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Sponsor / Company: Sanofi	**Study Identifiers:** NCT01169818, U1111-1116-2247
Drug substance(s): Insulin Glargine (HOE901)	**Study code:** LANTU_R_04889

Title of the study: Asian Treat to Target Lantus Study: A Randomized, Multicentre, Multinational, Open-Label, Parallel-Arm, 24-Week Phase IV Study evaluating the Effectiveness and Safety of Physician versus Patient-led Titration of Insulin Glargine in Type 2 Diabetes Mellitus [ATLAS].

Study center(s): The study was conducted at 48 centers across Japan (21) China (10), Russia (7), India (7), Philippines (1) and Pakistan (2).

Study period:

Date first patient enrolled: 05 Aug 2010

Date last patient completed: 12 Jun 2012

Phase of development: Phase 4

Objectives:

Primary:

To compare patient-led titration (intervention arm) versus physician-led titration (usual standard of care) in optimizing the clinical use of insulin glargine in an Asian population of patients with Type 2 diabetes mellitus (T2DM) uncontrolled on oral antidiabetic drugs (OADs). The primary endpoint was change (decrease) in mean HbA1c level from baseline at the end of the study.

Main Secondary:

To determine the difference in glycemic control, safety, quality of life and treatment satisfaction between patient-led titration and physician-led titration.

Methodology:

Prospective, randomized, multicenter, multinational, open-label, two-arm parallel-arm, 24-week phase IV study.

After a 2-week screening period participants were randomized using a 1:1 ratio to one the following two treatment arms: **Physician-led titration (usual standard of care arm)** or **Patient-led titration (intervention arm).**

In both study arms, treatment with OADs prescribed before study entry could continue at a fixed and stable dose during the trial. Increasing the dose of an existing OAD or adding new OADs was not permitted during the study. In the event of hypoglycemia, the use of sulphonylureas or glinides, where applicable, could be discontinued or the dose reduced at the discretion of the Investigator.

In both study arms, insulin naïve subjects were initiated on a fixed dose of insulin glargine (10 units/day; India 8-10 units/day; Japan: 4 units/day). Titration of insulin glargine then followed one of two algorithms:

- Physician-led titration: subjects had their basal insulin dose adjusted at each visit by a physician.
- Patient-led titration: subjects self-adjusted their basal insulin dose every 3 days.

All patients were assessed at baseline and at follow-up visits conducted at Weeks 2, 6, 12, 16 and 24. In addition, phone calls were made at Weeks 1, 3, 4, 5, 8, 10 and 20. Participants were required to keep a daily study diary to collect information on fasting blood glucose (FBG), medications taken and Adverse Events (AEs). Patients could call the provider as needed throughout the study period.

Number of patients**:**	Planned: 554 Randomized: 555 Treated: (dispensed insulin): 552
Evaluated:	Efficacy: 552 Safety: 548

Diagnosis and criteria for inclusion: Insulin-naïve patients with T2DM for at least 2 years, 40 to 75 years of age, being treated in the primary care setting, who have suboptimal diabetes control (glycosylated hemoglobin A1c [HbA1c] levels between 7 and 11% inclusive) despite the use of 2 OADs and who require a basal long-acting insulin/Lantus for the control of hyperglycemia. Patients must have received continuous treatment with stable doses of 2 OADs (including sulfonylureas, biguanides, alpha-glucosidase inhibitors, DPP-IV inhibitors, and glinides) for more than 3 months prior to randomization.

Study treatments

Investigational medicinal product(s): Insulin glargine

Formulation: 100 Units/mL solution for injection in a pre-filled SoloStar® pen (3 mL).

Route(s) of administration: Sub-cutaneous injection in the abdomen

Dose regimen: Patients randomized to either study arm were started on insulin glargine at an initial dose of 10 units/day (or 8-10 units/day for India or 4 units/day for Japan). Insulin glargine was to be administered once a day, in the evening, at bedtime. Titration was to occur each time the middle fasting blood glucose (FBG) value recorded over the last 3 consecutive days was above target (≤ 6.1mmol/L or 110mg/dL). As a rule, the FBG value used for this titration was the middle of the values recorded over the last three days, except if one of the three values was below 3.9 mmol/L or 70 mg/dL (in this case the low value was to be used).

The titration regimens for each arm were as follows:

Physician-led titration arm (titration at every visit, managed by physician)

Patients were reviewed by the physician at every visit, either in person or over the telephone. The middle value of the last 3 consecutive FBG values was used to perform the titration.

Patient-led titration arm (titration every 3 days, managed by patient)

Patients were empowered to adjust their insulin dose, under investigator's strict supervision. Patients were to use the middle value of their last 3 consecutive FBG values to perform the titration. They were to titrate their insulin dose every 3 days.

