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

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|---|---|
| **Sponsor / Company:** Sanofi<br>**Drug substance(s):** Insulin glargine | **Study Identifiers:** NCT01127269, UTN U1111-1116-9268<br>**Study code:** LANTU_L_04980 |
| **Title of the study:** Practical Implementation of ADA/EASD Consensus Algorithm in Patients with Type 2 Diabetes: Timely Insulin Initiation and Titration | |
| **Study center(s):** 17 centers located in Argentina | |
| **Study period:**<br>Date first subject enrolled: 26/May/2010<br>Date last subject completed: 19/Jun/2013 | |
| **Phase of development:** Phase 4 | |
| **Objectives:**<br>**Primary objective:**<br>Percentage of patients achieving glycosylated hemoglobin ($HbA_{1c}$) <7% with no severe or nocturnal hypoglycemic episodes at 6 months.<br>**Secondary objectives:**<br>1. $HbA_{1c}$ change from baseline to 6 months<br>2. Insulin glargine dose at 3 and 6 months<br>3. Hypoglycemic episodes (all types) | |
| **Methodology:** Non-controlled open label phase 4 study. | |
| **Number of** subjects**:** | Planned: 171<br>Randomized: 178<br>Treated: 178 |
| **Evaluated:** | Efficacy: 169<br>Safety: 169 |

**Diagnosis and criteria for inclusion:**

**Inclusion criteria**

1. Male and female patients between 21 and 80 years old.

2. Patients with a diagnosis of type 2 diabetes mellitus (T2DM) for more than 6 months.

3. Patients treated with oral anti-diabetics (OADs) (monotherapy or combination) with an $HbA_{1c}$ >7% and <10% and/or treated with neutral protamine Hagedorn (NPH) insulin with $HbA_{1c}$>7% and <10%.or treated with NPH insulin who have experienced severe and/or nocturnal hypoglycemia in the last 6 months.

4. Ability to perform self monitoring blood sugar (SMBS) and insulin self-titration under the physician's guidance.

5. Body Mass Index (BMI) >21 $kg/m^2$.

6. Signed informed consent.

**Exclusion criteria**

1. Hospitalized patients.

2. Pregnant women or with the intention of becoming pregnant.

3. Unexplained weight loss of more than 10% in the last 6 months.

4. Women with child bearing potential not using effective contraceptive methods.

5. Women in breast feeding period.

6. Patients on chronic treatment with systemic corticosteroids or protease inhibitors.

7. History of drug or alcohol abuse.

8. Diabetic retinopathy with surgical treatment in 3 months previous to study entry or patients that could require surgical treatment in the following 6 months to study entry.

9. Major systemic disease clinically important that would interfere with the implementation or interpretation of the study, at the discretion of the investigator.

10. Renal failure known as creatinine >1.4 mg/dL in women and >1.5 mg/dL in men.

11. Known hypersensitivity to glargine.

12. Patients with history of hospitalization due to cardiovascular event, cardiovascular procedure in the past 6 months.

**Study treatments**

**Investigational medicinal product(s):**

INN: Insulin glargine

Product Name®: Lantus

Formulation: solution for injection

Route(s) of administration: intravenous (IV)

Dose regimen: Patients will receive insulin glargine titrated based on standard of care as recommended by the American Diabetes Association/European Association for Study of Diabetes (EASD) Consensus Algorithm. Step1: Insulin glargine initiation regimen for insulin naïve patients/Switch to insulin glargine for patient already treated with basal insulin. Step 2: the insulin dosage of patients will be titrated according to the ADA/EASD Consensus Algorithm.

**Duration of treatment:** 6 months

**Duration of observation:** 12 months

**Criteria for evaluation:**

Efficacy:

**Primary endpoint:** Percentage of patients achieving $HbA_{1c}$ <7% with no severe or nocturnal hypoglycemic episodes at 6 months.

**Secondary efficacy endpoint measurements:**

- $HbA_{1c}$ at 6 months compared to baseline $HbA_{1c}$
- Insulin glargine dosages
- Number of all types of hypoglycemic episodes

Safety: Adverse events monitoring

**Statistical methods:**

Statistical analysis had a descriptive and analytical orientation. A description of the study population was included. Continuous variables were described as means or medians estimating their adjustment to the normal distribution; while proportions for discrete variables were used with their respective 95% confidence interval (CI).

To estimate the effectiveness of insulinization with insulin glargine, the percentage of patients who achieved $HbA_{1c}$ levels below 7% without episodes of severe and/or nocturnal hypoglycemia at 6 months was calculated. Means or medians of $HbA_{1c}$ levels at 3 and 6 months, glycemia by SMBS, and the number of episodes of severe and/or nocturnal hypoglycemia along the study were described.

For all these variables and parameters, confidence intervals were obtained considering a level of 95% (95% CI).

For comparison of $HbA_{1c}$ levels and at baseline and at the end of the study, a paired t test or the signed rank test (Wilcoxon test for paired samples) based on the distribution of observations were used.

