These results are supplied for informational purposes only.

Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00540709
		Study Code:	HOE901_4036
Generic drug name:	insulin glargine	**Date:**	11 October 2007

Title

Comparison of Multiple Daily Injection Regimen with Once-Daily Insulin Glargine [rdna origin] Basal Injection and Mealtime Insulin Lispro, and Continuous Subcutaneous Insulin Infusion (CSII) Therapy with Insulin Lispro: a Randomised, Open, Parallel Study

Investigator(s), study site(s)

Prof Geremia.B.Bolli, Department of Internal Medicine, Policlinico Monteluce, 06126 Perugia, Italy
Prof Philip Home, Department of Diabetes and Metabolism, The Medical School, Newcastle Upon Tyne, UK
Dr David Kerr, Diabetes and Endocrinology Centre, The Royal Bournemouth Hospital ,Bournemouth UK
Prof. Jean Louis Selam, Department of Diabetes and Endocrinology, Hotel Dieu, 75181 Paris, Cedex, France
Prof Fabio Capani, Servizio di Diabetologia, Oespedale Civile, 65100 Pescara, Italy

Study duration and dates	Date first subject was enrolled: 12. November 2002 Date last subject completed the study: 15. September 2003	**Phase** IV

Objectives

The primary objective of this exploratory study was to investigate whether a once-daily basal injection of insulin glargine together with mealtime injections of insulin lispro achieves equivalent glycaemic control (glycated haemoglobin, HbA1c) to administration of insulin lispro by continuous subcutaneous insulin infusion (CSII) in Type 1 diabetic subjects.

The secondary objectives of the study were:

1. To compare glycaemic control given by the treatment regimens as assessed by: Fasting Blood Glucose, Post Prandial Glucose, and response rates (ie the frequency at which blood glucose scheduled targets are met)
2. To Compare MAGE index using 8 point complete daily blood glucose profile (measured 3 times during last two weeks before each scheduled visit).

3. To compare safety and tolerability between the treatment regimens, including: the proportion of subjects with hypoglycaemia, the occurrence of hypoglycaemic events; the incidence of severe and nocturnal hypoglycaemic events and the occurrence of adverse events, serious adverse events and abnormal laboratory values in the two groups.
4. To compare treatment costs and subject satisfaction

Study design

This study was a randomised, open-label, parallel-group comparison of two insulin therapy regimens (insulin glargine once-daily basal injection + insulin lispro mealtime injections versus insulin lispro administered by continuous subcutaneous insulin infusion) in Diabetes Mellitus Type I subjects naïve to insulin glargine and CSII. It was performed in the UK, Italy, and France in five centers.
The study consists of a 1-week screening period followed by randomisation (1:1 ratio) into a 6- month (24 week) treatment period (including 4-weeks forced titration) and a follow-up assessment 2 weeks after final dose. The initial dose of insulin and the treatment dose reached after the titration are chosen by the investigator using the algorithms provided in this protocol.

Number of subjects planned

It was planned that 60 subjects would be randomised; 30 in each arm, assuming a drop out rate of 15% in each arm

Inclusion criteria

Consenting males or females between 18 and 70 years of age (inclusive) with a diagnosis of type 1 diabetes mellitus for at least one year. Subjects with no previous experience with Continuous Subcutaneous Insulin Infusion (CSII) or insulin glargine, although considered capable of managing a basal-bolus regimen and meeting glycaemic targets in accordance with the protocol. HbA1c ≥ 6.5 ≤ 9.0% at screening visit with evidence of lack of insulin secretion (e.g. fasting C-peptide concentration is < 0.1 nmol/l with fasting blood glucose (FBG) > 126 mg/dl).

Treatments

Subjects were randomised (1:1) to one of the following two open-label insulin treatment regimes.
• Multiple daily injection (MDI) : Insulin glargine (basal injection once daily in the evening) + insulin lispro (prandial)
• Insulin lispro administered by continuous subcutaneous insulin infusion (CSII)
Treatment lasted for 24 weeks, including a 4- week forced titration period. Dosage was determined by the investigator according to guidance algorithms provided in the protocol.

Efficacy data

Primary efficacy data was HbA1c at week 24 (the last day of the treatment period).
Secondary efficacy data included HbA1c at Week 8 and Week 16 after starting study medication and selfmonitored blood glucose (SMBG) measurements. Analysis of SMBG measurements includes:
levels of fasting blood glucose and pre-/post prandial blood glucose (where post-prandial is measured two hours after starting a meal) and response rate (frequency that a blood glucose scheduled target is achieved). Eight-point daily blood glucose measurements (taken on 3 days in the two-week period before each visit at 3am, pre-/post prandial, and bedtime) was analysed using Mean Amplitude of Glycaemic Excursion and other derived measures defined in the statistical plan.