Both treatment arms otherwise followed the same titration regimen as provided in the table below:

Fasting Blood Glucose		**Insulin Dose**
mg/dL	mmol/L	
FBG ≤ 56	FBG ≤ 3.1	Dose decrease at physician's discretion and upon physician's clinical judgment
≤ 70 or symptomatic hypoglycemia*	≤ 3.9 or symptomatic hypoglycemia*	- 2 U
70 < FBG ≤ 110	3.9 < FBG ≤ 6.1	No change
110 < FBG ≤ 160	6.1 < FBG ≤ 8.9	+ 2 U
FBG > 160	FBG > 8.9	+ 4 U

*Occurring independently of the FBG and defined as symptoms of hypoglycemia responding to ingestion of carbohydrate or an episode associated with a BG level ≤ 56 mg/dL [≤ 3.1 mmol/L]). Small departure from the titration scheme could be allowed (e.g. decrease of the insulin glargine dose), based on Investigator's judgement and patient's situation.

Duration of treatment: The maximum treatment period was 24 weeks per patient.

Duration of observation: to 27 weeks per patient.

Criteria for evaluation:

Efficacy:

The primary endpoint was change (decrease) in mean HbA_{1c} level from baseline at end of study in the patient-led titration arm compared with patients in the physician -led titration arm.

Secondary endpoints included the following:

- The percentage of patients achieving HbA_{1c} levels < 7.0% without experiencing severe hypoglycemia during the study in the intervention arm compared with the usual standard of care arm.

  *A severe hypoglycemia being defined as an event with clinical symptoms that are considered to result from hypoglycemia in which the patient required the **assistance of another person** because the patient could not treat her/himself due to acute neurological impairment directly resulting from the hypoglycemia (assistance by another person when the patient could have treated her/himself is not considered as requiring assistance) **and** one of the following criteria: the event was associated with a measured blood glucose level < 36 mg/dL (2 mmol/L), or the event was associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.*

- The percentage of patients achieving target HbA_{1c} levels (< 7.0% and <6.5%) during the study in patients from the intervention arm compared with patients receiving the usual standard of care.
- The number of patients having a drop of ≥1% in HbA_{1c} levels and/or a drop of at least 0.5%.
- Mean change in FBG and post prandial glucose (PPG) from baseline to end point in patients from the intervention arm compared with patients receiving the usual standard of care.
- Evolution of blood glucose profiles
- Incidence of symptomatic hypoglycemia defined as symptoms of hypoglycemia responding to ingestion of carbohydrate or an episode associated with a blood glucose level ≤ 56 mg/dL [≤ 3.1 mmol/L]).
- Incidence of nocturnal hypoglycemia; defined as hypoglycemia occurring while the subject was asleep responding to ingestion of carbohydrate or associated with a blood glucose level ≤ 56 mg/dL [≤ 3.1 mmol/L]
- Incidence of asymptomatic hypoglycemia; defined as hypoglycemia without clinical symptoms and confirmed by a blood glucose level ≤ 56 mg/dL [≤ 3.1 mmol/L]).
- Mean change in body weight at end of study in patients in the intervention arm compared with patients receiving the usual standard of care
- Mean insulin dose from baseline to end of study in patients in the intervention arm compared with patients receiving the usual standard of care

Accordingly, the following efficacy parameters were recorded at specific time points:

- HbA1c (screening, visit 11 [week 12] and visit 14 [week 24]),
- Self-monitored 7-point blood glucose profile (baseline [week 0], visit 6 [week 4], visit 9 [week 8], visit 11 [week 12], visit 12 [week 16], visit 13 [week 20], and visit 14 [week 24]). Patients self-monitored their BG values immediately before and 2 hours after breakfast, lunch and dinner and then again at bedtime,
- Self-monitored FBG measurements (in both treatment arms) over 3 consecutive days before visit at baseline [week 0], visit 8 [week 6], visit 11 (week 12), visit 12 (week 16) and visit 14 [week 24],
- Weight (screening [week-2], baseline [week 0], visit 11 [week 12], and visit 14 [week 24]),
- Insulin dose (all post-randomisation visits]).

In addition, the occurrence of hypoglycaemia was recorded throughout the study.

Safety:

Safety evaluation included adverse reported by the patient or noted by the Investigator, vital signs, physical examination and standard hematology and blood chemistry.

