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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00518427
		Study Code:	HOE901_4057
Generic drug name:	Insulin Glargine	Date:	19 March 2010

Title of the study:	A multicenter clinical trial to evaluate quality of life in patients with type 2 diabetes before and after changing therapy to a combination of insulin glargine and oral antidiabetic drugs in a real life situation (Study number HOE901/4057)
Investigator(s):	Principal investigator: Jan Bolinder, Karolinska University Hospital, SE-171 76 Stockholm, Sweden Co-investigators: Regina Wredling, Michael Alvarsson, Björn Eliasson, Areknaz Adjemian
Study center(s):	Karolinska University Hospital, Stockholm, Sweden Sahlgrenska University Hospital, Gothenburg, Sweden LäkarGruppen, Västerås, Sweden
Publications (reference):	Not applicable

Study period: Date first patient enrolled: Date last patient completed:	27-Oct-2005 27-Mar-2008	Phase of development: IV

Objectives:	Primary objective: To assess quality of life (QoL) changes and treatment satisfaction in a real life situation in patients with type 2 diabetes inadequately controlled on a combination of oral antidiabetic drugs (OAD) + Neutral Protamine Hagedorn (NPH) insulin treatment that are switched to insulin glargine. Secondary objectives: To determine: - change in glycosylated hemoglobin A1c (HbA1c) - comparison of the incidence of symptomatic hypoglycemia and severe hypoglycemia before and after introduction of insulin glargine - change in weight - change in insulin dose

Methodology:	This was a multicenter study to evaluate quality of life in patients with type 2 diabetes before and after changing therapy to a combination of oral antidiabetic drugs and insulin glargine. Patients were their own controls and the study was designed to reflect the everyday clinical care of the diabetes patient as far as possible. All decisions regarding dose adjustments, number of visits to the clinic, restrictions for the patient, concomitant medication, additional laboratory analyses etc were made by the responsible investigator. To assess the Quality of Life in the study the following self-administered questionnaires were used: Diabetes Treatment Satisfaction Questionnaire (DTSQ) 8 items The fear of hypoglycemia scale (HFS) 23 items 12-Item Well-Being Questionnaire (WBQ12) 12 items Treatment duration for the investigational product was 40 weeks.		
Number of patients:	Planned: 117	Randomized: 22	Treated: 19
Evaluated:	Efficacy/Pharmacodynamics: 19	Safety: 19	
Diagnosis and criteria for inclusion:	Patients with type 2 diabetes inadequately controlled on a combination of OAD (defined as treatment with sulfonylurea and/or metformin, with or without the addition of acarbose) + NPH insulin for more than 3 months Stable OAD therapy, for at least 3 months, according to the following specified daily dose: Glibenclamid ≥3.5 mg, Glipizid ≥5 mg, Glimeperid ≥2 mg, Metformin ≥1000 mg, Acarbose ≥150 mg HbA1c >7.0% Age >18 years Body Mass Index (BMI) ≤35 kg/m^2 (after change in protocol amendment)		
Investigational product: Dose: Administration:	Lantus® (insulin glargine [rDNA origin] injection) Individual dosing Subcutaneous injection, 100 IU/ml		
Duration of treatment: Insulin glargine was given for 40 weeks. OAD treatment was continued throughout the study with the same dose as before the switch to insulin glargine.	Duration of observation: Screening phase for 12 weeks + treatment and follow-up for 40 weeks		
Reference therapy: Dose: Administration:	Individual NPH insulin + OAD treatment before switch to insulin glargine Individual Subcutaneous injection (insulin) and oral (OAD)		
Criteria for evaluation:			
Efficacy/Pharmacodynamics:	QoL assessments were performed using a self-administered questionnaire at follow-up visits performed 12 weeks and 40 weeks after start of insulin glargine treatment. The results were compared with the QoL assessment done before switch to insulin glargine treatment (week 0) i.e. when the patient was treated with NPH insulin and OAD. The scales were: Diabetes Treatment Satisfaction Questionnaire (DTSQ) 8 items The fear of hypoglycemia scale (HFS) 23 items 12-Item Well-Being Questionnaire (WBQ12) 12 items		

