*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-aventis | **ClinicalTrials.gov Identifier:** | NCT00467376 |
| | | **Study Code:** | APIDR_L_00348 |
| **Generic drug name:** | Insulin Glulisine | **Date:** | 15 May 2009 |

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| **Title of the study:** | A 12-week, multicenter, controlled, open-label, 3:1 randomized, parallel clinical trial comparing insulin glulisine with insulin lispro injected subcutaneously in patients with type 1 or type 2 diabetes mellitus also using Lantus® | | |
| **Investigator(s):** | Prof. Wenying Yang, MD | | |
| **Study center(s):** | 10 centers | | |
| **Publications (reference):** | None | | |
| **Study period: 18 months**<br>Date first patient enrolled: 26-Feb-2007<br>Date last patient completed: 12-Jun-2008 | | **Phase of development:**<br>III | |
| **Objectives:** | Primary:<br>- To compare the efficacy (the change in HbA1c at week 12) of insulin glulisine with insulin lispro in patients with type 1 or type 2 diabetes mellitus<br><br>Secondary:<br>- To compare insulin glulisine with insulin lispro in terms of blood glucose parameters and treatment satisfaction in patients with type 1 or type 2 diabetes mellitus<br>- To compare the occurrence of hypoglycemia of insulin glulisine with insulin lispro<br>- To compare the safety of insulin glulisine with insulin lispro in patients with type 1 or type 2 diabetes mellitus | | |
| **Methodology:** | A multicenter, controlled, open-label, 3:1 randomized, parallel-group clinical trial | | |
| **Number of patients:** | Planned: 480 | Randomized: 484 | Treated: 484 |
| **Evaluated:** | Efficacy : 484(Full analysis set); 477(Per-protocol set) | Safety: 484 | |

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| **Diagnosis and criteria for inclusion:** | Patients with diabetes mellitus (type 1 or type 2) aged 18-70 years with HbA1c ranging from 6.5% to 11.0% measured at screening visit. Patient should have received at least three months of continuous insulin treatment prior to study entry. | |
| **Investigational product:**<br><br>Dose:<br><br>Administration: | Insulin glulisine (3mL/vial, 100IU/mL) + insulin glargine(3mL/vial, 100IU/mL) during the 12-week treatment period<br><br>individually dosed as appropriate<br><br>injected subcutaneously 0 to 15 minutes before a meal, t.i.d.; insulin glargine once daily before breakfast | |
| **Duration of treatment:** 12 weeks | | **Duration of observation:** 24 hours |

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| **Reference therapy:** | Insulin lispro (3mL/vial, 100IU/mL) + insulin glargine(3mL/vial, 100IU/mL) during the run-in period (all patients) and 12-week treatment period |
| Dose: | individually dosed as appropriate |
| Administration: | injected subcutaneously 0 to 15 minutes before a meal, t.i.d.; insulin glargine once daily before breakfast |
| **Criteria for evaluation:** | |
| **Efficacy:** | Efficacy evaluations included HbA1c, blood glucose parameters, quality of life, insulin dose, hypoglycemia events and blood lipid panel. The primary efficacy measure was the change from baseline to week-12 in the blood level of HbA1c. |
| **Safety:** | Safety evaluations included medical history, adverse events (AEs), vital signs, body weight, physical exam, electrocardiogram (ECG, 12-lead), hematology, blood chemistry and urinalysis. |
| **Statistical methods:** | The primary efficacy variable (mean change in HbA1c from baseline to week 12) as well as other continuous variables were analyzed using an Analysis of Covariance (ANCOVA), with treatment and study centers as factors, baseline as a covariate.<br><br>For the primary endpoint, the equivalence margin was defined as 0.4% as per protocol. The 95% confidence interval of the between-group difference in mean change from baseline in the ANCOVA was used for equivalence assessment.<br><br>Categorical variables (e.g. frequency of hypoglycemic events) were presented by frequency distributions. Treatment groups were compared using the Cochran-Mantel-Haenszel (CMH) test stratified by center.<br><br>The primary efficacy analysis was based on full analysis set population. The significance level was set at 0.05 for all statistical tests (two-sided). |

