 4 patients (12.1%) did not complete the study period according to the protocol: 3 patients (9.1%) due to AE (chest pain, Visceral leishmaniasis, and pneumonia) and 1 patient (3.0%) died (Table 4). From all patients randomized to the Control Group, 6 patients (15.4%) did not complete the study according to the protocol: 1 (2.6%) due to AE (autonomic neuropathy), 2 (5.1%) due to protocol violation, 1 (2.6%) due to lost to follow up, 1 (2.6%) due to consent withdrawal, and 1 (2.6%) due to non-adherence (Table 4).

Table 4. Study completion

Study completion	Test Group N=33 (100%)		Control Group N=39 (100%)	
Yes	29 (87.9%)		33 (84.6%)	
No	4 (12.1%)		6 (15.4%)	
Reason				
Adverse event	3 (9.1%)	Chest pain (V_7)* Visceral leishmaniasis (V_6)* Pneumonia (V_9)*	1 (2.6%)	Autonomic neuropathy (V_4)*
Protocol Violation	-		2 (5.1%)	GAD positive: exclusion criteria (V_5)* Urinary infection: exclusion criteria (V_1)*
Lost to follow up	-		1 (2.6%)	
Consent Withdrawal	-		1 (2.6%)	
Death	1 (3.0%)	Secondary to the adverse event hemorrhagic diathesis (V_9)*	-	
Non-adherence	-		1 (2.6%)	

*Last treatment visit performed by patient.

Study Population

The ITT population consisted of all 72 randomized patients as all of them received at least one dose of study treatment. From this total, 66 (30 in the Test Group and 36 in the Control Group) were considered in the m-ITT Population as they had at least one HbA_{1c} measurement after Visit V1 (Table 5).

Table 5. Study population

Distribution by group	Test Group	Control Group	TOTAL
Patients randomized	33 (45.8%)	39 (54.2%)	72 (100%)
ITT Population	33 (45.8%)	39 (54.2%)	72 (100%)
m-ITT Population	30 (45.5%)	36 (54.5%)	66 (100.0%)

Treatment exposure

Table 6 summarizes the extent of investigational medicinal products exposure. The treatment exposure in Test Group ranged from 38 to 187 days, with a mean of 157 days (SD=37). In the Control Group the treatment exposure ranged from 21 to 181 days, with a mean of 149 days (SD=50). One patient in the Control Group had used only insulin NPH and the patient was discontinued from study due to exclusion criteria - urinary infection - at time of inclusion.

Table 6. Treatment exposure

Extension of treatment exposure (days)	Test Group N=33 (100%)	Control Group N=39 (100%)
Mean ± S.D	157 ± 37	149 ± 50
Median	168	168
Min – Max	38 - 187	21 – 181

Efficacy results:

Primary analysis

Table 7 summarizes the primary efficacy endpoint by treatment groups: proportion of patients who reached the target of HbA_{1c} <7% in the absence of confirmed symptomatic nocturnal hypoglycaemia.

The proportion of patients who reached the primary endpoint was higher in the Test Group: 5 patients (16.7%) in the Test Group with an associated 90% CI of [5.5%; 27.8%] and 2 patients (5.6%) with an associated 90% CI of [0%-11.8%] in the Control Group (Table 7).

Table 7. Primary efficacy endpoint (m-ITT Population)

Primary endpoint	Test Group N=30 (100%)	Control Group N=36 (100%)
HbA_{1c} < 7% in the absence of confirmed symptomatic nocturnal hypoglycaemia	5 (16.7%)	2 (5.6%)
90% CI	[5.5% – 27.8%]	[0% – 11.8%]

Assuming that the difference observed between groups (Table 7) is considered as clinically significant to detect a statistically significant difference between Test and Control Groups with the same magnitude, at least 126 patients per arm should be randomized. It was adopted for sample size calculation:

- Power of 80%

- Type I error (alpha) of 5%

- Proportion of patients who reached the target of HbA_{1c} <7% in the absence of confirmed symptomatic nocturnal hypoglycaemia of 16.7% in Test Group and of 5.6% in the Control Group.

Secondary analyses

Table 8 summarizes the proportion of patients who reached HbA_{1c} <7% and the proportion of patients with FBG ≤100 mg/dL at the end of study (Last value available after Visit V1).

