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:** NCT00399724
	Study Code: HOE901_3504
Generic drug name: insulin glargine	**Date:** 11 October 2007

Title

A multicentre, multinational, randomised, open study to establish the optimal method for initiating and maintaining *Lantus*® (insulin glargine) therapy based on a comparison of two treatment algorithms to determine optimal metabolic outcomes, safety, and satisfaction in subjects with Type 2 Diabetes Mellitus.

"AT.LANTUS": A Trial comparing Lantus® Algorithms to achieve Normal blood glucose Targets in subjects with Uncontrolled blood Sugar.

Investigator(s), study site(s)

Multinational (611 centres in 59 countries)

Study duration and dates	18 months with a six-month treatment period. First subject randomised: March 02 Last subject randomised: February 03 Last subject completed: August 03	**Phase**	IIIb/IV

Objectives

Primary objective:

To determine the optimal treatment algorithm for the clinical use of insulin glargine based on the incidence of severe hypoglycaemia.

Secondary objectives

To determine for each treatment algorithm the incidence of asymptomatic, symptomatic and nocturnal hypoglycaemia.

To determine the difference in glycaemic control as measured by HbA1c and fasting blood glucose between the treatment algorithms.

To determine the difference in glycaemic control as measured by HbA1c and fasting blood glucose between baseline and end of treatment.

To obtain safety data on the use of insulin glargine in each treatment algorithm.

To measure change in subject weight and insulin dose between baseline and end of treatment.

To determine subject quality of life and treatment satisfaction.

Study design

An open-label, randomised (1:1), controlled, two-arm parallel design. The study consisted of a screening period of up to 4 weeks and a 24-week treatment period.

Number of subjects planned

7376

Inclusion criteria

Subjects aged at least 18 years with Type 2 Diabetes Mellitus on antidiabetic treatment (oral and/or insulin therapy) for > 6 months, who require a basal long-acting insulin for the control of hyperglycaemia, with HbA1c values > 7.0% and < 12 %, and a BMI < 40 kg/m^2.

Treatments

Two treatment algorithms were compared. In the first, insulin naïve subjects commenced on a fixed dose of insulin glargine (10 IU/day) which was titrated, according to fasting blood glucose levels, by either 2, 4, 6 or 8 units of insulin on a weekly basis at clinic visits. In the second, insulin naïve subjects commenced on a dose in IU numerically equivalent to the highest of the last seven consecutive fasting blood glucose values measured in mmol/L, which was then titrated by the subjects themselves by two units every time the mean fasting blood glucose level is above target for three consecutive days. Subjects previously treated with insulin commenced insulin glargine in accordance with the recommendations documented in the Summary of Product Characteristics.

Safety data

Apart from safety parameters related to the study objectives, safety data collection was restricted to adverse event reporting.

Statistical procedures

The primary efficacy variable (frequency of severe hypoglycaemia) was evaluated using an equivalence analysis. A two-sided 90% confidence interval for the difference of the proportions of subjects who experienced severe hypoglycaemia in the two algorithms was computed, the two algorithms being declared equivalent if the 90% confidence interval is contained in the predefined equivalence bounds (-1.5%, 1.5%).

Interim analysis

No interim analysis was planned or performed.

Results - Study subjects and conduct

5033 subjects were randomised into the study in the 59 participating countries. The full analysis population included 4961 subjects. Of these, 2493 were randomised to receive insulin glargine according to algorithm 1 and 2468 according to algorithm 2. Of the subjects entering the treatment phase, 260 (5.2% of randomised subjects) left the study before its end, and 113 subjects (2.3%) were excluded for major protocol violations, leaving a completed population of 4588 subjects (92.3% of randomised subjects). Compliance with treatment was high, with >92% of subjects using study medication for at least 22 weeks. Both genders were equally represented and the median age of the cohort was 58 years. In general, subjects could be considered to have advanced diabetes, with a mean duration of disease of twelve years and a mean duration of insulin treatment of five years. Fifty five percent of subjects had late diabetic complications at entry which is representative of the type 2 population. There were no differences in the reported demographic or clinical parameters between the two study arms.

Results - Pharmacokinetics and pharmacodynamics

None

Results – Efficacy (CP)

