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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00135941
Generic drug name:	Insulin glulisine	**Study Code:**	HMR1964A/3508

Title of the study: Lantus® (insulin glargine) plus Apidra® (insulin glulisine) MDI versus Premix insulin treatment in subjects with diabetes mellitus (type 1 or type 2) evaluating differences in patient reported outcomes. A randomized, multicenter, cross-over study.

Investigators: Coordinating investigators were Donald C. Simonson, MD, Division of Endocrinology, Hypertension and Diabetes, Department of Internal Medicine, Brigham and Womens Hospital, 220 Longwood Avenue, Boston, MA 02115, and Lawrence Blonde, MD, Ochsner Medical Center, Endocrinology, 1514 Jefferson Highway, New Orleans, LA 70121. Co-investigators were Marcia A. Testa, MPH, PhD, Department of Biostatistics, Harvard School of Public Health, 655 Huntington Avenue, Boston MA 02115 and Ralph R. Turner, PhD, MPH, Phase V Technologies, 20 Walnut Street, Wellesley Hills, MA 02481.

Study centers: Multicenter: 65 sites were initiated in the United States (US); 52 sites enrolled patients

Publications (reference): Testa MA, Blonde L, Gill J, Turner RR, Simonson DC. A cross-over trial of insulin glargine + glulisine versus premix analog insulin. Abstract presented at the ADA 70th Scientific Session, Orlando, FL, June 2010.

Study period:

Date first patient enrolled: 08 September 2005

Date last patient completed: 20 September 2007

Phase of development: IIIB; Efficacy, safety, and patient-reported outcomes

Objectives:

Primary Objective

The primary objective of the study was to test for superiority in improvements from baseline in patient-reported outcomes (quality of life [QOL], treatment satisfaction) in patients with type 1 or type 2 diabetes when treated with Lantus plus rapid-acting Apidra versus treatment with premix insulin (either Humalog® mix 75/25 or Novolog® mix (70/30).

Secondary Objectives

Clinical efficacy

To assess whether there was a difference between treatment groups in variability in blood glucose (BG) control as estimated by the continuous glucose monitoring system (CGMS).

To assess whether there were differences between treatment groups in any of the following measures:

- The proportion of patients in each group achieving hemoglobin A1c (HbA1c) <7.0%
- Case Report Form (CRF)-reported hypoglycemic events
- Change in HbA1c
- Change in low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol, and triglyceride levels

An additional objective was to assess the correlation between patient-reported outcomes and glucose variability, as measured by CGMS.

Safety

Secondary safety objectives of the study were to investigate the relative differences from baseline to end of study in:

- Occurrence of hypoglycemia
- Adverse events
- Laboratory values: chemistry and hematology

- Clinical values: physical examination, vital signs, and weight

Patient-reported outcomes

- Phase V® Health Outcomes Information System Clinic Questionnaires at Weeks –3, 0, 8, 12, 20, and 24, and at unscheduled exit (early withdrawal) visit that evaluated domains of QOL (physical, mental and emotional, cognitive, work and social role and sexual functioning) and treatment satisfaction with diabetes medications and insulin.
- Phase V® Health Outcomes Information System Electronic C.A.R.E. (Comprehensive Adverse Reaction Evaluation) Home Diaries assessed throughout the study, measured symptoms related to hypo- and hyperglycemia, overall health, well being, mood, symptom distress and corresponding home BG.

Methodology: This was a multicenter, US, open-label, controlled, 1:1, randomized, cross-over study of up to 27 weeks in insulin-treated adults with type 1 or 2 diabetes mellitus who were randomized to either Lantus + Apidra or Premix insulin. After the first 12 weeks of treatment, patients crossed over to the other randomized treatment and were followed for an additional 12 weeks.

Number of patients: Planned: 375 patients
Randomized: 388 patients
Treated: 388 patients

Evaluated: Efficacy: 388 patients
Safety: 388 patients

Diagnosis and criteria for inclusion: Male or female patients, 21 to 70 years of age, with type 1 or 2 diabetes mellitus for at least 6 months, with a HbA1c level at screening of ≥ 7.0% and ≤ 9.0%. Daily use for the last 3 months of premix insulin 75/25, 70/30, isophane (NPH), or Lantus with short-acting insulin consisting of 2 or more injections per day, with or without concomitant therapy consisting of metformin, thiazoldinedione, and/or alpha-glucosidase inhibitors**;** willing and able to inject Lantus and multiday dosing of Apidra; willing and able to perform self-monitoring of BG and CGMS. Females of child-bearing age were required to be willing and able to use adequate contraception.

