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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00552370
		Study Code:	HOE901_4045
Generic drug name:	Insulin Glargine	**Date:**	14 December 2009

Title of the study: Glycemia optimization treatment (GOT): to assess the safety of glucose control as measured by the frequency of severe hypoglycemia events using dosing algorithms based on different fasting blood glucose goals with Lantus® (insulin glargine [rDNA origin]) in adult individuals with type 2 diabetes who have not achieved the target A1c goal of <7% with oral hypoglycemia agents: a randomized, open-label, parallel-design trial (HOE 901/4045)

Investigator(s): Robert Tanenberg, MD, FACP at The Brody School of Medicine at East Carolina University, Greenville, NC, US and Ariel Zisman MD at University of Miami School of Medicine, Miami, FL, US

Study center(s): Multicenter – 1200 US sites

Publications (reference):

Strange P. Treat-to-target insulin titration algorithms when initiating long or intermediate acting insulin in Type 2 diabetes. Journal of Diabetes Science and Technology, 2007;1(4):540-8.

Tanenberg RJ, Zhang Q, Zisman A. Psychosocial adjustment and outcomes of glycaemic control with basal insulin therapy in patients with type 2 diabetes mellitus (T2DM) [abstract]. Diabetologia. 2007;50 Suppl 1: Abs 1054. 43rd Annu Meet Eur Assoc Study Diabetes (EASD); 2007 Sep 17-21; Amsterdam, The Netherlands.

Zisman A, Miller M, Tanenberg R. Relationship between prior mild-moderate hypoglycaemic events and the risk of subsequent severe hypoglycaemia in patients with type 2 diabetes mellitus treated with basal insulin according to fasting BG targets: a time-dependent covariate analysis [abstract]. Diabetologia. 2007;50 Suppl 1: Abs 0184. 43rd Annu Meet Eur Assoc Study Diabetes (EASD); 2007 Sep 17-21; Amsterdam, The Netherlands.

Tanenberg RJ, Zhang Q, Zisman A. Psychosocial adjustment and outcomes of glycemic control with basal insulin therapy. 67th Annu Sci Sess Am Diabetes Assoc (ADA), Chicago, IL (Jun 2007), Abstr. 1970-P. Diabetes 2007;56(Suppl 1).

Tanenberg RJ, Zhang Q, Zisman A. Psychosocial adjustment and outcomes of glycemic control with basal insulin therapy. Poster presented at: 67th Scientific Session of the American Diabetes Association (ADA); June 22-26, 2007; Chicago, Illinois.

Tanenberg RJ, Zisman A, Stewart JA. Glycaemia optimization treatment (GOT): Glycaemic control and rate of severe hypoglycaemia for 5 different dosing algorithms of insulin glargine (GLAR) in patients with type 2 diabetes mellitus (T2DM) 42nd Annu Meet Eur Assoc Study Diabetes (EASD), Copenhagen and Malmoe (Sep 2006), Abstr. 0986. Diabetologia 2006;49(Suppl 1):601-2..

Tanenberg RJ, Zisman A, Stewart JA. Glycaemia optimization treatment (GOT): Glycaemic control and rate of severe hypoglycaemia for 5 different dosing algorithms of insulin glargine (GLAR) in patients with type 2 diabetes mellitus (T2DM). Poster presented at: 42nd Annual Meeting of the European Association for the Study Diabetes (EASD); September 14-17, 2006; Copenhagen, Denmark

Publications (reference) *(continued)*:

Tanenberg RJ, Zisman A, Stewart J. Glycemia optimization treatment (GOT): glycemic control and rate of severe hypoglycemia for five different dosing algorithms of insulin glargine (GLAR) in patients with type 2 diabetes mellitus (T2DM). 66th Sci Sess Am Diabetes Assoc (ADA), Washington, DC (Jun 2006), Abstr. 567-P. Diabetes 2006;55(Suppl 1):A135.

Tanenberg RJ, Zisman A, Stewart J. Glycemia optimization treatment (GOT): glycemic control and rate of severe hypoglycemia for five different dosing algorithms of insulin glargine (GLAR) in patients with type 2 diabetes mellitus (T2DM). Poster Presented at: 66th Scientific Session of the American Diabetes Association (ADA); June 9-13, 2006; Washington, District of Columbia.