The proportion of patients who reached HbA_{1c} <7% was 30.0% in the Test Group with an associated 90% CI of [16.3%; 43.7%] and 22.2% in the Control Group with a 90% CI of [10.9% - 33.6%]. The proportion of patients who reached FBG ≤100 mg/dL at end of treatment was 73.3% in the Test Group with an associated 90% CI of [60.1%; 86.6%] and 69.4% in the Control Group with a 90% CI of [56.9% - 82.0%].

Table 8. Secondary efficacy endpoint: HbA_{1c} <7% (m-ITT Population)

Secondary endpoint	Test Group N=30 (100%)	Control Group N=36 (100%)
HbA_{1c} <7%	9 (30.0%)	8 (22.2%)
	90% CI: [16.3% – 43.7%]	90% CI: [10.9% – 33.6%]
FBG ≤100	22 (73.3%)*	25 (69.4%)
	90% CI: [60.1% – 86.6%]	90% CI: [56.9% – 82.0%]

*1 missing information

Safety results:

Hypoglycaemia

Table 9 describes the proportion of patients with at least one episode of hypoglycaemia according to its type during the treatment period and the respective total number of events.

Table 9. Episodes of hypoglycaemia

Type of hypoglycaemia	Test Group		Control Group	
	N=33 (100%)	Number of events	N=39 (100%)	Number of events
confirmed symptomatic nocturnal hypoglycaemia [1]	15 (45.5%)	76	27 (69.2%)	137
symptomatic nocturnal hypoglycaemia [2]	16 (48.5%)	79	27 (69.2%)	150
confirmed symptomatic hypoglycaemia associated with a quick recovery after administration of carbohydrates [3]	27 (81.8%)	429	36 (92.3%)	662
severe symptomatic hypoglycaemia [4]	3 (9.1%)	5	3 (7.7%)	5

[1] Symptomatic hypoglycaemia, confirmed by a plasma glucose measure ≤70 mg/dL and associated with a rapid recovery after oral administration of carbohydrate, which occurred while the subject is asleep after lying down (after insulin injection) and before waking (before the morning measurement of fasting plasma glucose).

[2] Symptomatic hypoglycaemia that occurs while the patient is asleep after lying down (after insulin injection) and before waking up (before the morning measurement of fasting plasma glucose).

[3] Symptomatic hypoglycaemia confirmed by plasma glucose ≤70 mg/dL and associated to a quick recovery after administration of oral carbohydrates.

[4] Symptomatic hypoglycaemia that required assistance from other person due to patient's inability because acute neurological impairment resulting from hypoglyceamia, associated to plasma glucose <36 mg/dL or to a quick recovery after administration of oral carbohydrates, IV glucose or glucagon.

Weight change

The absolute change in weight from baseline (Visit V_1) to end of treatment (last available value after Visit V_1) is described in Table 10. For both study groups, the mean weight change had increased: 1.08 kg (SD=3.32) for Test Group and 3.32 kg (SD=3.37) for Control Group.

Table 10. Weight change from baseline to end of study

Weight change (kg)	Test Group N=33 (100%)	Control Group N=39 (100%)
Mean ± S.D	1.08 ± 3.32	3.32 ± 3.37
Min – Max	-9.7 – 7.1	-1.3 – 13.5
Median	1.7	2.4
Patients with weight reduction	10 (30.3%)	4 (10.5%)

Adverse events

From 33 patients randomized to Test Group, a total of 71 adverse events (AEs) in 28 patients (84.8%) were reported during treatment period (treatment-emergent adverse event [TEAE]). From 39 patients randomized to the Control Group, 28 (71.8%) patients reported of a total of 78 AEs during the treatment period. Six (18.2%) patients in the Test Group and 5 patients (12.8%) in the Control Group had AEs related to any of the study medication (Table 11). A listing of all AEs possibly related to any of the study medication can be found in Table 12.

Eight patients (24.2%) from Test Group and 8 patients (20.5%) from Control Group had 8 and 11 serious adverse events (SAE), respectively, of which 1 SAE in the Test Group and 6 in the Control Group were related to the study medication which were as follows: One medication error (accidental application of 100 IU of glulisine) in the Test Group; hypoglycaemia (3 patients with a total of 5 events) and syncope in the Control Group. Two SAEs in the Test Group, causing death, were not considered related to study medication: pneumonia and hemorrhagic diathesis (Table 11). List of all SAEs can be found in Table 13.

Three patients (9.1%) in the Test Group were withdrawn from study due to AEs, but none of them were considered related to the study medication (Table 11). The events were: chest pain, visceral leishmaniasis, and pneumonia.