Investigational product: Lantus; Apidra

Dose:

Lantus - The initial daily dose of Lantus was calculated by first splitting the total insulin dose from the previous treatment in half (ie, 50% of the previous total insulin dose was the basal insulin dose and 50% was the bolus dose). A further reduction of 20% (per the Lantus package insert) resulted in the total basal dose of Lantus. That is, the initial dose of Lantus was to be 80% of the half (ie, 40%) of the total daily insulin from the previous treatment. The dose was to be titrated weekly according to the self-monitored blood glucose (SMBG) value, based on the mean of the last 3 morning fasting plasma glucose (FPG) values, according to the protocol-specified algorithm.

Apidra - Patients who were already receiving other rapid-acting analogues or regular human insulin were transferred to the same dose of Apidra. Patients who were to receive multiple daily injections for the first time, received Apidra based on the preprandial (up to 15 minutes before the start of the meal) BG values. The initial total daily bolus dose of Apidra was to be 50% of the total daily insulin from previous treatment. Total daily bolus insulin was to be divided to provide appropriate mealtime coverage during the day, based on the rule of "6ths." Apidra was to be titrated weekly according to the protocol-specified algorithm.

Administration: subcutaneous injection for 12 weeks
Lantus: once daily
Apidra: immediately (0 to 15 minutes) before a meal

Duration of treatment: up to 27 weeks

Duration of observation: up to 27 weeks + 1 day

Reference therapy: Premix insulin (Humalog Mix 75/25 or Novolog Mix 70/30)

Dose: Premix insulin was dosed by adding the total insulin dose, which was divided 2/3 prior to breakfast and 1/3 prior to supper (dinner). Premix insulin was titrated weekly according to the protocol-specified algorithm. The morning dose was based on the mean of the last 3 days of before dinner BG values, and the evening dose was based on the mean of the last 3 days of before breakfast FPG values.

Administration: subcutaneous injection, twice daily for 12 weeks

Criteria for evaluation:

Efficacy: HbA1c, FPG, preprandial BG, insulin doses, SMBG values using diary collection, BG profiles, and plasma lipid analysis.

Health Outcomes: Phase V® Health Outcomes Information System was used to evaluate patient-reported QOL, treatment satisfaction with diabetes medications and insulin, and symptoms of hyper- and hypoglycemia, overall health, well being, mood, symptom distress, and corresponding home BG.

Safety: Hypoglycemic events, adverse events, standard clinical chemistry and hematology, physical examinations, vital signs, and weight.

Statistical methods: The Net Benefit Treatment Satisfaction scale and the Quality of Life Factor Score were identified as co-primary endpoints with a shared alpha of 0.05. Linear mixed models were employed to test the effects of treatment, period and treatment sequence adjusting for the baseline values and covariates on primary and secondary patient-reported, efficacy and safety endpoints.

Summary:

Patient Reported Outcomes results:

The following conclusions are drawn from the analysis of the Patient Reported Outcomes:

- The co-primary efficacy endpoints:
  - Combining the treatment effects for Periods 1 and 2, the Net Benefit treatment satisfaction improved from a baseline value of 51.1 to 60.5 ± 1.2 for Lantus-Apidra compared to a deterioration in satisfaction with Premix to 45.43 ± 1.2. The treatment difference was statistically significant at $p < 0.00001$.
  - The Quality of Life Factor Score favored Lantus-Apidra by 0.13 ± 0.04 Z-score units (Lantus-Apidra 0.07 ± 0.03 versus Premix -0.06 ± 0.03; $p < 0.001$).
- Treatment satisfaction:
  - Each of the individual satisfaction subscales that comprised the Net Benefit scale demonstrated a statistically significant improvement for Lantus-Apidra as compared to Premix.
  - The differences between treatments in the Regimen Acceptance treatment satisfaction scale was comparable although individual scales favored 1 treatment over the other. Statistically significant differences in favor of Lantus-Apidra were observed on the scales measuring Flexibility, Side Effects, and Interference. Statistically significant differences in favor of Premix were observed on the scales measuring Burden, Convenience, and Pain.
  - Both the subscales Hassle and Social were favorable to Lantus-Apidra; however, neither achieved statistical significance.
  - The Overall Satisfaction scale showed a statistically significant improvement from baseline for Lantus-Apidra while worsening for Premix.
- Quality of life:
  - As noted above, the Quality of Life Factor Score was statistically significantly different in favor of Lantus-Apidra.
  - The Perceived Health Scale, the Composite Itemwise QOL Scale, the Mean Psychosocial Scale, the Overall Symptom Distress Scale, the General Perceived Health and the 2 subscales General Health Status and Vitality were all statistically significantly different in favor of Lantus-Apidra.
  - Sleep was comparable between the 2 groups.
  - The Overall Mental Health Composite scale trended towards an improvement in favor of Lantus-Apidra.
  - None of the individual subscales of mental health, nor the composite scales of Psychological Well-Being or Psychological Distress showed any statistically significant differences between the 2 treatments.
  - Health Limitations due to Other Non-Diabetes Symptoms demonstrated a statistically significant improvement for Lantus-Apidra.
  - Health Limitations due to Diabetes Symptoms showed no statistically significant differences between the 2 treatments. Health Limitations as measured by the Duke Activity Scale were comparable between the 2 treatments. The Overall Composite Cognitive Scale along with the 3 subscales were comparable between the 2 treatments.