Tanenberg RJ, Zisman A, Stewart J. Glycemia optimization treatment (GOT): glycemic control and rate of severe hypoglycemia for five different dosing algorithms of insulin glargine (GLAR) in patients with type 2 diabetes mellitus (T2DM). Poster Presented at: The Insulin Congress; November 10-12, 2006; Washington, District of Columbia.

Tanenberg RJ, Zisman A, Stewart J. Glycemia optimization treatment (GOT): glycemic control and rate of severe hypoglycemia for five different dosing algorithms of insulin glargine (GLAR) in patients with type 2 diabetes mellitus (T2DM). Poster Presented at: The Hypoglycaemia Symposium; May 12–15 2007; Perguia, Italy.

Zisman A, Miller M, Tanenberg R. Attenuation of severe hypoglycemia (SH) risk by higher titration algorithm targets by prior mild/moderate hypoglycemia (MMH) in patients with type 2 diabetes mellitus (T2DM). Oral presentation at: 67th Scientific Session of the American Diabetes Association (ADA); June 22-26, 2007; Chicago, Illinois.

Zisman A, Miller M, Tanenberg R. Attenuation of severe hypoglycemia (SH) risk by higher titration algorithm targets by prior mild/moderate hypoglycemia (MMH) in patients with type 2 diabetes mellitus (T2DM). 67th Annu Sci Sess Am Diabetes Assoc (ADA), Chicago, IL (Jun 2007), Abstr. 0200-OR. Diabetes 2007;56(Suppl 1).

Study period:

    Date first patient enrolled: 27-Mar-2003

    Date last patient completed: 07-Mar-2005

Phase of development: IV: Postmarketing exploratory study

Objectives:

Primary Objective

To compare the frequency of severe hypoglycemia events for 5 dosing algorithms of Lantus, each of varying intensity and defined by their end-of-study target for self-monitored blood glucose (SMBG)

Secondary Objectives

To compare the percentage of patients whose final A1c was <7% at the end of the study for the 5 dosing algorithms

Additional secondary objectives were to assess whether there were differences in any of the following measures between the 5 arms of the study in terms of:

- Change in A1c from beginning to end of study

- Describe factors associated with severe hypoglycemia, such as meal patterns, exercise, or time of insulin dosing that appear to lead to such events

- Postprandial SMBG in each arm:

    – Change in the increase of the 2-hour postprandial blood glucose levels based on a 6-point profile (premeal and 2-hour postmeal SMBG for each meal [breakfast, lunch, and dinner] from the beginning to the end of the study

    – Percentage of patients who reached a 2-hour postprandial blood glucose level of ≤180 mg/dL after supper at the end of the study.

- The percentage of patients in the following 5 categories:

    – A final Alc of <7.0% and no hypoglycemia events

    – A final Alc of <7.0% with no severe hypoglycemia events, and no hypoglycemia events with SMBG <50 mg/dL

    – A final Alc of <7.0% with at least 1 confirmed hypoglycemia event of moderate intensity (SMBG <50 mg/dL), but no severe hypoglycemia events

    – A final Alc of <7.0% with at least 1 severe hypoglycemia event

    – A final Alc of ≥7.0%

- Rate of all confirmed hypoglycemia events

- Rate of all moderate to severe hypoglycemia events

- Change in weight in each treatment arm from beginning to the end of the study

- Final insulin dose in each arm at the end of the study

- Psychosocial Adjustment to Illness Scale – Self Report (PAIS-SR) --- global and each of the 7 domains:

    – Change from the beginning to end of study

    – Change in PAIS-SR scores from the initial values to end of study in relationship to the number of hypoglycemia events as documented by:

        o An SMBG <70 mg/dL or a severe hypoglycemia event or

        o An SMBG <50 mg/dL or a severe hypoglycemia event or

        o The number of severe hypoglycemia events or

        o The change in A1c

Other secondary objectives were to assess:

- The algorithm that yielded the best results in terms of hypoglycemia and glucose control for individual patients based on their baseline characteristics.

- A subanalysis on the patient's current antihyperglycemia agents

Methodology: This was a 26-week, randomized, open-label, parallel-group, 5-arm multicenter study. Patients included individuals with type 2 diabetes mellitus treated with oral antidiabetic agents who were not currently on insulin therapy. Five different dosing algorithms for insulin glargine (Lantus) were evaluated in this trial.