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| **Summary:**<br>Efficacy results: | In the study, 92.3% patients in the glulisine group and 95.0% in the insulin lispro group were type 2 diabetes mellitus; mean duration of their diabetes mellitus was 10.3 vs. 10.3 years and mean duration of insulin treatment prior to study entry was 3.3 vs. 3.2 years, respectively.<br><br>After 12-week treatment, the reduction of HbA1c level from baseline to week-12 was -0.81% in insulin glulisine group and -0.94% in insulin lispro group, respectively, which were highly significant within each group (both *P*=0.000), The primary objective of the study, to demonstrate clinical equivalence of insulin glulisine compared with insulin lispro in the change in HbA1c from baseline to week-12, was achieved and demonstrated by the 95% confidence interval (CI) being within the predefined equivalence range of [-0.4%, 0.4%]. The adjusted least square mean [95% CI] both from the full analysis set was 0.05% [-0.14, 0.23], and that in the per-protocol analysis set was 0.03% [-0.15, 0.22], well within the above equivalence range. All these showed that both treatments significantly decreased HbA1c value over 12 weeks treatment.<br><br>The treatment effect on reduction of HbA1c value was also assessed using proportion of patients who met targeted HbA1c levels after 12-week treatment. 15.7% patients (57 out of 363) in insulin glulisine and 13.2% (16 out of 121) in insulin lispro met the level of HbA1c <7.0%, respectively (*P*=0.5117). Similar results were found with respect to HbA1c value <6.5% (*P*=0.6853). This also showed similar efficacy.<br><br>Plasma glucose levels after standard breakfast were assessed, including levels of premeal, 1- and 2-hour postmeal, etc. These secondary endpoints measurement were compared between baseline and week 12. It was found that plasma glucose levels of premeal, 1- hour postmeal showed statistically significant decrease compared to baseline within each treatment group (all *P*<0.02). However, no significant difference was found for these glucose endpoints between the two treatment groups (all *P*>0.40) (table below). All of these indicated that insulin glulisine and insulin lispro have comparable effect on the decrease in plasma glucose levels after standard breakfast. |

| | Glulisine | | Lispro | |
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| | n | Mean | n | Mean |
| Premeal glucose level | | | | |
| Baseline | 363 | 8.56 | 121 | 8.58 |
| Week 12 | 363 | 7.70 | 121 | 7.85 |
| Change from baseline to week 12 [c] | 363 | -0.85 [a] | 121 | -0.73 [a] |
| 1-hour postmeal glucose level | | | | |
| Baseline | 363 | 11.60 | 121 | 11.88 |
| Week 12 | 363 | 10.80 | 121 | 10.94 |
| Change from baseline to week 12 [c] | 363 | -0.80 [a] | 121 | -0.94 [b] |
| 2-hour postmeal glucose level | | | | |
| Baseline | 363 | 10.64 | 121 | 10.94 |
| Week 12 | 363 | 10.19 | 121 | 10.37 |
| Change from baseline to week 12 [c] | 363 | -0.44 [b] | 121 | -0.57 |

Note: a: *P*<0.01 within group; b: *P*<0.05 c: *P*>0.4 between group

The incidence of all categories of symptomatic hypoglycemia (including severe or nocturnal hypoglycemia) was comparable between insulin glulisine and insulin lispro group (31.13% vs. 33.06%) during 12-week on-treatment period.

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| | The insulin doses used were comparable between the two treatment groups at baseline (*P*=0.1495). The change in insulin dose from baseline to week-12 did not differ statistically significantly between treatment groups (*P*=0.2347). At week 12, both treatment groups presented a small similar increase in their insulin doses (e.g., glulisine vs. lispro: total daily insulin dose: +5.49 vs. +4.06IU; Insulin glargine doses: +2.98 vs. +3.22IU).<br><br>Diabetes Treatment Satisfaction Questionnaire (8 questions, 0-6 points) was used for quality of life assessment. Overall, an increase of satisfaction after a 12-week treatment was found both in the insulin glulisine group (+2.05 points, *P*=0.000) and insulin lispro group (+2.11 points, *P*=0.000), compared to baseline, respectively; the increase of scores was similar between the two treatment groups (*P*=0.4444). Except reported frequency of hypoglycemia episode, other 7 components basically presented a significant improvement compared to baseline within each treatment group. Also no significant difference was found between the two treatment groups (all *P*>0.10). These results showed that patients' quality of life was improved on insulin glulisine. |
| Safety results: | 30.03% (109 out of 363) patients in the insulin glulisine and 33.88% (41 out of 121) patients in the insulin lispro reported at least one TEAE during the 12-week treatment periods. The most common TEAEs were metabolism and nutrition disorder (13.22%), urinary system diseases (5.51%), myocardium, endocardium and pericardium valve damage (4.13%), respiratory system diseases (3.86%) in the insulin glulisine group and metabolism and nutrition disorder (19.01%), respiratory system diseases (5.79%), myocardium, endocardium and pericardium valve damage (4.13%) in the insulin lispro group.<br><br>Nine (9) patients (glulisine: 3; lispro:6) reported 12 TEAEs as serious in the study but none was considered by investigator as related to study drug. 11 patients (glulisine: 7; lispro:4) were withdrawn due to TEAEs, of them 10 patients were due to metabolism and nutrition disorders. No death occurred in the study. |
| **Date of report:** | 11-Dec-2008 |