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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00642915
		Study Code:	HOE901_4039
Generic drug name:	insulin glargine	**Date:**	18 Feb 2008

Title

A 24 week, open-label, single arm, multi-center clinical study to document the benefits of the combination of Lantus® (insulin glargine) and Amaryl® (glimepiride) in ethnic Japanese type 2 diabetic patients living outside of Japan (in United States [US] or Brazil), who failed good metabolic control with oral antidiabetic drugs (OADs).

Investigator(s), study site(s)

Multicenter: 8 sites in Brazil; Coordinating investigator: Freddy Goldberg Eliaschewitz, MD

Study duration and dates	13 June 2003 - 02 July 2004	**Phase**	IV

Objectives

• To estimate the efficacy of combination therapy with Lantus® plus Amaryl® in controlling blood glucose (BG), as measured by improvement of fasting plasma glucose (FPG) before breakfast and hemoglobin A1c (HbA1c) in Japanese patients with type 2 diabetes having failed OAD therapy, and

• To document the ability to preserve the endocrine pancreatic function with Lantus plus Amaryl combination therapy (via Sustacal test and blood C-peptide).

Study design

This was a 24-week, open-label, single arm, multicenter clinical study in type 2 diabetes mellitus patients with poor metabolic control (HbA1c values ≥8.0% and ≤11% and FPG values ≥140 mg/dL), as a result of failed therapy with either sulfonylurea monotherapy or double OAD including use of a sulfonylurea. The goal was for patients to achieve a target FPG of ≤100 mg/dL and ≥72 mg/dL. Hemoglobin A1c values were measured at Screening and at every visit thereafter. Patients were to

continue their current OADs until they satisfied all entry criteria. Upon entering the treatment phase of the study, patients were switched to Amaryl alone at a stable dose of 3 mg for 1 week. Starting with Week 1 of the treatment phase, patients began administration of Lantus.

The study consisted of a screening/training phase and a 24-week treatment phase.

Number of patients planned

One hundred patients were planned for enrollment in order to achieve 80 evaluable patients.

Inclusion criteria

All patients planned for enrollment into this study had to have noninsulin-dependent diabetes mellitus (NIDDM) (type 2 diabetes) and were not able to maintain good metabolic control with OADs. Enrolled patients could be male or female, of documented Japanese ethnic origin, and between the ages of 20 and 70 years, inclusive.

Treatments

Lantus (insulin glargine) cartridge containing 3-mL solution to be administered as a subcutaneous injection (1 mL contained 100 IU). Starting doses of Lantus were 6 units/day if the patient's FPG was ≥140 mg/dL or, if <140 mg/dL, Lantus was titrated according to an algorithm. Throughout the trial, patients' FPG levels were monitored and treatment adjusted accordingly.
Amaryl (glimepiride), 1-mg oral tablets. Treatment was to be started with three 1-mg tablets. Amaryl was administered once daily, in the morning with breakfast or the first meal of the day in a stable dose of 3 mg, from the start of the treatment phase until discontinuation of the study.

Efficacy data

The primary efficacy endpoint was BG control as measured by changes in HbA1c (Week 0 to completion [discontinuation] of treatment). Secondary endpoints included BG control measured by changes in FPG; 2-hour postprandial plasma glucose (PPG); in 24-hour, 8-point blood glucose (BG) control, and percentage of patients reaching target HbA1c (≤7.0%) and/or FPG (≤100 mg/dL). Additionally, endogenous insulin secretion was measured by changes in fasting blood C-peptide, postprandial blood C-peptide, and Sustacal test.

Safety data

Adverse events (AEs) reported by the patients were noted by the investigators. Hypoglycemia

(including symptomatic, nocturnal, and severe hypoglycemia) were monitored as events of special interest. Standard hematology and blood chemistry values were monitored and vital signs recorded and monitored.

