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| Sponsor/Company: sanofi-aventis | Study Identifier: NCT00174824 |
| Drug substance: Lantus (HOE901) | Study code: LTS6036 (HOE901-4016) |
| Title of the study: Evaluation of diabetic retinopathy progression in subjects with type 2 diabetes mellitus treated with Insulin. | |
| Study centers: Multicenter with a total of 55 centers, 39 in the United States and 16 in Canada. | |
| Study period: Date first patient enrolled: 18 June 2001 Date last patient completed: 27 April 2007 | |
| Phase of development: Phase 4 | |
| Objectives: The primary objective of this study was to compare the percentage of patients with a 3-step or greater progression in the Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy scale at study endpoint after treatment with insulin glargine or neutral protamine hagedorn (NPH) human insulin. The secondary objectives were to compare the 2 treatment groups with regard to percentage of patients with a 3-step or greater progression in the ETDRS retinopathy scale after 3, 6, 12, 24, 36, 48, and 60 months of treatment, the development of proliferative retinopathy, distribution of change on the ETDRS retinopathy severity scale, development of clinically significant macular edema, overall hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) lowering effects, overall incidence and rate of symptomatic hypoglycemia, symptomatic nocturnal hypoglycemia, and severe hypoglycemia, daily insulin dose, and safety including adverse events (AEs), lipids and weight change. | |
| Methodology: This was an open-label, NPH human insulin-controlled, stratified, randomized (1:1) parallel-group study. Eye efficacy parameters were analyzed based on masked, systemic, prospective grading of standard 7-field stereoscopic fundus photography by a central grading facility. | |
| Number of patients: Planned: 840 (420 patients per group); Randomized: Lantus® 515 and NPH 509; Treated and efficacy: intent to treat population (ITT) Lantus® 513 and NPH 504, per protocol population (PP) Lantus® 374 and NPH 363; safety: Lantus® 514 and NPH 503 | |
| Diagnosis and criteria for inclusion: Patients, 30 to 70 years of age with type 2 diabetes and either no or mild retinopathy (ETDRS score up to and including 47/47), treated with oral agent(s) alone, insulin alone, or oral agent(s) in combination with insulin for at least 3 months prior to study entry, and a baseline HbA1c between 6.0 and 12.0%, inclusive. | |
| Investigational product: Insulin glargine (Lantus®) | |

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| <p>Dose: US sites: vial containing 10 mL solution (100 IU/mL) Canadian sites: cartridge containing 3 mL solution (100 IU/mL)</p> |
| <p>Administration: Subcutaneous injection once daily at bedtime</p> |
| <p>Duration of treatment: 5 years (60 months) Duration of observation: From June 2001 to April 2007</p> |
| <p>Reference therapy: NPH human insulin Humulin® N</p> <p>Dose: US sites: vial containing 10 mL solution (100 IU/mL) Canadian sites: cartridge containing 3 mL solution (100IU/mL)</p> <p>Administration: Subcutaneous injection twice daily, in the morning and at bedtime</p> |
| <p>Criteria for evaluation:</p> <p>Efficacy: The primary efficacy measure was percent of patients with a 3-step or greater progression in diabetic retinopathy on the ETDRS scale from baseline to study endpoint.</p> <p>The secondary efficacy measures were a 3-step or greater progression from baseline in the ETDRS retinopathy scale at each study visit, change from baseline in the ETDRS retinopathy severity scale at each study visit and study endpoint, developing proliferative diabetic retinopathy (PDR) during treatment, developing clinically significant macular edema (CSME), retinal thickening score at each study visit and at study endpoint, achieving target HbA1c \leq6.5, 7.0, and 8.0% at each study visit and at study endpoint, change from baseline in self-monitored and laboratory-determined FPG at each study visit and at study endpoint, change from baseline in body weight at each study visit and at study endpoint, daily dose of basal insulin (glargine and sum of morning and bedtime doses for NPH) and short-acting insulin on the day prior to each study visit and at study endpoint, total daily dose of insulin (basal and short-acting) on the day prior to each study visit and at study endpoint, and yearly rate of clinically important hypoglycemia, symptomatic hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia.</p> <p>Safety: Safety assessment included AEs, serious hypoglycemia, ophthalmologic exams, physical exams, vital signs, lipids, clinical chemistry, hematology, and urinalysis.</p> |
| <p>Statistical methods:</p> |
| <p>Efficacy: Primary efficacy: The primary efficacy analysis compared the proportions of patients with 3-step or greater progression in ETDRS from baseline to endpoint between the 2 treatments. The primary analysis population was the per-protocol (PP) population with adjustment for baseline HbA1c strata. The primary efficacy analysis was conducted using a generalized linear model (SAS GENMOD) with the response of 3-step or greater progression in the ETDRS from baseline to endpoint as the dependent variable, treatment and baseline HbA1c strata as the classified independent variables, and with binomial distribution and identity link function.</p> <p>A stepwise closed testing approach was used for the primary efficacy analyses. Step 1 was to assess noninferiority. The upper bound of the 95% CI (Lantus – NPH) was compared with the noninferiority margin of 10%. Noninferiority was demonstrated if the upper bound of the CI for the treatment difference in patients with a 3-step or greater progression in the ETDRS from baseline to endpoint was \leq10%. Step 2 was to test for noninferiority (ie, whether the upper bound of the 95% CI was \leq10%) and superiority (<0%) on the ITT population. Because this stepwise approach was a closed procedure, the overall significance alpha level was controlled at the 0.05 level.</p> |