Efficacy results:

The following conclusions are drawn from the analysis of the clinical variables:

- Continuous glucose monitoring:
  - The mean (SE) sensor glucose during treatment decreased statistically significantly more for Lantus-Apidra compared to Premix, decreasing from a baseline of 164.22 mg/dL to 147.81 ± 1.83 mg/dL for Lantus-Apidra versus 160.43 ± 1.88 mg/dL for Premix.
  - The mean (SE) intraday variability of the sensor glucose as calculated by the standard deviation for the 288 values within a 24-hour period decreased statistically significantly more for Lantus-Apidra compared to Premix, decreasing from a baseline of 47.24 mg/dL to 42.64 ± 0.84 mg/dL for Lantus-Apidra versus 48.54 ± 0.855 mg/dL for Premix.
  - The mean (SE) percent Time >140 mg/dL decreased more for Lantus-Apidra than Premix, decreasing from a baseline of 57.2% to 46.05 ± 1.1% for Lantus-Apidra versus 53.73 ± 1.13% for Premix.
  - The change in the mean (SE) percent time <70 mg/dL from a baseline of 6.44% was not statistically significantly different between Lantus-Apidra (7.80 ± 0.474%) and Premix (6.66 ± 0.484%).

- Achievement of HbA1c <7%:
  - In Period 2 at the crossover baseline, the percentage of patients who had a HbA1c <7% was statistically significantly larger in the group that had just finished treatment with Lantus-Apidra (HbA1c <7% (55.8% versus 31.4%; p<0.001). In addition, at Week 24 (LOCF) the group that had been receiving Lantus-Apidra since Week 12 had a statistically significantly higher percentage of patients with a HbA1c <7% (HbA1c <7% (56.8% versus 45.1%; p<0.0284).
- Occurrence of hypoglycemic events:
  - There was no statistically significant difference between treatment groups in hypoglycemic event occurrence in Periods 1 or 2 (Odds ratio (95% CI) of Lantus-Apidra vs Premix for Period 1: 1.08 [0.87, 1.34], Period 2: 0.88 [0.69, 1.11].
- Change from baseline/crossover baseline in HbA1c:
  - In Period 1, the mean (SD) decrease from baseline at Week 12 (LOCF) in HbA1c was statistically significantly greater for Lantus-Apidra compared to Premix (-0.73% [0.71] versus -0.43% [0.75]; p<0.001).
  - In Period 2, the mean (SD) decrease from crossover baseline at Week 24 (LOCF) in HbA1c was statistically significantly greater for Lantus-Apidra compared to Premix (-0.33% [0.66] versus +0.15% [0.63]; p<0.001).
- Change from baseline/crossover baseline in other laboratory parameters:
  - In Period 1, the mean (SD) decrease from baseline at Week 12 (LOCF) in FPG was statistically significantly greater for Lantus-Apidra compared to Premix (-28.98 mg/dL [71.36] versus -0.31 mg/dL [84.86]; p<0.001).
  - In Period 2, the mean (SD) decrease from crossover baseline at Week 24 (LOCF) in FPG was statistically significantly greater for Lantus-Apidra compared to Premix (-16.52 mg/dL [75.35] versus +13.38 [79.30]; p<0.001).
  - There was no statistically significant difference between treatment groups in mean change from baseline at Week 12 (LOCF) or in mean change from crossover baseline at Week 24 (LOCF) for total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides.
- Correlation between patient-reported outcomes and glucose variability, as measured by the CGMS:
  - In an analysis of all patients, the association between Net Benefit and percent glucose <70 mg/dL was not statistically significant. In an analysis of only patients with type 2 diabetes, the association was statistically significant.
  - Intraday SD Glucose was a statistically significant predictor of Net Benefit treatment satisfaction, while it was not a predictor of General Perceived Health.