Statistical procedures

The primary efficacy endpoint in relation to BG control is the change in HbA1c from Baseline to Endpoint. Baseline is the HbA1c value prior to the start of treatment, and Endpoint is the value at the completion (discontinuation) of treatment. Change from Baseline to Endpoint in HbA1c was analyzed using a paired t test. The test was 2-sided at the 0.05 level of significance with the null hypothesis that there is no difference between HbA1c values at Baseline and Endpoint. The estimated change in HbA1c from Baseline to Endpoint and the corresponding 95% confidence interval are presented in a summary table. This summary table also presents descriptive statistics of HbA1c for each study visit, as well as the change from Baseline to each point in time. These analyses were performed for the intent-to-treat (ITT) and per-protocol (PP) populations. Means (with the standard deviations) of the changes from Baseline in HbA1c to each postbaseline visit are presented graphically by time point for the ITT population.

Secondary efficacy endpoints measuring BG control include FPG, 24-hour, 8-point measurement of BG; 2-hour PPG; percentages of patients reaching target HbA1c (≤7.0 %); and FPG (≤ 100 mg/dL).

Interim analysis

Not applicable to this study.

Results – Study patients and conduct

All 100 patients who enrolled received study. No patients died or left the study due to an AE, lack of efficacy, or were lost to follow-up, or left due to administrative reasons. One patient discontinued because of repeated hypoglycemic episodes despite reduction in study dose; 2 patients were withdrawn from the study because they took prohibited medications.

Amaryl was administered for the first week of study treatment as a daily dose of 3 mg. Lantus was started after the patient had taken his/her first week of Amaryl and the Lantus dosage varied according to the patient's blood glucose level and condition. The total duration of treatment was for 24 weeks.

One hundred patients were in the all enrolled and the safety populations. The ITT population consisted of 97 patients; 3 patients were excluded because they did not have an efficacy endpoint value. The PP population had 85 patients; the 3 ITT patients previously mentioned were excluded as were 11 additional patients who had protocol deviations or violations and 1 patient did not complete the study. The study population was fairly similarly divided between males (47 patients, 47%) and

females (53 patients, 53%). The median age was 59.0 years with ages ranging from 24 to 70 years. The median body mass index was 24.860 kg/m2, with a range of 17.36 to 29.94 kg/m2.

Previous OAD treatment was administered for a median of 8.78 years among the 100 patients in the safety population. Eighty-two percent of all patients had a family history of diabetes mellitus, with a median of 10.35 years since diagnosis. Ninety-three percent of all patients were taking concomitant medications; 42.0% were taking acetylsalicylic acid, 23.0% were taking paracetamol, and 16 (16.0%) were taking atenolol.

Results – Efficacy

The primary efficacy endpoint was BG control as measured by changes from Baseline in HbA1c.

Secondary endpoints included BG control measured by changes in FPG, changes in PPG, changes in 24-hour PG control, and the percentage of patients reaching the target HbA1c of ≤ 7.0% and FPG of ≤100 mg/dL. Additionally, endogenous insulin secretion was measured by changes in fasting blood C-peptide, postprandial blood C-peptide, and Sustacal test. In the protocol, weight, cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), and triglycerides were originally designated as efficacy endpoints. After a review of the data and prior to database lock, it was decided that these parameters would be analyzed as safety variables because these are not exclusive of strong surrogate efficacy markers for BG control in this study.

Among patients in the ITT population (N=97), the mean decrease in HbA1c was clinically meaningful and statistically significantly different (P<0.0001) between Baseline and Endpoint.

The actual change from Baseline is a decrease of 1.54 points and the 95% confidence interval (CI) is between -1.79 and -1.29. Mean values began a decline as early as Week 4 and declined steadily at Weeks 8, 12, 16, 20, and 24 suggesting that the longer the patient maintained study drug therapy, the greater the decrease in HbA1c.

The mean decrease in FPG was clinically meaningful and statistically significantly different (P<0.0001) between Baseline and Endpoint. The actual change from Baseline is a decrease of 88.3 mg/dL and the 95% CI is between -99.5 and -77.1. Mean values began a decline as early as Week 4 and declined steadily at Weeks 8, 12, 16, and 24 suggesting that the longer the patient maintained study drug therapy, the greater the decrease in FPG.

