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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00390728
		Study Code:	HOE901_3505
Generic drug name:	insulin glargine	**Date:**	11 October 2007

Title

A phase IIIb/IV, multinational, multicentre, 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 1 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 (409 centres in 57 countries)

Study duration and dates	18 months with a six month treatment period. First patient randomised: 05.04.2002 Last patient randomised: 07.02.2003 Last patient completed: 25.08.2003	**Phase**	IIIb-IV

Objectives

Primary objective

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

Secondary objectives

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

To determine the difference in glycaemic control as measured by HbA1c and Fasting Blood Glucose (FBG) between treatment algorithms and 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 in each treatment algorithm.

To determine subject quality of life and treatment satisfaction.

Study design

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

Number of subjects planned

With an expected non-evaluable rate of approximately 20%, a total of 2346 patients (1173 in each regimen group) should be recruited.

Inclusion criteria

Subjects aged at least 18 years with type 1 diabetes mellitus who require a basal long-acting insulin for the control of hyperglycemia, with HbA1c values > 7.0% and < 12 %, and a body mass index (BMI) < 40 kg/m^2.

Treatments

Two treatment algorithms were compared. In the first, subjects commence on a dose of insulin glargine considered appropriate by the investigator, which is then titrated in order to reach a target FBG value of 80-120 mg/dl in increments of at least 10% of the previous dose (but not more than 4 IU) on a twice-weekly basis during an initial titration phase, and weekly thereafter. In the second, subjects commence on a dose of insulin glargine considered appropriate by the investigator, which is then titrated to reach the FBG target of 80-120 mg/dl in increments of 1 to 6 IU on a twice-weekly basis during an initial titration phase, and weekly thereafter.

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 was contained in the predefined equivalence bounds (-4% to -4%).

Interim analysis

No interim analysis was planned or performed.

Results - Study subjects and conduct

2442 subjects were randomised into the study in the 57 participating countries. The full analysis population included 2410 subjects. Of these, 1172 were randomised to receive insulin glargine according to algorithm 1 and 1238 according to algorithm 2. Of the subjects entering the treatment phase, 165 (6.8% of randomised subjects) left the study before its end, and 118 subjects (4.9%) were excluded for major protocol violations, leaving a completed population of 2140 subjects (88.6% of randomised subjects; 1046 in algorithm 1 and 1094 in algorithm 2). Compliance with treatment was high, with >92% of subjects using study medication for at least 22 weeks. Median age at inclusion was 34 years and there was a slight over-representation of female subjects (55.7%). The median age of the cohort at disease onset was 19 years. The median body weight at inclusion was 69 kg, corresponding to a median body mass index of 24 kg/m^2. The median fasting blood glucose levels at baseline was 179 mg/dl and the mean HbA1c was 8.51%. The

mean duration of disease was 14.8 years at onset. There were no differences in the reported demographic or clinical parameters between the two study arms.

Results - Pharmacokinetics and pharmacodynamics

None

Results - Efficacy

The primary efficacy criterion for this study was to compare the incidence of severe hypoglycaemic episodes between the two treatment algorithms in the completed population. Such episodes were observed in 7.7% of subjects assigned to algorithm 1 and in 6.8% of those assigned to algorithm 2 (7.8% and 6.7% respectively for the full analysis population). The 90% confidence limit of the difference in incidence (-2.8% to 0.9%) was included in the predefined equivalence region (-4.0% to 4.0%), thus demonstrating that the two algorithms are equivalent for the primary endpoint. Concerning this primary endpoint, it can thus be concluded that there is no difference between the two treatment algorithms in terms of the incidence of severe hypoglycaemia. There was also no significant difference in the incidence of asymptomatic, symptomatic and nocturnal hypoglycaemia between treatment algorithms.

An improvement in metabolic control as assessed by changes in fasting blood glucose and in HbA1c was observed in both groups over the course of the study. HbA1c levels fell during the study by 0.64% in algorithm 1 and by 0.72% in algorithm 2. The change in HbA1c from baseline to week 24 was not significantly different between the two treatment groups. These changes were accompanied by a general shift in the distribution of HbA1c bands towards lower values, with a decline of nearly a half in the proportion of subjects whose HbA1c was over 8%. Change in blood glucose levels was a secondary outcome criterion. Both treatment algorithms led to a fall in fasting blood glucose, nocturnal blood glucose, 3 am blood glucose and mean daily blood glucose. The change from baseline to endpoint in all three blood glucose measurements was similar in the two treatment algorithms. By the end of the study, 46.5% of subjects in algorithm 1 and 46.8% in algorithm 2 had achieved the fasting blood glucose target of 80-120 mg/dl.

