| *These results are supplied for informational purposes only.*<br>*Prescribing decisions should be made based on the approved package insert in the country of prescription* | | | |
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| Sponsor/company: | sanofi-aventis | ClinialTrials.gov Identifier: | NCT00653302 |
| | | Study Code: | HOE901_4043 |
| Generic drug name: | Insulin glargine | Date: | 02-Dec-2008 |

Title of the study:

Evaluation of Lantus® (glargin insulin) combined with Glucophage® (metformin hydrochloride) in type-2 diabetics, in initial insulin therapy after failure of oral treatment GALATEE (Glucophage Combined with Lantus in Type-2 Diabetics: Evaluation of Efficacy).

Investigator(s) and study center(s):

Prof. Charles Thivolet, Lyon, France. A French multicentre study conducted in 66 research centres (hospital centres and diabetologists in private practice).

| Study period | Phase of development : |
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| The duration of the trial was 8 months of treatment preceded by a two-week screening period.<br>The first patient was enrolled on 07 April 2003, and the last patient ended the treatment phase of the study on 20 June 2005. | IV |

Objectives:

Primary: To evaluate the efficacy of the combination of Lantus® and Glucophage® in terms of percentage of responders. A responder was defined by final HbA1c value < 7% as an absolute value and/or final reduction of HbA1c by more than 15% as compared to initial value (final HbA1c - initial HbA1c).

Secondary:

Safety

- To describe adverse events.
- To evaluate the safety of use by counting episodes of hypoglycaemia (symptomatic, diurnal, nocturnal, severe).

Methodology:

A multicentre, open-label, non-comparative study in patients with type 2 diabetes treated with Lantus® (1 injection per day) and Glucophage® 1000 mg by oral route (2 tablets per day) during a period of 8 months.

Planned number of patients:

It was planned to enrol 500 patients in approximately 120 centres.

Diagnosis and criteria for inclusion:

Patients enrolled in this study were male and female, 30 to 69 years of age, with type 2 diabetes for at least 2 years, having given their written consent. They had to have an HbA1c value ≥ 7.5 and < 11.0% on 2 different tests from at least one year beforehand, a body mass index strictly between 25 and 35 kg/m2 and to have been treated for diabetes with dual or triple oral therapy for at least six months before baseline. Patients had to have no history of insulin treatment during the 6 months prior to baseline. Women of childbearing potential were not to be pregnant or nursing, and had to use an effective method of contraception.

Investigational product:

The study treatment was glargin insulin (Lantus® 100 IU/mL) injected subcutaneously with the OptiPen Pro once per day at a time chosen by the patient (before breakfast, before dinner or at bedtime) and maintained throughout the study. The dose was initially 0.2 IU/kg and was to be adjusted individually throughout the study in order to obtain fasting blood glucose every day between 0.80 and 1.20 g/L with a weekly mean ≤ 1 g/L.

Titration algorithm (twice a week, based on the Fasting Blood Glucose over 3-4 days) :

+ 4 UI/day if FBG >1.6 ; + 2 UI/day if FBG >1.2 ; + 1 UI/day if FBG >1 no change if 0.8<FBG<1 ; - 2 UI/day if FBG < 0.8

The study treatment was combined with metformin hydrochloride 1000 mg (Glucophage® 1000 mg), administered by oral route in the morning during breakfast and in the evening with dinner. This dose had to remain unchanged throughout the study.

Criteria for evaluation

Efficacy:

- HbA1c: measured by HPLC in a central laboratory at visits V1 (initial visit) and V6 (final visit at month 8) or upon early withdrawal from the study (if this took place after V3 (month 1 visit).
- Fasting capillary blood glucose: measured every morning before breakfast by the patient throughout the entire duration of the study.

Safety:

- Hypoglycaemia: classified as symptomatic, severe or nocturnal.
- Adverse events (AE): collected throughout the study (with notification within 24 hours following occurrence of serious AE).

Statistical methods:

Sample size justification:

This study assume a null hypothesis of a 50% overall clinical response rate (final HbA1c value < 7% as an absolute value and/or final reduction of HbA1c by more than 15% as compared to initial value) and an alternative hypothesis of a 60% response rate. With type I error no more than 0.05 and power at least 99%, the study would require 460.

Difficulties of recruitment led to the inclusion of only 255 patients. A re evaluation of statistical power before data base lock showed that this power was still sufficient with a population of 227 evaluable patients (=90.5%).