Patients were randomized to 1 of the following 5 treatment arms: fasting blood glucose (FBG) goal of 80 mg/dL (Arm A), 90 mg/dL (Arm B), 100 mg/dL (Arm C), 110 mg/dL (Arm D), or 120 mg/dL (Arm E).

The study consisted of a 2-week screening period, a randomization visit, and a 24-week treatment period. There was no follow-up period.

Number of patients: Planned: 6000 patients to be enrolled to yield 5100 completing the study

Randomized: 5102

Treated: 5062

Evaluated:

Efficacy: 4108

Analysis population	Treatment arm					Total
	120 mg/dL	110 mg/dL	100 mg/dL	90 mg/dL	80 mg/dL	
Screened						6240
Randomized	1007	1029	1031	1007	1028	5102
Safety	998	1021	1021	1003	1019	5062
Intent-to-treat	951	974	972	948	974	4819
Completer	929	949	952	921	942	4693
Per-protocol	825	829	814	806	834	4108

Diagnosis and criteria for inclusion: Males and females ≥18 years of age with a diagnosis of type 2 diabetes mellitus for at least 6 months with a body mass index (BMI) of ≥25.0 kg/m^2 and a hemoglobin A1c (HbAlc) ≥7.0% and who had received diabetes therapy in the previous 2 months with oral antidiabetic agents only.

Investigational product: Lantus (insulin glargine [rDNA origin] injection)

Dose: Patients were titrated using a dosing algorithm according to the weekly average of fasting SMBG in order to achieve FBG targets of 80, 90, 100, 110, and 120 mg/dL, depending on treatment arm

Administration: self-administered each day at bedtime by subcutaneous (SC) injection

Duration of treatment: 24 weeks

Duration of observation: 26 weeks, including screening

Reference therapy: None

Criteria for evaluation:

Efficacy:

Primary efficacy: severe hypoglycemia events

Secondary efficacy: HbA1c, SMBG, weight, and PAIS-SR

Safety: adverse events (AEs) reported by the patient or noted by the investigator, vital signs, and weight

Statistical methods:

Primary efficacy: Hypoglycemia event rates were determined by Poisson regression. The protocol-specified hypothesis was that the severe hypoglycemia incidence between the most and the least aggressive Lantus-treated patients would not exceed 2-fold.

Secondary efficacy: The significance of between-arm differences in the change from baseline in HbA1c and the change from baseline in the difference between preprandial and postprandial SMBG was determined by analysis of covariance (ANCOVA). The significance of between-arm differences in the percentage of responders and the percentage of patients achieving a 2-hour postprandial blood glucose concentration ≤180 mg/dL after supper at Week 24 was determined using a logistic regression model. The degree of correlation between global PAIS-SR score and the change from baseline in HbA1c and between PAIS-SR scores and hypoglycemia event rates were estimated by Pearson's and Spearman's correlation coefficients. The relationships between oral antidiabetic medication use, presence of anti-glutamic acid decarboxylase (GAD) antibodies, and C-peptide concentrations and hypoglycemia and the change from baseline in HbA1c at Week 24 were analyzed by ANCOVA.

Safety: Adverse events were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) body system category, preferred term, severity, relationship to study medication, and seriousness. Vital signs were summarized using descriptive statistics and shift tables. The number and percentage of patients with low, normal, and high values in each treatment arm were tabulated. The number and percentage of patients with predefined change abnormal (PCA) results in vital signs observations were summarized by treatment arm at Weeks 12 and 24 and overall for last-observed PCAs.

Weight and BMI were summarized using descriptive statistics (ie, number of patients, mean, standard deviations, median, minimum and maximum) by visit and treatment arm. In addition, the number and percentage of patients with weight increases or decreases greater than 5% and 10% were calculated. The change from baseline in weight was compared between treatment arms by ANCOVA.

The percentages of patients in each treatment arm with symptomatic hypoglycemia, nocturnal symptomatic hypoglycemia, and severe symptomatic hypoglycemia, as well as the number of episodes per patient, were calculated. Differences between arms were evaluated using a Cochran-Mantel Haenszel procedure.