Patient-reported outcome (PRO):

- Change from baseline in Diabetes Treatment Satisfaction Questionnaire status (DTSQs) and change (DTSQc) to 24 weeks endpoint in patients in the intervention arm compared with patients receiving the usual standard of care
- Change from baseline in EuroQoL-5 Dimension (EQ-5D) to 24 weeks endpoint in patients in the intervention arm compared with patients receiving the usual standard of care.

Statistical methods:

The primary efficacy variable was the change in HbA1c from baseline to study endpoint in the Intent To Treat (ITT) population, defined as all patients in the randomized population that have been dispensed at least one dose of study medication and contributed at least one on treatment efficacy value.

A sample of 470 patients (235 in each of two arms) was to provide an overall 5% significance level (2-sided) and 90% statistical power to exclude a difference of 0.3% HbA_{1c} between the 2 arms, based on an expected baseline adjusted HbA_{1c} decrease of 1.8% in the intervention and usual care arms. With an estimated 15% rate of non-evaluable patients, 554 patients needed to be randomized (277 in each arm). Similarly the study had 90% power to detect a difference of 0.3% HbA1c which was to be tested if the non-inferiority criterion was met.

Primary statistical analysis:
A mixed model repeated measures (MMRM) analysis was performed on the ITT population with the change from baseline in HbA1c as the dependent variable and treatment arm visit, country and treatment by visit as categorical fixed effect, and baseline HbA1c value and visit by baseline HbA1c as continuous fixed effects. The contrast at Visit 14 (week 24) was used to assess the primary objective of non-inferiority. The 95% confidence interval excluding 0.3% was considered as evidence of non-inferiority of patient-led titration, and the same confidence interval also excluding 0.0% was considered as evidence of superiority of patient-led titration. A similar analysis using the PP population was considered supportive.

Secondary efficacy analyses involved similar statistical methods for changes in FBG, PPG, 7-point blood glucose profiles, body weight, insulin dose and PROs. Risk differences were estimated for binary efficacy endpoints: achieving HbA1c targets and incidence of hypoglycemia, using a generalised linear model with binomial distribution and identity link

Safety analysis
The safety analysis was descriptive.

Summary:

Population characteristics:

Median age of the overall population was 58 years, ranging from 40 to 75 years, including few (7.6%) patients over 70 years of age. The sex ratio was close to 50/50. Median disease duration was 8.8 years, ranging from 1 to 50 years. Most patients had had diabetes for less than 15 years. Patients were insulin naïve with mediation duration of OAD treatment of 6.7 years, ranging 0 to 40 years. Glycemic control at baseline was characterized by a median HbA1c of 8.6% (range: 7.0 to 11.0%), a median FBG of 8.67 mmol/L [156 mg/dL] (range: 3.0 to 16.8 mmol/L [54 to 303 mg/dL), and a median PPG of 11.74 mmol/L [212 mg/dL] (range: 5.0 to 24.4 mmol/L [90 to 440 mg/dL]). Median BMI was 26.7 kg/m2 (range: 17 to 40 kg/m2), the majority of the patients being overweight (43%) or obese (38%). This profile was consistent across treatment arm and consistent with a diabetic patient population. Some variation was observed among countries with regard to baseline characteristics, indicating some degree of heterogeneity.

Efficacy results:

A significant ($p < 0.001$) drop in HbA1c relative to baseline was observed in both treatment arms as early as Week 12. The results of the primary analysis (conducted on the ITT population) supported the non-inferiority of Patient-led versus Physician-led titration, with a treatment difference at Week 24 of -0.15 (95% CI: -0.29, -0.00; $p = 0.043$). The supportive analysis conducted in the PP population supported the primary analysis in terms of change from baseline in HbA1c at Week 12 and Week 24 and confirmed the non-inferiority of Patient-led titration compared to Physician-led titration, with a treatment difference at Week 24 of -0.07 (95% CI: -0.22, 0.08; $p = 0.348$). The results of this analysis on a per-country basis were similar, with no significant difference between treatment arms, indicating that in spite of some heterogeneity in patients' baseline characteristics between countries, the response to the tight titration algorithm was consistent in both treatment arms of the study.

Approximately 36% of the patients overall achieved target HbA_{1c} (< 7.0%) without hypoglycemia at any time throughout the study; approximately 28.8% of the patients achieved the target at Week 24, and approximately 16.8% of the patient at both Week 12 and Week 24. There was no significant difference between treatment arms in this regard. Few patients achieved a HBA1c value < 6.5% (~12.9% overall at any time throughout the study, ~ 11.% at Week 24, and ~ 5.2% at both Week 12 and Week 24), once again with no significant difference between treatment arms. Most patients experienced a drop in HbA1c of 1% or more, or 0.5% or more, at least once during the study period as well as at Week 24, particularly in the Patient-led titration arm of the study.

