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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00258804
		Study Code:	HOE901_4055
Generic drug name:	insulin glargine	**Date:**	27 November 07

Title of the study:	Evaluation (safety and efficacy) of treatment with insulin glargine and glimepiride in patients with type 2 diabetes before, during and after the period of fasting in Ramadan (HOE901_4055)	
Investigator(s):	Dr Abdul JABBAR, Department of Medicine, The Aga Khan University Hospital, Karachi 74800, Pakistan	
Study center(s):	This study was conducted in 49 centres of 14 countries: Bangladesh (7), China (2), Egypt (5), India (1), Indonesia (1), Jordan (1), Kuwait (3), Lebanon (2), Malaysia (2), Morocco (9), Oman (1), Saudi Arabia (3), Tunisia (11), and United Arab Emirate (1).	
Publications (reference):	Oral presentation of the First results at the 7th Pan Arab Congress on endocrinology and Diabetes, Rabat, May 2006.	
Study period: **Date first patient enrolled**: 13-Mar-2005 **Date last patient completed**: 12-Feb-2006		**Phase of development:** IV

Objectives:	**Primary objective:** To compare the number of hypoglycaemic events (severe, symptomatic, asymptomatic, nocturnal) in patients with type 2 diabetes treated with insulin glargine (Lantus®) and glimepiride (Amaryl®), before, during and after the period of fasting in Ramadan. ▪ Severe hypoglycaemia event is defined as events with symptoms of hypoglycaemia for which subjects required the assistance of another person, which is associated with a blood glucose level below 60 mg/dL or prompt recovery after oral carbohydrate or intravenous glucose, or glucagons administration. These events include all episodes in which neurologic impairment was severe enough to prevent self-treatment and which were thus thought to place subjects at risk for injury to themselves or others. Requires assistance means that the subject could not help her-himself. Someone being kind that assists the subject when not necessary does not qualify as requires assistance. ▪ Symptomatic non severe hypoglycaemia event is defined as events where symptoms consistent with hypoglycaemia are experienced and either the subjects responds to ingestion of carbohydrate/snack or the episode is associated with a glycaemia below 60 mg/dL. ▪ Asymptomatic hypoglycaemia event is defined as events where no symptoms of hypoglycaemia are experiences but the episode is associated with a blood glucose below 60 mg/dL. ▪ Nocturnal hypoglycaemia event is defined as events where symptoms occurring during night with a glycaemia below 60 mg/dL. **Secondary objectives:** ▪ To assess glycaemic control before, during and after Ramadan in terms of HbA1c, FBG, and 8-point blood glucose profile (FBG and 8-point blood glucose profile will be collected with a blood glucose monitor through a monthly patient diary). ▪ To assess the relationship between hypoglycaemia events during Ramadan and blood glucose control prior and during Ramadan. ▪ To assess patient satisfaction To document adverse events (all serious adverse events, non serious adverse events) throughout the study (all events will be collected through the monthly patient diary).		
Methodology:	Open, descriptive, observational, multicentric, multinational		
Number of patients:	Planned: 450	Randomized: NA	Treated: 441
Evaluated:	Efficacy : 349	Safety: 492	

	The treated population is the population that was enrolled in the study after the pre-selection period (visit V2) (441 patients). The efficacy was evaluated on the per-protocol population which is all patients assessed at pre-Ramadan Visit, with inclusion and exclusion criteria at inclusion visit, under Lantus® and Amaryl® treatment at pre-Ramadan visit and who completed the study without major protocol deviations (349 patients). The safety population consists of all patients included at baseline visit (visit V1) and for whom safety data are available (492 patients).
Diagnosis and criteria for inclusion:	Male or female subjects aged at least 35 years were eligible if they had type 2 diabetes mellitus (without a history of ketoacidosis) and were willing to fast during Ramadan. Insulin-naïve patients were enrolled if they had baseline glycated hemoglobin (HbA1c) greater than 7.5% and had received two OADs at the maximum tolerated dose for six months. Patients already receiving insulin (either insulin glargine or requiring a switch to insulin glargine and glimepiride) were enrolled with any HbA1c value.
Investigational product: Dose: Administration:	Insulin Glargine/Glimepiride Insulin glargine was titrated from 10IU according to fasting blood glucose and glimepiride was given at 4mg per day. ▪ Before and after Ramadan: o Glimepiride in the morning (before the first meal); o Insulin glargine at bedtime; ▪ During Ramadan: o Glimepiride at the time of breaking the fast ("Iftar" in the evening); o Insulin glargine any time before bedtime (same time every day)

Duration of treatment: A two-month titration period, a pre-Ramadan observation period (maximum 3 months), the Ramadan period (1 month) and a post-Ramadan observation period (2 months)	**Duration of observation:** From the pre-selection period (up to 3 month before the titration period, up to the post Ramadan period.