Considering MedDRA dictionary, the most frequent AEs - coded by System Organ Class (SOC) - were Infections and Infestations, with 12 patients (36.4%) reporting 18 events in the Test Group and 13 patients (33.3%) reporting 19 events in the Control Group. Also, Gastrointestinal Disorders (8 events), General Disorders And Administration Site Conditions (7 events), and Metabolism And Nutrition Disorders (7 events) were the following 3 most frequent events in the Test Group. In the Control Group, after Infections And Infestations, the 3 most frequent events were: Metabolism And Nutrition Disorders (10 events), Nervous System Disorders (9 events), and Musculoskeletal And Connective Tissue Disorders (7 events). Complete list of all AEs (serious and non-serious) by SOC is provided in Table 14.

Table 15 lists four extra reports for AEs - 3 in the Test Group and 1 in the Control Group - that were not considered as a TEAE, as they have occurred more than 7 days after the end of study medication. Three of them, all in the Test Group, refer to SAE, leading to death in 2 cases. The AE reported in the Control Group occurred about 2 years after the end of study medication and was not considered serious. None of these 4 events were included in Tables 11 to 14.

Renal function change

Table 16 shows a descriptive summary for creatinine clearance changes from baseline to end of study.

Table 11. Adverse Events Summary (treatment-emergent)

TEAE	Test Group		Control Group	
	Number of Patients N=33 (%)	Number of Events	Number of Patients N=39 (%)	Number of Events
Any	28 (84.8)	71	28 (71.8)	78
Related to, according to the investigator	5 (15.2)	8	4 (10.3%)	7
Insulin Glargine	1 (3.0)	1	-	-
Insulin Glulisine	3 (9.1)	3	-	-
Insulin Glargine+Glulisin	2 (6.1)	4	-	-
Insulin NPH	-	-	1 (2.6)	1
Insulin Regular	-	-	1 (2.6)	1
Insulin NPH+REGULAR	-	-	3 (7.7)	5
Serious	8 (24.2)	8	8 (20.5)	11
Serious and related to study medication	1 (3.0)	1	4 (10.3)	6
Insulin Glargine	-	-	-	-
Insulin Glulisine	1 (3.0)	1	-	-
Insulin Glargine+Glulisin	-	-	-	-
Insulin NPH	-	-	1 (2.6)	1
Insulin Regular	-	-	1 (2.6)	1
Insulin NPH+REGULAR	-	-	2 (5.1)	4
Causing death	2 (6.1)	2	-	-
Related and causing death	-	-	-	-
Leading to study withdrawal*	3 (9.1)	3	-	-
Related and leading to study withdrawal	-	-	-	-

*One patient of Control Group developed autonomic neuropathy – an exclusion criteria and withdrawal from study.

Table 12. List of Adverse Events (treatment-emergent) possibly related to the study medication, according to MedDRA Preferred Term

TEAE – possibly related to study medication Preferred Term	Test Group		Control Group	
	Number of Patients N=33 (%)	Number of Events	Number of Patients N=39 (%)	Number of Events
TEAE possibly related to:				
Insulin Glargine and/or Glulisine	**5 (15.2)**	**8**	**-**	**-**
HYPOGLYCAEMIA	3 (9.1)	5	-	-
MEDICATION ERROR	1 (3.0)	1	-	-
ACCIDENTAL OVERDOSE	2 (9.1)	2	-	-
Insulin NPH and/or Regular	**-**	**-**	**4 (10.3)**	**7**
SYNCOPE	-	-	1 (2.6)	1
HYPOGLYCAEMIA	-	-	4 (10.3)	6

Table 13. List of Serious Adverse Events (treatment-emergent) according to MedDRA System Organ Class and Preferred Term