Safety results:

The following conclusions are drawn from the analysis of safety data in this study:

- In Period 1, 1 patient (0.52%) receiving Lantus-Apidra died following a cardio-respiratory arrest; in the opinion of the Investigator, the event was not related to treatment with Lantus or Apidra. There were no deaths during Period 2.
- In Period 1, 2 patients (1.04%) receiving Lantus-Apidra and 1 patient (0.51%) receiving Premix discontinued study medication permanently due to an adverse event. In Period 2, 4 patients (2.31%) receiving Premix discontinued study medication permanently due to an adverse event.
- In Period 1, 4 patients (2.08%) receiving Lantus-Apidra and 2 patients (1.02%) receiving Premix experienced coma/loss of consciousness, and 4 patients (2.08%) receiving Lantus-Apidra and 1 patient (0.51%) receiving Premix experienced a seizure. In Period 2, 1 patient (0.57%) receiving Lantus-Apidra and 1 patient (0.58%) receiving Premix experienced coma/loss of consciousness, and 1 patient (0.57%) receiving Lantus-Apidra experienced a seizure.
- Serious adverse events experienced by ≥ 2 patients in Period 1 were hypoglycemic seizure (3 patients, 0.77%), and hypoglycemia, hypoglycemic coma, and dyspnea (2 patients each, 0.52%). Serious adverse events experienced by ≥ 2 patients in Period 2 were coronary artery disease (3 patients, 0.86%), followed by hypoglycemia (2 patients, 0.57%).
- The adverse event profile for patients receiving Lantus-Apidra and patients receiving Premix were similar in both treatment periods. In Period 1, 48.96% of patients receiving Lantus-Apidra and 42.86% of patients receiving Premix experienced at least 1 TEAE. In Period 2, 36.36% of patients receiving Lantus-Apidra and 37.57% of patients receiving Premix experienced at least 1 TEAE. In Period 1, the TEAE experienced by the most patients overall was upper respiratory infection (17 patients, 4.38%), followed by sinusitis (15 patients, 3.87%), nasopharyngitis (14 patients, 3.61%), and nausea (8 patients, 2.06%). In Period 2, the TEAE experienced by the most patients overall was peripheral edema (15 patients, 4.30%), followed by diarrhea and nasopharyngitis (9 patients each, 2.58%), sinusitis (8 patients, 2.29%), and upper respiratory infection (7 patients, 2.01%).
- Hypoglycemia episodes were common, occurring in 66.67% of patients receiving Lantus-Apidra and 68.37% of patients receiving Premix in Period 1. Hypoglycemia episodes occurred in 64.20% of patients receiving Lantus-Apidra and 67.63% of patients receiving Premix in Period 2. Most of these events were mild.
  - Severe hypoglycemia occurred in 11.46% and 12.24% of patients receiving Lantus-Apidra and patients receiving Premix in Period 1, respectively. Severe hypoglycemia occurred in 11.93% and 10.98% of patients receiving Lantus-Apidra and patients receiving Premix in Period 2, respectively. There was no significant difference in the incidence of severe hypoglycemia between treatment groups in either Period 1 or Period 2.

- Serious hypoglycemia occurred in 2.60% and 1.53% of patients receiving Lantus-Apidra and patients receiving Premix in Period 1, respectively. Serious hypoglycemia occurred in 1.14% and 0.58% of patients receiving Lantus-Apidra and patients receiving Premix in Period 2, respectively. There was no significant difference in the incidence of serious hypoglycemia between treatment groups in either Period 1 or Period 2.

- Nocturnal hypoglycemia episodes occurred in 41.15% of patients receiving Lantus-Apidra and 39.29% of patients receiving Premix in Period 1. Nocturnal hypoglycemia episodes occurred in 30.68% of patients receiving Lantus-Apidra and 35.26% of patients receiving Premix in Period 2. Most of these events were mild.
  - Severe nocturnal hypoglycemia occurred in 4.69% and 3.57% of patients receiving Lantus-Apidra and patients receiving Premix in Period 1, respectively. Severe nocturnal hypoglycemia occurred in 3.98% and 4.05% of patients receiving Lantus-Apidra and patients receiving Premix in Period 2, respectively. There was no significant difference in the incidence of severe nocturnal hypoglycemia between treatment groups in either Period 1 or Period 2.
  - Serious nocturnal hypoglycemia occurred in 0.52% and 0% of patients receiving Lantus-Apidra and patients receiving Premix in Period 1, respectively. The difference was not significant. Serious nocturnal hypoglycemia did not occur in either treatment group in Period 2.
- The proportions of patients with abnormal hematology values were small, except for RDW. In Period 1, abnormally high RDW values were observed in 50 patients (26.46%) receiving Lantus-Apidra and in 39 patients (20.42%) receiving Premix. In Period 2, abnormally high RDW values were observed in 50 patients (28.74%) receiving Lantus-Apidra and in 49 patients (28.99%) receiving Premix. The proportions of patients with values other than serum glucose (ie, routine chemistry panel, serum lipids) were generally low.
- Clinically significant ECG abnormalities were infrequent during abnormal chemistry the study. In the Lantus-Apidra to Premix group, 1 patient (0.6%) had a clinically significant abnormal ECG at Week 24 or early withdrawal. In the Premix to Lantus-Apidra group, 2 patients (1.1%) had a clinically significant abnormal ECG at Week 24 or early withdrawal.
- Mean changes from baseline and from crossover baseline in systolic and diastolic blood pressure, and pulse rate were minor and not clinically meaningful.