All data were analyzed using SAS on Solaris.

Populations definitions:
- Population FAS (Full Analysis Set):
The FAS population was defined as all treated patient having an available HbA1c value at baseline (V1) and at the final evaluation (V6 or premature discontinuation after V3).
- Safety Population
The safety population was defined as all subjects exposed to study treatment, regardless of the amount of treatment administered.

Analysis of the primary endpoint was performed on the FAS population. The primary endpoint was defined as the percentage of patients who were "responders" to Lantus® plus Glucophage® treatment. The exact 95% confidence interval of the percentage of patients with good response to Lantus® plus Glucophage® treatment was calculated at the end of the study.

- Final HbA1c (V6 or early withdrawal after V3) and its variation as compared to its initial value (V1) (∆HbA1c and ∆HbA1c%).
- Weight variations in the values recorded at each visit (V3, V4, V5, V6) and initial value recorded at V2 (absolute and relative differences).
- Mean blood glucose at each time.
- Dose of Lantus®.

Safety analysis: descriptive analyses of the following parameters:

- AE, SAE
- Hypoglycaemia

Intermediate analysis: Not performed.

Summary

The FAS population (N = 227) was 47% female and 53% male. Patients were between 31 and 71 years of age, with a mean age of 57.1 ± 7.5 years. The mean weight was 81.5 ± 12.3 kg. The mean BMI was 23.4 ± 3.3 kg/m2. Patients had a mean duration of 12.5 years between diagnosis of diabetes and the enrolment in the study.
The mean HbA1c was 8.9 ± 1.2% and the mean fasting blood glucose was 2.06 ± 0.49 g/L at baseline.
The majority of patients (85.46%) were taking glucose-lowering sulfamides at the time of selection, and all patients except for one were taking metformin. 26.43% of patients had a third oral treatment (alphaglucosidase inhibitor in the majority of cases).
Between 20 and 30% of patients were suffering from nephropathy, diabetic neuropathy or retinopathy.

Efficacy results

At the end of the study, the rate of "responders" in the FAS population was 51.1% with a $CI_{95\%}$ of [44.4%, 57.8%]. All analyses of efficacy were therefore only descriptive.

A reduction HbA1c of -1.2% ± 1.5% (7.7 ± 1.2% at V6 versus 8.9 ± 1.2% at V1) was observed at the end of the study in the FAS population.

Mean fasting blood glucose went from 2.06 ± 0.49 g/L at screening to 1.2 ± 0.3 g/L at V6 (i.e. after 8 months of treatment).

The mean dose of Lantus® taken by patients increased throughout the study to reach 0.6 IU/kg at V6.

The mean weight of patients in the FAS population had a tendency to increase over the course of the study: mean weight went from 81.4 ± 12.4 kg at baseline to 83.6 ± 12.7 kg at visit 6.

Safety results

Among the 255 patients in the safety population, 127 (49.8%) presented with 209 Adverse event (AEs) during the treatment period.
The most commonly reported AEs (between 2% and 3.1% of patients) were bronchitis (without other information), nasopharyngitis, headaches, diarrhoea, lipodystrophy, arthralgia, tendonitis and flu-like symptoms.
The majority of AEs collected were mild or moderate in intensity and not related to the treatment.
Eighteen AEs (8.6%) that occurred in 17 patients (6.7%) were considered to be possibly related to the treatment. One-third of these AEs that were possibly related to the treatment were lipodystrophies.
Five patients (2.0%) withdrew from the study early following the occurrence of an AE. In 3 cases, these were non-treatment-emergent SAEs, and the other two cases were abdominal pain with a possible relationship to the study treatment (Lantus®).
The majority of AEs resolved without sequelae.
No cases of death occurred during the study.
Twenty-two patients (8.6%) presented with at least one SAE during the treatment period, only two patients had SAEs that were possibly related to the study treatment (aggravated hypertension and diabetic retinopathy).

During the study, The number of episodes of hypoglycaemia was a mean of 3.4 ± 9.3 episodes/patient/year :
85 patients (33.3%) had 364 episodes of diurnal hypoglycaemia, and 24 patients (9.4%) had 65 episodes of nocturnal hypoglycaemia. Only one patient (0.4%) had one serious severe diurnal hypoglycaemia. This patient had taken double the amount of Lantus®, due to incorrect use of the pen.

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| Date of report: | October 2008 |