The mean decrease in PPG from Week 1 (289.2 mg/dL) to Week 20 (180.8 mg/dL) was

statistically significantly different (P<0.0001). The mean decrease of 112.6 mg/dL is clinically meaningful, especially in these patients who had not previously responded to OAD treatment.

The 95% CI for the change is between -128.2 and -97.0.

The analysis of 24-hour, 8-point BG measurement showed that the mean decrease from Week 0 to Week 24 was statistically significantly different (P<0.0001) at each of the 8 time points. The greatest decrease in BG occurred before breakfast, with a mean change between Week 0 and Week 24 of -74.3 mg/dL (P<0.0001; 95% CI between -85.4 and -63.1). The smallest decrease occurred when BG measurements were taken before dinner with a mean change between Week 0 and Week 24 of -23.8 (P=0.0079; 95% CI between -41.2 and -6.4). Since Lantus was taken at bedtime, these findings are consistent with treatment modalities.

Thirteen (13.4%) patients reached the target HbA1c of ≤7.0% and FPG ≤100 mg/dL at least once during the study. Overall, 65 (67.0%) patients in the ITT population reached an FPG ≤100 mg/dL at least once during the study and 27 (27.8%) patients reached the target HbA1c of ≤7.0% at least once. The greatest number of patients achieving the FPG target occurred at Weeks 12 and 16, with 19 (19.6%) patients at each of those weeks. For HbA1c, the greatest number of patients reaching the target was 7 (7.2%) patients at Week 16. An examination of individual patient blood glucose data shows that once the target goals were achieved, some patients were able to maintain their target goal at every reporting interval.

Fasting blood C-peptide decreases from Baseline to Week 12 and Baseline to Week 24 were observed among patients in the ITT population. A statistically (P<0.0001) and clinically significant mean decrease of 1.142 ng/mL in blood C-peptide was observed between Week 0 and Week 24. The 95% CI for the change is between -1.363 and -0.921.

Postprandial blood C-peptide changes from Week 1 to Week 20 showed a statistically significant (P=0.0083) and clinically significant decrease of 0.427 ng/mL. The 95% CI for the change is between -0.742 and -0.113.

Sustacal test changes as AUC analyses between Baseline (Week 0) and Endpoint (Week 24) showed a statistically (P<0.0001) and clinically significant mean decrease of 31.319 nmol/mL x minutes, demonstrating that glucose control could be maintained after meals after receiving the study drug combination therapy for 24 weeks. The 95% CI for the change is between -42.568 and -20.069.

Results – Safety

In this study, there were no deaths and no patient discontinued due to an AE. The overall pattern of AEs appears to be consistent with these patients' underlying disease. Causal relationships of some events to study drug also would be in keeping with recognized risk factors associated with antidiabetic therapy, particularly with the use of insulin.

Eighty-five (85.0%) patients reported 461 AEs. Forty-seven (47.0%) reported events in the general disorders and administration site conditions system organ class (SOC), with the most commonly reported events being injection site hemorrhage and injection site reaction (unspecified). The infections and infestations SOC had the next most frequently events; 44 (44.0%) patients reported 66

AEs. Twenty (20.0%) and 12 (12.0%) patients reported 24 incidences of influenza and 13 incidences of nasopharyngitis, respectively.

Two hundred sixty-three events of the 461 AEs reported were judged not related to study drug. Events that were considered related to study drug administration included AEs in the general disorders and administration site conditions, investigations, metabolism and nutrition disorders, nervous system disorders, skin and subcutaneous tissue disorders, and vascular disorders SOCs. Injection site reactions (bruising, burning, discomfort, pain, etc), were considered possibly related to study drug. Most AEs had short durations, approximately 1 week or less.