Safety data

Safety and tolerability data includes reports of hypoglycaemia, adverse events, serious adverse events and abnormal laboratory values.
Non-severe hypoglycaemia is an event with symptoms consistent with hypoglycaemia which does not require the assistance of another person. Blood glucose (whole blood) may be confirmed as < 72mg/dl.
Severe hypoglycaemia is defined in as an event with symptoms consistent with hypoglycaemia and which *requires the assistance* of another person and either the blood glucose level was below 36 mg/dl [2 mmol/l] or prompt recovery occurred after oral carbohydrate, intravenous glucose, or subcutaneous glucagon administration.
Nocturnal hypoglycaemia is defined as hypoglycaemia which occurs while the subject is asleep between bedtime and before getting up in the morning (i.e., before the morning determination of fasting blood glucose and before the morning injection).
'Symptoms of hypoglycaemia' include one or more of: headache, dizziness, general feeling of weakness, drowsiness, confusion, paleness, irritability, trembling, sweating, rapid heart beat, a cold clammy feeling and in severe cases: seizure, loss of consciousness, or coma.
'Requires assistance' means that the neurologic impairment was such that the subject could not help him/herself. Someone helping the subject when this was not actually necessary does not count as required assistance.

Other Assessments

Subject satisfaction with treatment (Diabetes Treatment Satisfaction Questionnaire, DTSQ) and treatment costs were compared in the two treatment groups.

Statistical procedures

This study was exploratory and descriptive statistics are primarily utilized. The inferential statistics described below were used to discover trends rather than be considered confirmatory. ANCOVA for continuous efficacy endpoints (HbA1c, FBG) with centre and group as fixed effects and baseline value as covariate and Cochran-Mantel-Haenszel statistic stratified by center for discrete endpoints (eg response rate, hypoglycaemic events). Two-sided 95% confidence intervals for treatment differences were calculated without adjustment for multiple endpoints. Demographic variables, baseline characteristics, changes in laboratory values, vital signs and adverse events were compared using a Wilcoxon Test for unpaired observations (continuous variables) or $\chi 2$ tests (discrete parameters).

Interim analysis

No interim analysis was performed.

Results - Study subjects and conduct

A total of 67 subjects were screened and entered into the study. 9 subjects were identified as screen failures prior to randomisation. 1 subject was identified as a screen failure but was randomised in error. Thus the total number of subjects classed as screen failures within the screening period came to 10. 58 subjects were randomised and 8 of these were found to be ineligible for the per protocol analysis. Thus the per protocol analysis included 50 subjects (24 CSII, 26 MDI). There were 3 major deviators in the CSII group and 4 major deviators in the MDI group. Seven subjects dropped out from the study (3 before visit

V3, 2 before visit V4 and 2 before visit V6). Three of these Drop-Outs were due to withdrawn consents, one due to an adverse event, two due to subject's compliance and one due to pregnancy.

Results – Efficacy

Differences between CSII and MDI regarding HbA1c and all secondary efficacy parameters related to blood glucose control were statistically non-significant. A significant difference was demonstrated for the treatment satisfaction DTSQ status (DTSQs) score, but no significant difference was observed for the corresponding parameter of the DTSQ change (DTSQc) score. Centre differences were observed as demonstrated by significant centre effects for some measures of glucose variability (e.g. FBG Coefficient of Variation (CV), 8-point Standard deviation (SD), Eurotouch SD, 8-point CV and Eurotouch CV).

Results – Safety

A total of 115 adverse events were reported, one of which was not treatment emergent. Treatment emergent AE were observed in 40 subjects, 18 subjects in the CSII group (32% of total) and 22 in the MDI group (39% of total). 79% (CSII) and 86% (MDI) experienced AE that were assessed as not related to the study medication, two events (both MDI) led to withdrawal from the study. 22% of events in the CSII group and 7% in the MDI group were assessed as being related to the study medication, 76% (CSII) and 69% of mild and 3% (CSII) and 0% (MDI) of severe intensity. Two Serious Adverse Events (SAEs) were observed in the CSII group. No significant differences were observed in overall incidence of hypoglycaemia for the whole study period between CSII and MDI. However, there were highly significant differences between early and late phases of the study in CSII compared to MDI, in favour of MDI.

Results – Pharmacokinetics

This was not a pharmacokinetic study

Results – Pharmacodynamics

This was not a pharmacodynamic study

Results – Quality-of-life

A significant difference was demonstrated for the DTSQs score, but no significant difference was observed for the corresponding parameter of the DTSQc score.

Results – Health economics

Comparisons from the cost of treatment analysis have shown that equivalent (non-inferior) glycaemic control can be achieved with an insulin glargine based MDI regimen at a fraction the cost of CSII : £4475.13 (CSII) and £1102.25 (MDI).

Date of report

10 October 2004