Sensitivity Analysis:

Good Clinical Practice (GCP) noncompliance and/or scientific misconduct was identified at 5 investigator sites in other sanofi-aventis US-sponsored clinical trials. Efficacy data from 7 randomized patients at 2 of these sites (Sites 1483 and 3729) were excluded from the analyses. Sensitivity analyses with and without the data from these 2 sites were performed. Results excluding data from these 7 patients are provided in the efficacy analysis sections of this report and results including data from these 7 patients are provided in Appendix. Significant GCP noncompliance and/or scientific misconduct was identified in other sanofi-aventis US sponsored clinical trials at 3 additional sites (Sites 2366, 2447, and 3132); however, these sites did not enroll any patients for this HOE901/4045 study. Therefore, there were no data from these sites included in any datasets. All randomized patients, with the exception of those who were never treated with study medication, were included in the safety analyses.

Summary:

This study was terminated prematurely on 30 August 2004 prior to achieving the target sample size.

Overall, there were 6240 patients screened, 5062 in the Safety population, 4819 in the Intent-to-treat (ITT) population, 4693 in the Completer population, and 4108 in the Per-protocol (PP) population.

These numbers represent total, overall numbers of patients in the study. Seven patients at 2 sites, at which GCP noncompliance and/or scientific misconduct was identified in other sanofi-aventis US-sponsored clinical trials, were included only in the Safety population. The proportion of patients completing the study was comparable across treatment arms (ie, 83.3% to 85.9%). There were 775 patients who discontinued from the study. Among patients who discontinued, the most common reason for discontinuation was that the patient did not wish to continue in the study (ie, 25.3% to 31.9%).

There were no significant differences between treatment arms for any of the demographic and baseline variables for the Safety population. The study population was predominantly white (ie, 67% to 71%), 47% to 48% male, 52% to 53% female, and had a mean age of 55–56 years across treatment arms. The mean BMI ranged from 34.5 to 35.9 kg/m^2.

Efficacy results:

Primary efficacy variable: The modeled rates of severe hypoglycemia in the PP population ranged from 0.03 events/patient-year in the 120 mg/dL arm to 0.17 events/patient-year in the 80 mg/dL arm (see table below). These results show that the protocol-specified hypothesis that the severe hypoglycemia incidence between the most and the least aggressively Lantus-treated patients would not exceed 2-fold was not supported. (The lower confidence bounds exceed 2-fold.) The results were regimen-dependent; that is, the highest incidence rate of severe hypoglycemia was observed in the treatment group with the most aggressive regimen (target 80 mg/dL).

At Week 24, an approximately 4- to 6-fold increase in rate of severe hypoglycemia was observed as the FBG goal was lowered from 120 mg/dL to below 100 mg/dL, whereas at FBG targets of 110 or 100 mg/dL a lesser increment (approximately 2-fold for each arm) in rate was seen.

The risk of confirmed, clinically relevant severe hypoglycemia was no different between patients who achieved and those who did not achieve an HbA1c target of <7.0% at the end of the study. The annualized rate of confirmed, clinically relevant severe hypoglycemia for PP population patients on the most aggressive regimen was 0.17 events/patient-year (0.14 events/patient-year for those who met the HbA1c target and 0.20 events/patient-year for those who did not).

Incidence of confirmed, clinically-relevant severe hypoglycemia (Model II) (PP population), N=4108

Treatment Group	Events/Patient-Year	SE	95% CI
80 mg/dL	0.17	0.040	(0.09; 0.25)
90 mg/dL	0.11	0.026	(0.06; 0.17)
100 mg/dL	0.06	0.017	(0.03; 0.09)
110 mg/dL	0.07	0.022	(0.03; 0.12)
120 mg/dL	0.03	0.009	(0.01; 0.04)

CI = confidence interval, SE = standard error

Secondary Efficacy Variables: At Week 24 in the PP population, statistically significant reductions from baseline in mean HbA1c concentration occurred at all time points for all target FBG groups (p=0.0001) with the main reduction occurring by 12 weeks. Mean changes in HbA1c concentration at Week 24 ranged from -1.66% (120 mg/dL group) to -1.92% (80 mg/dL group). Based on comparison of these changes for each FBG titration target group to the 80 mg/dL group, the most aggressive FBG titration group (80 mg/dL) did not afford better glycemic control than the 90 or 100 mg/dL groups.