**Summary:**

**Population characteristics:** Patients with type 2 diabetes with a duration of more than 6 months, BMI >21 kg/m$^2$, treated with OADs as monotherapy or combined and / or NPH insulin therapy ($HbA_{1c} \geq$ 7% and <10%) or treated only with insulin NPH with severe or nocturnal hypoglycemia during the last 6 months.

Between 26 May 2010 (First Subject enrolled) and 19 Jun 2013 (Last Subject Completed), 243 patients were enrolled in the study, of which 53.09% were male and 46.91% female. Of the 178 patients who fulfilled the eligible criteria, 169 were evaluated for analysis and 103 patients completed the study.

**Table 1: Demographic characteristics, vital signs and anthropometric data**

| N: 243 | Mean (SD) | Median (IR) |
|---|---|---|
| Age | 58.5 (10) | 59 (52-66) |
| SAP | 132 (14.7) | 130 (121-140) |
| DAP | 73.15 (21.42) | 80 (70-82) |
| Heart Rate | 76 (7.9) | 76 (72-80) |
| Weight | 83 (21.7) | 81 (72-94) |
| Height | | 1.65 (1.58-1.72) |
| BMI | | 30.64 (27-34) |

SD: Standard deviation, IR: Interquartile range

**Table 2: Comorbidities at enrollment**

| | N |
|---|---|
| Arterial Hypertension | 175 |
| Dyslipidemia | 48 |
| COPD | 10 |
| Neoplasia | 4 |
| Smoking habit | 32 |

COPD: Chronic obstructive pulmonary disease

**Table 3: Diabetes complications. (N: 243)**

| Complication | Total (%) |
|---|---|
| MIA | 12 (5) |
| Angina | 4 (1.6) |
| CAD | 12 (5) |
| Heart failure | 2 (0.8) |
| Stroke | 6 (2.5) |
| TIA | 3 (1.2) |
| Peripheral vascular disease | 10 (4) |
| Amputation | 6 (2.5) |
| Diabetic Neuropathy | 29 (12) |
| Diabetic Nephropathy | 18 (7.4) |
| Diabetic retinopathy | 37 (15.2) |

CAD Coronary artery disease; TIA Transient ischemic attack

Diabetic retinopathy (15.2%) and Neuropathy (12%) were the most frequent complications associated with diabetes.

**Table 4: Antidiabetic medication**

| Medication | N (%) |
|---|---|
| Metformin | 200(83) |
| Sulfonylurea | 124(51) |
| Ascarbose | 1(0.4) |
| DPP IV inhibitors | 12(5) |
| Thiazolindiones | 15(6) |
| Meglitinides | 3(1) |
| NPH Insulin | 117(48.7) |

**Primary endpoint:**

Proportion of patients achieving the goal of metabolic control defined as $HbA_{1c}$ <7% with no severe and/or nocturnal hypoglycemia at 24 weeks was 30% in a total of 103 patients who completed the study.

**Secondary endpoints:**

1- $HbA_{1c}$ levels between baseline and 6 months.

There was a statistically significant difference between the values of glycosylated hemoglobin between baseline and final, as well as between fasting plasma glucose between the two visits. (Table 5).

**Table 5: Paired analysis of HbA1c between V1 and V3**

| | V1 Median (IR) | V3 Median (IR) | p Value(*) |
|---|---|---|---|
| Fasting plasma glucose | 170 (131-208) | 125 (97-146) | 0.000 |
| HbA1C | 8.7 (8.0-9.2) | 7.3 (6.6-8.2) | 0.000 |

(*) Wilcoxon Ranksum paired test

2-Dose of insulin glargine at 3 and 6 months is described in Table 6.

**Table 6: Dose of insulin glargine at 3 and 6 months**

| | V2 (3 months) | V3 (6 months) |
|---|---|---|
| Mean (SD) | 38.9 (27.35) | 43.5 (29.8) |
| Median (IR) | 33 (17.5-55.5) | 32 (22-62) |

3- Episodes of Hypoglycemia.

In total 314 episodes of hypoglycemia, corresponding to 70 patients, were recorded, of which 58.39% were classified as “minor asymptomatic” episodes; 35.16% were classified as "minor symptomatic" episodes; 4.52% were severe and 1.94 % was due to nocturnal episodes.

**Table 7: Glycemia value and type of hypoglycemia**

| Glycemia value (mg/dl) | Nocturnal | Severe | Minor asymptomatic | Minor symptomatic |
|---|---|---|---|---|
| Mean (SD) | 47.6(9.7) | 38( 12) | 51.7 (9) | 53(8) |
| Median (IR) | 49 (40-54) | 38 ( 32-39) | 54(45-58) | 53.5(48-57) |

**Safety results**: A total of 145 adverse events (AEs) were recorded, of which 142 were analyzed. Of the 142 AEs analyzed, 84.5% were of mild intensity, 13.38% were moderate, and 2.11% were severe. Four of them were serious adverse events.

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