Severe events were reported by 8 patients. All patients reported recovery without sequelae, except Patients 0301 (sciatica), 0309 (hypertriglyceridemia), and 0602 (pituitary tumor) whose events were ongoing at the time of study end.

Four patients reported 5 SAEs. Details of SAEs reported by Patient 0316 (traumatic brain injury, traumatic hematoma), Patient 0521 (deafness neurosensory), Patient 0602 (pituitary tumor), and Patient 0804 (vertigo) are presented in narratives in Section 14.

Sixty (60.0%) patients reported 274 symptomatic hypoglycemic events, Thirty-two (32%) patients reported nocturnal hypoglycemic events. None of these events were deemed serious or severe.

Hypoglycemic events such as shakiness, hands tremor, headache, palpitations, sweating, or weakness were treated with oral carbohydrates. Many of the nocturnal events occurred in the early morning hours. Two hundred of the symptomatic hypoglycemic events did not require a change in study drug; 68 events resulted in a decrease in study drug dose, and 6 events resulted in temporary discontinuation of study drug.

Median values between Baseline and Endpoint were increased for fasting cholesterol (from 190.5 mg/dL to 201.0 mg/dL) and LDL values (109.0 mg/dL to 122.0 mg/dL). Fasting HDL values, 47.0 mg/dL, were unchanged between Baseline and Endpoint. Fasting triglyceride values showed a median decrease of 18.0 mg/dL from 157.0 mg/dL to 136.0 mg/dL. None of these changes appear to be clinically meaningful.

Median erythrocyte, hemoglobin, hematocrit, leukocyte, and neutrophil values were decreased from Baseline and do not appear clinically meaningful, although there were individual patient variations.

Median eosinophil percentages increased from 2.95% at Baseline to 3.00% at Endpoint. The eosinophil count remained the same (180.0/mm3). Median basophil percentages and counts remained the same (0.60% and 40.0/mm3, respectively). Median lymphocyte and monocyte percentages increased from 29.35% and 6.90%, respectively, to 31.05% and 7.05% and counts increased from 1885.0/mm3 and 440.0 mm3, respectively, to 1914.5/mm3 and 445.0/mm3, respectively. Median platelet counts decreased from 241.0 k/mm3 to 227.0 k/mm3. No patients reported an AE related to any hematology abnormalities.

Median SGPT and SGOT values were 25.5 U/L and 21.0 U/L, respectively, at Baseline and were 24.0 U/L and 22.0 U/L at Endpoint. Median serum creatinine values increased for 0.795 mg/dL at Baseline to 0.800 mg/dL at Endpoint. No patient reported an AE associated with a serum chemistry laboratory abnormality and the median value changes appear clinically insignifican.

The number of normal/abnormal findings between Screening and Endpoint remained similar, with most changes from normal to abnormal and vice versa most likely attributable to transient conditions such as multinodular goiter, toenail dystrophy, or edema. During the study, there were reports of physical finding abnormalities, such as tooth extractions, glaucoma, conjunctivitis, increased lacrimation, blurred vision, gingival edema, ear infection, and fungal skin infections.

Changes in median weight, blood pressure, and heart rate do not appear clinically meaningful.

Median weight increased from 62.45 kg to 65.80 kg, which was expected as weight gain is frequently seen among patients taking antidiabetic medications, particularly with insulin. Weight increase was reported as an AE by 16 patients during the study and all were considered possibly related to study drug. Two AEs of hunger were reported, 1 judged related and the other judged not related to study drug. An examination of individual patient data shows that most patients tended to gain from 1 kg to 5 kg over the 24-week treatment period, although weight gains of almost 10 kg were seen in a few cases. Median systolic blood pressure increased from 129.0 mm Hg at Baseline to 130.0 mm Hg at Endpoint. There was no median value change from Baseline in diastolic blood pressure (80.00 mm Hg). Median heart rate values also remained unchanged from Baseline (76.0 beats per minute). Again, these changes do not appear to be clinically meaningful.

Report Date

12 November 2004