In this study of patients who were refractory to oral antidiabetic agents, the percentage of responders (patients achieving HbA1c <7.0%) in the PP population at Week 24 was regimen-dependent. Decreasing the FBG target to 80 mg/dL resulted in a greater proportion of responders, ranging from 30.2% in the 120 mg/dL arm to 44.6% in the 80 mg/dL arm (95% CI of odds: 0.33-0.42 and 0.73-0.91, respectively).

The postprandial (premeal to postmeal) changes in SMBG were essentially the same at baseline and after 24 weeks of treatment. The more aggressive FBG titration targets did not affect the peak postprandial SMBG concentrations. The mean SMBG values were decreased by a similar amount across all pre- and postmeal time points. The percentage of patients in the PP population with a 2-hour postprandial SMBG ≤180 mg/dL after supper at Week 24 ranged from 35.5% to 39.2% across treatment arms with the greatest reductions in SMBG occurring in the more aggressive treatment arms.

Comparison in the PP population of mean changes in FBG concentrations from baseline to Week 24 between the 80 mg/dL treatment arm and the other arms showed that mean changes for the 90 and 100 mg/dL groups were not significantly different from those in the most aggressive titration group.

Mean changes from baseline in weight and BMI were analyzed in the PP population. At Week 24, the weight gain and change in BMI in the 120 mg/dL group were statistically significantly lower than in the 80 mg/dL group (p=0.0070 for weight and BMI). Mean changes in weight and BMI for the 110, 100, and 90 mg/dL groups did not differ from changes in the 80 mg/dL group.

With the exception of the 90 mg/dL arm, the mean (adjusted) daily insulin doses at Week 24 in the PP population were statistically significantly lower than the 80 mg/dL arm in all treatment arms (p=0.0001). The mean (unadjusted) daily insulin dose at Week 24 was greater with increasingly aggressive FBG titration goal (61.6, 64.3, 72.4, 76.7, and 80.6 IU in the 120, 110, 100, 90, and 80 mg/dL groups, respectively).

Safety results:

The mean daily Lantus dose in the Safety population at Week 24 ranged from 61.2 IU (120 mg/dL group) to 81.3 IU (80 mg/dL group). The mean duration of Lantus treatment was similar (ie, 155 to 159 days) across treatment groups.

The 5 most frequently reported AEs were upper respiratory tract infection (range of 2.1% to 3.5% across treatment groups), sinusitis (range 1.7% to 2.5%), diarrhea (range 0.8% to 2.4%), chest pain (range 1.0% to 2.1%), and headache (range 0.9% to 2.1%). There were no possibly-related AEs affecting more than 1.0% of patients in any treatment arm with the most frequent being hypoglycemia, ranging from 0.3% to 1.0% across treatment groups from least to most aggressive FBG goal.

The only possibly-related serious adverse event (SAE) affecting more than 0.5 % of patients in any treatment arm was 'hypoglycemia. The highest incidence was observed in the 80 mg/dL arm (0.7% of patients).

Overall, 14/5062 (0.3%) patients died; most deaths were due to cardiovascular events and none were considered by the

investigator to be related to study drug. Across treatment groups, 84/5062 (1.7%) patients had a final status of discontinuing the study due to AEs, the most frequent event being possibly-related hypoglycemia.

The percentage of patients with confirmed, moderate-to-severe hypoglycemia events ranged from 8.6% to 22.0% across treatment groups in the Safety population. The percentage incidence of events was lowest in the 120 mg/dL treatment group and greatest in the 80 mg/dL treatment group. Annualized rates of occurrence of these events increased with increasingly aggressive FBG targets across the 120, 110, 100, 90 and 80 mg/dL treatment arms (0.34, 0.68, 0.76, 1.25, and 1.49 events/patient-year, respectively).

Modest increases in systolic blood pressure, diastolic blood pressure, and heart rate were observed in a small percentage (ie, 0.1% to 1.5% across all treatment arms) of patients but there was no obvious correlation to treatment arm and the changes were not considered clinically significant.

In the Safety population, the mean change from baseline to Week 24 in weight was 2.14, 2.63, 2.81, 3.03, and 2.80 kg for the 120, 110, 100, 90, and 80 mg/dL treatment arms. Mean change from baseline to Week 24 in BMI was 0.77, 0.90, 0.96, 1.08, and 0.98 kg/m2 for the treatment arms, respectively.

Date of report: 02-December-2009