The primary efficacy criterion for this study was the frequency of severe hypoglycaemic episodes (i.e. number of episodes in a given time period). Such episodes were infrequent in both treatment arms (30 episodes in subjects assigned to treatment algorithm 1 and 44 episodes in subjects assigned to algorithm 2). The incidence of severe hypoglycaemia during the study (i.e. number of subjects with at least one episode) was 0.9% of subjects for algorithm 1 and 1.1% for algorithm 2, the overall incidence being 1%. The projected incidence of severe hypoglycaemia would be 1.87 events per 100 subject years for treatment algorithm 1 and 2.36 per 100 subject years for treatment algorithm 2. The confidence limit of the difference in frequency was included in the predefined equivalence region, therefore the two algorithms are equivalent for the primary endpoint. The incidence of symptomatic hypoglycaemic episodes was significantly lower in the subjects in treatment algorithm 1 (26.3% of subjects compared to 29.7% for treatment algorithm 2). Incidence of nocturnal hypoglycaemia was 3.2% vs 4.1% respectively (90% confidence interval 0.0 – 1.9%). Since these differences were modest they were not considered clinically relevant. No statistical difference was observed for asymptomatic or all-night hypoglycaemic episodes. Change in blood glucose levels was a secondary outcome criterion. Both treatment algorithms led to a significant and clinically relevant fall in fasting blood glucose, nocturnal blood glucose and mean daily blood glucose, with 60.8% of subjects using treatment algorithm 1 achieving the target of ≤100 mg/dl by study end compared to 71.5% with treatment algorithm 2. There was a more rapid and significantly greater ($p < 0.001$) decrease in fasting blood glucose from baseline to endpoint in treatment algorithm 2. Similarly, HbA1c levels reduced during the study by more than one percentage point, with 11.1% of subjects meeting the target of ≤ 6.5% with treatment algorithm 1 and 14.5% with treatment algorithm 2. Again, the change in HbA1c was significantly greater ($p < 0.001$) in treatment algorithm 2. These data are compatible with a sustained improvement in glycaemic control with insulin glargine. Mean weight gain during the study was modest with both treatment algorithms (1.16 kg). Increases in insulin glargine dose from visit 2 to endpoint were significant for both algorithms ($p<0.001$) with statistical differences between the algorithms at endpoint (0.22 vs 0.25 IU/kg, $p = 0.002$). Similar results were obtained in the full analysis population and in the completed population (see Table).

	Completed Population			Full Analysis Population		
	Algo 1 (N = 2315)	**Algo 2 (N = 2273)**	***p* or CI**	**Algo 1 (N = 2493)**	**Algo 2 (N = 2468)**	***p* or CI**
Primary efficacy variables						
Incidence of severe hypoglycaemia (in subject centuries)	1.87	2.36	0.45;1.41 (RR)	2.21	2.68	0.49;1.39 (RR)
Secondary efficacy variables						
Incidence of any hypoglycaemia	29.8%	33.8%	0.01	29.1%	32.6%	0.01
Incidence of symptomatic hypoglycaemia	26.3%	29.7%	1.5%;5.7%	25.6%	29.2%	1.5%;5.7%
Incidence of nocturnal hypoglycaemia	3.2%	4.1%	-0.1%;1.6%	3.2%	3.9%	0.0%;1.9%
Incidence of asymptomatic hypoglycaemia	10.3%	10.3%	-1.3%;1.5%	10.0%	10.1%	-1.5%;1.5%
Adjusted mean change in Hb1Ac (%)	-1.08	-1.22	<0.001	-1.03	-1.16	<0.001
Adjusted mean change in FBG (mg/dl)	-57	-62	<0.001	-57	-61	<0.001
Adjusted mean change in NBG (mg/dl)	-41	-48	< 0.001	-41	-48	<0.001
Adjusted mean change in MBG (mg/dl)	-38	-43	0.002	-38	-43	0.002
% pf subjects at v12 with Hb1Ac ≤ 6.5 %	11.1%	14.5%	NS	10.9%	14.1%	NS
% pf subjects at v12 with Hb1Ac ≤ 7.0 %	26.2%	30.1%	0.004	25.8%	29.5%	0.005
% pf subjects at v12 with FBG ≤ 100 mg/dl	39.8%	48.2%	< 0.001	32.2%	40.8%	<0.001
Weight change (kg)	1.05	1.26	0.03	1.01	1.24	0.01
Change in insulin glargine dose v2 – v12 (IU)	18.7	21.6	0.003	18.7	21.5	0.003

CI: 90% confidence intervals for difference between algorithms; FBG: fasting blood glucose; NBG: nocturnal blood glucose; MBG: mean daily blood glucose; RR: relative risk; NS: not significant.

Results Safety (SP)

Treatment-emergent adverse events (TEAEs) were reported in 48.7% of the subjects and their overall frequency was similar in the two treatment algorithms. The most frequently encountered adverse events were respiratory tract infections and injection site reactions. In a majority of subjects, the adverse events encountered were rated as mild and moderate (> 95% of all TEAEs). Eleven percent of adverse events were considered possibly related to the study treatment, principally injection site reactions. Otherwise, the adverse events reported were unsurprising for the diabetic population included. Serious adverse events were encountered in 5.1% of subjects. Treatment discontinuation due to adverse events occurred in 47 subjects, corresponding to < 1% of all adverse events. Thirteen deaths occurred during the study (twelve during the treatment phase) and there was one case of significant overdose.

Results - Pharmacokinetics

None

Results - Pharmacodynamics

None

Results - Quality-of-life

Quality of life was evaluated on a subgroup of 1289 subjects. It improved over the study duration as assessed both with the DTSQs and DTSQc. In addition, perceived hyperglycaemia decreased during the study, whilst perceived hypoglycaemia increased. The changes in perceived hyperglycaemia and hypoglycaemia were significantly greater in subjects randomised to treatment algorithm 2. The change in perceived hypoglycaemia was significantly correlated to objectively measured blood glucose levels.

Results - Health economics

None

Date of report

2 August 2004