Serious TEAE ***System Organ Class*** ***Preferred Term***	**Test Group** **Number of Patients N=33 (%)**	**Number of Events**	**Control Group** **Number of Patients N=39 (%)**	**Number of Events**
Any Serious TEAE	8 (24.2)	8	8 (20.5)	11
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (3.0)	1	-	-
HAEMORRHAGIC DIATHESIS	1 (3.0) #	1	-	-
CARDIAC DISORDERS	2 (6.1)	2	2 (5.1)	2
ANGINA PECTORIS	1 (3.0)	1	-	-
ANGINA UNSTABLE	1 (3.0)	1	-	-
CARDIAC FAILURE	-	-	2 (5.1)	2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3.0)	1	-	-
CHEST PAIN	1 (3.0)	1	-	-
INFECTIONS AND INFESTATIONS	3 (9.1)	3	3 (7.7)	3
DIABETIC FOOT	1 (3.0)	1	-	-
PNEUMONIA	1 (3.0)#	1	1 (2.6)	1
VISCERAL LEISHMANIASIS	1 (3.0)	1	-	-
BURN INFECTION	-	-	1 (2.6)	1
WOUND INFECTION	-	-	1 (2.6)	1
INJURY POISING AND PROCEDURAL COMPLICATIONS	1 (3.0)	1	-	-
MEDICATION ERROR	1 (3.0)*	1	-	-
METABOLISM AND NUTRITION DISORDERS	-	-	3 (7.7)	5
HYPOGLYCAEMIA	-	-	3 (7.7) *	5 *
NERVOUS SYSTEM DISORDERS	-	-	1 (3.0)	1
SYNCOPE	-	-	1 (3.0) *	1 *

#Lead to study withdrawal; *Possibly related to study medication

Table 14. List of Adverse Events (treatment-emergent) according to MedDRA System Organ Class

TEAE System Organ Class	Test Group		Control Group	
	Number of Patients N=33 (%)	Number of Events	Number of Patients N=39 (%)	Number of Events
Any TEAE	28 (84.8)	71	28 (71.8)	78
INFECTIONS AND INFESTATIONS	12 (36.4)	18	13 (33.3)	19
GASTROINTESTINAL DISORDERS	4 (12.1)	8	2 (5.1)	4
METABOLISM AND NUTRITION DISORDERS	5 (15.2)	7	8 (20.5)	10
GENERAL DISORDERS AND ADMINISTRATION	5 (15.2)	7	4 (10.3)	5
MUSCULOSKELETAL AND CONNECTIVE TISSUE	5 (15.2)	5	5 (12.8)	7
RESPIRATORY, THORACIC AND MEDIASTINAL	4 (12.1)	4	4 (10.3)	4
NEUROLOGICAL DISORDERS NEC	3 (9.1)	4	3 (7.7)	3
NERVOUS SYSTEM DISORDERS	2 (6.1)	3	6 (15.4)	9
INJURY POISING AND PROCEDURAL	3 (9.1)	3	2 (5.1)	2
INJURY POISING AND PROCEDURAL	3 (9.1)	3	2 (5.1)	2
CARDIAC DISORDERS	3 (9.1)	3	2 (5.1)	2
VASCULAR DISORDERS	1 (3.0)	2	4 (10.3)	4
SKIN AND SUBCUTANEOUS SKIN DISORDERS	2 (6.1)	2	1 (2.6)	1
EAR AND LABYRINTH DISORDERS	1 (3.0)	1	3 (7.7)	3
EYE DISORDERS	1 (3.0)	1	2 (5.1)	2
PSYCHIATRIC DISORDERS	1 (3.0)	1	1 (2.6)	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (3.0)	1	1 (2.6)	1
RENAL AND URINARY DISORDERS	1 (3.0)	1	-	-
VISION DISORDERS	-	-	1 (2.6)	1

Table 15. List of Adverse Events occurred at least 7 days after end of study medication

Group	Preferred Term for AE	Serious?	Death?	days after end of study medication
Test Group	SEPSIS	yes	yes	79
Test Group	ACUTE RENAL FAILURE	yes	no	14
Test Group	METASTASES TO LUNG	yes	yes	13
Control Group	MACULOPATHY	no	-	739

Table 16. Descriptive summary for creatinine clearance changes from baseline to end of study

Creatinine clearance mL/min/1.73m^2	**Test Group N=33 (%)**	**Control Group N=39 (%)**
Visit V_S		
mean ± SD	38.1 ± 11.2	40.8 ± 12.4
min. / max.	19 / 57	15 / 58.9
Visit V_{13}		
mean ± SD	36.1 ± 14.2	41.6 ± 13.8
min. / max.	15 / 61.3	7 / 61.8
Difference (V_{13}-V_S)		
mean ± SD	0.26 ± 11.4	0.22 ± 7.22
min. / max.	- 20.9 / 26.7	- 12.7 / 24.0
Proportion of patients with reduction of Clearance of creatinine at V_{13}		
V_{13}-V_S<0	11 (33.3%)	16 (41.0%)

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