Reference therapy:	NA
Criteria for evaluation:	
Efficacy:	Hypoglycemic event s (severe, symptomatics, noctural) before, during and after Ramadan Glycemic control before, during and after Ramadan in terms of HbA1c, fasting blood glucose, 8-points blood glucose profile

Safety:	Adverse events reported by the patient or noted by the investigator.
Statistical methods:	The efficacy parameters (hypogycaemic events, HbA1c, FBG, 8-point 24 hours blood glucose profile, glargine and glimepiride daily doses) at each visit (when available) or period (adaptation before, during and after Ramadan) as well as the changes from one period to another are tabulated for the ITT and PP populations. Hypoglycaemic events were studied through: • total number of hypoglycaemic events • number of hypoglycaemic events by patient • incidence and prevalence of hypoglycaemic events • proportion of patients with at least one hypoglycaemic event. 4 periods of follow-up have been used for these analyses: - Adaptation period before Ramadan from V2 to V5: pooling V2, V3, V4, V4 bis (if available) and V5; - Pre-Ramadan from V5 to V6: visit V6; - Ramadan period from V6 to V7: visit V7; - Post-Ramadan from V7 to V9: pooling V8 and V9. Efficacy analysis are provided for the ITT and PP populations. Some specific analysis were realized: - Analysis of 8-point 24 hours blood glucose profile was provided for all patients and for patients with at least one hypoglycemic event at visit 6, 7 or 8. - Correlations between hypoglycaemic events during Ramadan (V7) and following parameters were calculated for total number of hypoglycaemic events and by type of events: - HbA1c just before Ramadan - Fasting blood glucose before (V6) and during Ramadan (V7) - 8 point blood glucose profiles before and during Ramadan - Predictive factors of hypoglycaemic events during Ramadan (V7) were studied using a logistic regression: a bivariate analysis and a multivariate one using a forward method (different steps to include one by one the most significant factor at each level) among all factors tested in the bivariate analysis (except Lantus® daily dose at V6, strongly correlated with weight, and waist circumference correlated to the ratio waist/hip). The statistical level for model selection was set at 5%.

Summary:	
Efficacy results:	Hypoglycemic episodes increased from 156 pre-Ramadan to 346 during Ramadan (p<0.001) and decreased to 153 post-Ramadan (p=0.0002).The increase during Ramadan was attributed to increased symptomatic hypoglycemic episodes. The overall prevalence of severe and nocturnal hypoglycemia was low throughout the study. Fasting blood glucose and HbA1c levels improved during the titration period and did not change throughout Ramadan or the month after Ramadan. Reduced levels of fasting blood glucose at the start of Ramadan correlated with hypoglycemia (p<0.0002), symptomatic hypoglycemia (p=0.0198) and asymptomatic hypoglycemia (p<0.0006) during Ramadan. Before Ramadan, glucose levels at wake-up on day 1 (p=0.0005), at noon (p=0.0019) and at wake-up on day 2 (p=0.0069) correlated with hypoglycemic events. During Ramadan, glucose levels at noon (p=0.0014), 2pm (p=0.0007) and before dinner (p=0.0008) correlated with hypoglycemic events. The research of predictive factor shows that patients with lower body weight, smallest weight circumference or fasting blood glucose (> 120 mg/dL) were more at risk of presenting a hypoglycemic event during Ramadan.
Safety results:	The incidence of adverse events was slightly higher in insulin-naïve than in insulin-treated patients and most events occurred during the titration period. The most frequent adverse event was hypoglycemia. The number of serious adverse events was low in both groups.
Date of report:	31-May-2007