A significant ($p < 0.001$) drop in FBG relative to baseline was observed in both treatment arms as early as Week 4. The drop in FBG relative to baseline was significantly greater in the Patient-led arm of the study at all time-points. This decrease in FBG could be explained by a significant increase in insulin daily dose relative to baseline ($p < 0.001$) from ~ 9 units at Week 1 to more than 20 units by Week 24, this increase being significantly greater in Patient-led titration arm at all time-points($p < 0.001$) except for Week 1. The incidence of hypoglycemia was low, with 32.6% of the patients overall. Overall, 30.8% of the patients experienced symptomatic hypoglycemia, and 11.4% experienced nocturnal hypoglycemia. The incidence of these events was significantly greater in the Patient-led arm of the study. Asymptomatic hypoglycemia was reported by 4.7% of the patients, and severe hypoglycemia by 4 patients overall, 2 in each treatment arm. Taken together, these results suggest that patients in the Patient-led titration arm were more aggressive in following the titration regimen, using higher insulin doses and therefore achieving greater decrease in FBG, in spite of a higher incidence of hypoglycemia, which was rarely reported as severe. It should also be noted that no episodes of hypoglycemia were reported as serious.

The results of the analysis of patient-reported outcomes, including DTSQs and DTSQc, were indicative of a relatively satisfied status at baseline. Nevertheless, patient satisfaction improved significantly relative to baseline. DTSQs total score improved significantly relative to baseline in both treatment arms ($P < 0.001$ at all time-points) and at each visit, with no significant difference between treatment arms. Similarly, DTSQc showed improved satisfaction in both treatment arms ($p < 0.001$) at study end, with no significant difference between treatment arms. The results of the analysis of patient-reported outcomes, including EQ-5D index score and EQ-5D VAS, were also indicative of a relatively good QOL at baseline. A small but significant improvement relative to baseline was observed for EQ-5D VAS, with no significant difference between treatment arms. More importantly, there was no evidence of deterioration in QOL.

Safety results:

A total of 548 patients were included in the safety population, with a total treatment exposure of 240.9 patients-years, and a median treatment duration of 168 days (range 8 to 231 days).

Approximately a third (184/548; 33.6%) of the patients overall experienced at least 1 TEAE, the most common of which was nasopharyngitis (8.9%). Most patients experiencing a TEAE reported mild events (137/184; 74.5%). A total of five patients experienced a total of eight severe TEAEs including fall, fracture, intracranial hemorrhage, multi-organ failure, hypertension, accelerated hypertension, trigeminal neuralgia, and musculoskeletal chest pain, none of which were considered related to treatment.

Few patients (11/548; 2.0%) experienced a TEAE that was considered possibly related to treatment, including, hunger, injection site induration, injection site pain, edema, peripheral edema, weight increase, hepatic enzyme increase, abdominal pain, nausea, dizziness and eczema. None of these events occurred in more than 1 patients in either treatment arm, and none of them were severe.

Few patients (14/548; 2.6%) experienced SAEs. Serious adverse events included incision site hemorrhage (1 patient), limb injury (1 patient), thermal burn (1 patient), trigeminal neuralgia (1 patient), arteriosclerosis obliterans (1 patient), musculoskeletal chest pain (1 patient), breast cancer (1 patient), malignant lung neoplasm (1 patient), and uterine polyps (1 patient) in the Patient-led titration arm, and sudden hearing loss (1 patient), hepatitis, hepatitis E, accelerated hypertension, and pleural effusion (1 patient), fall, fracture, intracranial hemorrhage and multi-organ failure (1 patient), carpal tunnel syndrome and cubital tunnel syndrome (1 patient), and hypertension (1 patient) in the Physician-led tritation arm. As described above, 6 of these events were severe in intensity. No SAEs were considered related to treatment. Of note, no episodes of hypoglycemia were reported as serious.

Few (6/548; 1.1%) experienced TEAEs that led to permanent treatment discontinuation. Treatment-emergent adverse events leading to permanent discontinuation included breast cancer, malignant lung neoplasm, carpal tunnel syndrome and cubital tunnel syndrome (1 patient), fall, fracture, intracranial hemorrhage and multi-organ failure (1 patient), epileptic psychosis, and uterine polyps. None of these events were considered related to treatment.

One subject died during the course of the study as a result of a climbing fall, with ensuing fracture, intracranial hemorrhage and multi-organ failure, with no relationship to study treatment.

Changes in laboratory parameters were minimal, with few changes reported clinically significant or as adverse events. There were no unexpected findings in hematology, clinical chemistry, or vital signs.

This above profile was consistent across treatment arms.

Issue date: 05-Jul-2013