Secondary efficacy:

The analysis of binary indicator (Yes/No) of a 3-step or greater progression in the ETDRS retinopathy scale at each study visit was performed identically to that of the primary efficacy variable. Outcomes based on fundus photography were primarily based on the per-protocol population (including the primary outcome) but they were also analyzed for the ITT population. The ITT population was used to analyze all other outcome variables. For development of proliferative diabetic retinopathy, development of CSME, and the ETDRS progression/regressions, the Cochran-Mantel-Haenszel test stratified by pooled center was used to test the hypothesis of no difference between the treatment groups. For HbA1c, FPG, clinical laboratory determined FPG, and body weight, the change from baseline to each study visit and to study endpoint was analyzed using an analysis of covariance (ANCOVA) to test the hypothesis that there was no difference between the 2 treatment groups. The model included fixed effect terms for treatment, pooled center and stratum ($6.0\% \leq \text{HbA1c} \leq 9.0\%$ or $9.0\% < \text{HbA1c} \leq 12\%$) with the corresponding baseline value as a covariate. The mean daily total dose of insulin basal and insulin short-acting over all study visits was analyzed using an analysis of variance (ANOVA) to test the hypothesis that there was no difference between the 2 treatment groups. The ANOVA model included fixed effect terms for treatment and pooled centers and strata (≥ 6.0 to ≤ 9.0 HbA1c or >9.0 to ≤ 12 HbA1c).

Hypoglycemia:

The primary analysis for hypoglycemia was the yearly rate of clinically important hypoglycemia (defined as required assistance from another person to treat and/or accompanied by a plasma glucose ≤ 36 mg/dL) from Month 3 to end-of-study. Also analyzed were symptomatic, nocturnal and severe hypoglycemia. The number of patients at risk was provided for each time period (Month 3 to end-of-study). Yearly rates of all types of hypoglycemia were compared between treatment groups using rank analysis of variance.

Summary:**Baseline data:**

At baseline, both treatment groups were comparable in terms of demography and disease status with a mean age of 55.1 years, 53.9% males, 85.4% Caucasians and a mean body mass index of 34.3kg/m². Patients had T2DM for a mean of 10.7 years, and the majority (68.6%) was treated with insulin at baseline. At baseline, more patients had retinopathy in the Lantus versus the NPH group (15.6%, versus 12.1%) and mean baseline ETDRS scores were also higher in the Lantus group (3.06 for Lantus, 2.85 for NPH). At baseline, clinically significant macular edema in the right eye were found in 10 patients in the Lantus group, versus 3 patients in the NPH group, and the corresponding figures for the left eye were 12 patients and 3 patients, respectively. Mean baseline HbA1c and FPG values were 8.41% and 189.7 mg/dL, respectively in the Lantus group compared to 8.31% and 179.6 mg/dL in the NPH group.