Weight gain during the study was modest and did not differ between the two treatment algorithms. The mean weight gain observed was somewhat higher in males (1.08kg) than in females (0.44kg). The average daily insulin glargine dose in both algorithms increased between baseline and endpoint. Modest changes in prandial insulin dose were also observed.

The data obtained are compatible with an improvement in glycaemic control with insulin glargine in subjects with type 1 diabetes already on insulin treatment. Similar results were obtained in the full analysis population compared to the completed population (see Table). It can be concluded that both insulin glargine treatment algorithms are similar in terms of the extent of glycaemic improvement and the incidence of hypoglycaemia.

	Full Analysis Population			Completed Population		
	Algo 1 (N = 1172)	Algo 2 (N = 1238)	*p* or CI for algorithms	Algo 1 (N = 1046)	Algo 2 (N = 1094)	*p* or CI for algorithms
Primary efficacy variables						
Incidence of severe hypoglycaemia (< 50 mg/dl)	7.8	6.7	-2.8%;0.7%	7.7	6.8	-2.8%;0.9%
Incidence of severe hypoglycaemia (< 36 mg/dl)	5.9	5.1	-2.3%;0.7%	5.8	5.0	-2.4%;0.8%
Secondary efficacy variables						
Incidence of any hypoglycaemia	84.8%	84.2%	NS	86.0%	86.4%	NS
Incidence of symptomatic hypoglycaemia	78.1%	77.9%	-2.9%;2.7%	79.7%	80.1%	-2.5%;3.2%
Incidence of asymptomatic hypoglycaemia	50.1%	47.7%	-5.7%;1.0%	51.0%	49.5%	-5.0%;2.1%
Incidence of nocturnal hypoglycaemia	21.8%	21.0%	-3.5%;2.0%	22.6%	22.1%	-3.4%;2.5%
Adjusted mean change in Hb1Ac (%)	-0.60	-0.68	NS	-0.64	-0.72	NS
Adjusted mean change in FBG (mg/dl)	-58	-60	NS	-57	-59	NS
Adjusted mean change in NBG (mg/dl)	-35	-33	NS	-34	-32	NS
Adjusted mean change in MBG (mg/dl)	-22	-24	NS	-23	-25	NS
% of subjects at V12 with Hb1Ac ≤ 6.5 %	9.9%	11.1%	NS	10.4%	11.0%	NS
% of subjects at V12 with Hb1Ac ≤ 7.0 %	25.9%	25.7%	NS	26.4%	26.2%	NS
% of subjects at V12 with FBG 80-120 mg/dl	46.6%	46.5%	NS	46.5%	46.8%	NS
Weight change (kg)	0.77	0.67	NS	0.81	0.65	NS
Change in insulin glargine dose (IU [IU/kg])	5.78 [0.07]	5.95 [0.08]	NS	5.7 [0.07]	5.9 [0.08]	NS

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

Results - Safety

Treatment-emergent adverse events (TEAEs) were reported in 51.3% 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 or moderate (96.5% of all TEAEs). 10.0% 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 4.4% of subjects. Treatment discontinuation due to adverse events occurred in 15 subjects, corresponding to < 1% of all adverse events. One death occurred during the study.

Results - Pharmacokinetics

None

Results - Pharmacodynamics

None

Results - Quality-of-life

Diabetes-related quality of life improved over the study duration as assessed both with the Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) and the DTSQ change version (DTSQc). Significant improvements were also apparent for perceived hyperglycaemia. There was no significant change in perceived hypoglycaemia over the study period as measured with the DTSQs, although the

DTSQc, revealed a decrease in this parameter. The changes in perceived hypoglycaemia, and to a lesser extent perceived hyperglycaemia, were significantly correlated with objectively measured blood glucose levels.

Results - Health economics

None

Date of report

9 August 2004