	Additional analyses: HbA1c values were assessed before switch to insulin glargine treatment (at week -2), and at 12 weeks and 40 weeks of follow-up. Weight and insulin dose were recorded before the switch to insulin glargine (week 0) and at 12 weeks and 40 weeks of follow-up.
Safety:	Symptomatic hypoglycemia and severe hypoglycemia were recorded in diary cards during the study. Adverse events (AEs) were reported by the patient or noted by the investigator.
Statistical methods:	Efficacy/Pharmacodynamics: QoL assessments: DTSQ was analysed as 3 subscores, item 1, 4-8 as 1 subscore, item 2 as 1 subscore, and item 3 as 1 subscore. HFS was analysed as 2 subscores, item 1-10 as 1 subscore, and item 11-23 as 1 subscore. WBQ12 was analysed as 3 subscores, item 1-4 as 1 subscore, item 5-8 as 1 subscore, item 7-12 as 1 subscore, and a total score, item 1-12. All scores were calculated as sum of the items. If 1 item was missing, e.g. 1 item of 4, this was calculated as 4/3*mean. Change from baseline (week 0) to follow-up visits, week 12 and week 40, was calculated as the difference between the 2 values, for each patient and for each score. One sample t-tests were used to analyze QoL. Tests for no change from baseline were performed at alpha = 5%, double-sided. No corrections for multiple testing were used. Change from baseline to follow-up visits, week 12 and week 40 was calculated for HbA1c, body weight and insulin dose. Tests for no change from baseline were performed at alpha = 5%, double-sided. One sample t-tests were used for HbA1c and body weight. Wilcoxon Signed Rank test was used for insulin dose. No corrections for multiple testing were used. Baseline was defined as week -2 for HbA1c, and week 0 for body weight and insulin dose. Safety: The assessment of safety was based on the frequency of symptomatic hypoglycemia episodes, and frequency, intensity and type of AEs. Change from baseline to the follow-up visits of the treatment period was calculated for symptomatic hypoglycemia. Baseline was defined as week -12 to week 0, follow-up week 12 was defined as week 0 to 12 and follow-up week 40 was defined as week 12 to 40. Symptomatic hypoglycemia was tested using Wilcoxon Signed Rank test. Tests for no change from baseline were performed at alpha = 5%, double-sided. No corrections for multiple testing were used. Any severe hypoglycemia reported during the study would have been tested using similar methods.

Summary: Subjects:	This study was terminated prematurely due to recruitment difficulty. In total, 22 patients (15 males and 7 females) of the planned 117 were included in the study, 19 were treated and 17 patients completed the study. Five (5) patients withdrew from the study. The reasons for withdrawal were protocol violations for 4 patients and an AE (muscle pain at high blood glucose) for 1 patient. The randomized patients had a mean age of 61 years (range: 47 to 78 years), a mean BMI of 30.0 kg/m^2 (range: 21 to 36 kg/m^2) and a mean waist to hip-ratio of 1.006 (range 0.82 to 1.13) at screening. A waiver was given by the Sponsor to allow inclusion of the patient with a BMI of 36 kg/m^2.
Efficacy/Pharmacodynamic results:	Based on the 19 patients (of 117 planned) that were treated and included in the efficacy analysis, there were some statistically significant changes in the QoL and treatment satisfaction scores after the switch to insulin glargine treatment. The overall treatment satisfaction (sum of Items 1, 4, 5, 6, 7 and 8 of the DTSQ) increased by a mean of 6.8 at week 12 and by a mean of 5.9 at week 40 compared to baseline. The score for perceived frequency of unacceptably high blood sugar levels (Item 2 of the DTSQ) was reduced by a mean of 2.0 at week 12 and by a mean of 1.2 at week 40. There was also a mean increase of 1.3 from baseline to week 12 in the score of perceived energy levels (Sum of Items 5 to 8 of the WBQ). The change in energy levels was not statistically significant at week 40. There were no statistically significant changes in the scores of the Fear of Hypoglycemia Scale. There was a statistically significant reduction in HbA1c both at week 12 and week 40 after switching to insulin glargine treatment. Mean HbA1c was 8.77% at baseline, 7.63% at week 12 and 8.02% at week 40. The maximum individual change in HbA1c was -3.2 percentage units. There was a small but statistically significant increase in body weight from baseline to week 40. The change was not statistically significant at week 12. The mean change from baseline was +0.64 kg at week 12 and +1.15 kg at week 40. The largest individual weight increase was 5.3 kg during the 40 weeks of treatment. There was a statistically significant increase in daily insulin dose both at 12 weeks and 40 weeks after the switch to insulin glargine. The median increase in insulin dose from baseline was 11.1% at week 12 and 33.3% at week 40. The largest individual dose increase was +122%, at week 40.

Safety results:	Seven (7) patients in the safety analysis set reported a total of 9 AEs during the study. There were no serious AEs. Study treatment was stopped in 1 patient due to an AE. This patient had muscle pain at high blood glucose, which started after 26 weeks of glargine treatment and lasted for 6 days. The patient recovered without receiving any concomitant treatment. There was no statistically significant difference between the frequency of symptomatic hypoglycemia episodes before and after switch to glargine treatment (corrected for the difference in length of the 2 time periods). In total, 33 episodes were reported by 6 patients during the 12 weeks before start of glargine treatment and 49 episodes by 9 patients during the 40 weeks of insulin glargine treatment. There were no reports of severe hypoglycemia, but 5 episodes (2 before and 3 after switch to glargine treatment) had no specification of symptomatic or severe.
Date of report:	03-Feb-2010