Efficacy:

At study endpoint, a 3-step ETDRS progression was observed in 53 of 374 patients in the Lantus group (14.2% of the PP population) and 57 of 363 Patients in the NPH group (15.7% of the PP population) showing noninferiority of Lantus over NPH (95% CI -7.02% to 3.06%). Similar results were found for the ITT population (12.5% Lantus, 14.6% NPH, 95% CI -6.29% to 2.09%).

There was no significant difference from baseline to study endpoint between treatments in the distribution of changes in ETDRS score. Overall p-value for last observation carried forward (LOCF) analysis was 0.4251 and overall mean change in ETDRS score from baseline to study endpoint was 0.94 for the Lantus group, and 0.95 for the NPH group ($p=0.9061$). The mean ETDRS score in the 2 groups changed in parallel over time.

Clinically significant macular edema developed in 15.6% of the patients in the Lantus group versus 14.6% in the NPH group ($p=0.7674$, PP population), and proliferative diabetic retinopathy developed in 5.4% of the patients in the Lantus group versus 3.9% the NPH group ($p=0.5064$).

At baseline, mean HbA1c scores were slightly lower (0.1%) and stayed lower at all postbaseline visits (0.1% to 0.2%) in the NPH group compared to the Lantus group, with an LS mean difference in change from baseline to study endpoint between the groups (L – N) at study endpoint of 0.21% ($p=0.0053$).

More patients in the NPH group than in the Lantus group achieved HbA1c values of 7% or less, and 6.5% or less, at each visit. Fasting plasma glucose was the target of titration in both treatment groups, and the LS mean difference between treatment groups was -0.73 mg/dL ($p=0.8414$). Less insulin was used in the Lantus group than in the NPH group (61.8 IU versus 72.3 IU) at

endpoint and at every visit throughout the study but the mean total insulin dose at endpoint was similar between treatments (88.6 IU for Lantus, 91.8 IU for NPH). At study endpoint, short-acting insulin was used by 67.2% of Lantus-treated patients and by 69.2% of NPH-treated patients.

Lantus-treated patients gained on average of 1.2 kg less body weight than NPH-treated patients over the 5-year study ($p=0.0505$), and experienced less severe and clinically important hypoglycemia. Clinically important hypoglycemia was seen in 35.5% of Lantus-treated patients versus 43.7% of NPH-treated patients ($p=0.0083$), and severe hypoglycemia occurred in 7.6% of the Lantus group and in 11.1% of the NPH group ($p=0.0439$).

Safety:

Over the 5 years of the trial, a similar safety profile of the 2 types of insulin, insulin glargine or NPH insulin was observed with no new or unusual safety concerns for insulin glargine. A high incidence of 95% treatment-emergent adverse events (TEAEs) was reported for both treatment groups that was mostly unrelated to treatment. The percentage of patients with serious TEAEs was similar in both treatment groups, 41.1% in the Lantus group and 42.7% in the NPH group. Likewise, the percentage of patients who permanently discontinued due to TEAEs was similar, 3.1% in the Lantus and 2.3% in the NPH group. The percentage of patients with TEAEs leading to death was low, 2.7% in the Lantus group and 2.2% in the NPH group.

The most frequently reported TEAEs were infections and infestations, musculoskeletal and connective tissue disorders, nervous system disorders, gastrointestinal disorders, general disorders and administration site conditions, and eye disorders. The incidences of these TEAEs were very similar between treatment groups with the exception of eye disorders with a slightly higher prevalence in the Lantus group compared to the NPH group (40.3% versus 33.2%). These were derived from observer-dependent (not blinded to treatment group) assessments rather than based on the blinded fundus photograph readings, which were the basis for the evaluation of the primary and secondary outcomes. The most commonly occurring eye disorder was cataract with a slightly higher incidence in the Lantus group (18.1%) compared to the NPH group (15.9%) but a medical history of cataracts at baseline was already more common in the Lantus group (10.0%) than in the NPH group (8.5%). The frequency of other TEAEs was comparable between both treatment groups and no differences in changes from baseline in laboratory parameters, or in the incidence of clinically important changes in the values of these laboratory variables was noted.

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