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Sponsor: Sanofi	**Study Identifiers:** U1111-1172-2903, NCT02836704
Drug substance(s): INSULIN GLARGINE	**Study code:** LANTUL07191

Title of the study: Comparison of efficacy and safety of standard vs higher starting dose of insulin glargine 100U/mL in overweight and obese Chinese patients with type 2 diabetes

Study center(s): 47 sites in China which randomized at least one subject (51 sites were opened and screened patients but 4 were closed early due to failure to recruit)

Study period:

Date first subject/patient enrolled: 9 September 2016

Date last subject/patient completed: 26 April 2018

Phase of development: IV

Objectives:

Primary objective

To test the hypothesis that a higher starting dose of insulin glargine 100 U/mL (0.3 U/kg) is non-inferior to the standard starting dose (0.2 U/kg) based on the percentage of patients with at least one episode of hypoglycemia (≤3.9 mmol/L or severe) during 16 weeks of treatment in overweight and obese type 2 diabetes patients uncontrolled with oral anti-diabetic drugs (OADs).

Secondary objectives

- To evaluate the percentage of patients achieving HbA1c <7.0% at week 16.
- To evaluate the percentage and accumulated percentage of patients achieving fasting plasma glucose (FPG) target (<5.6, <6.1 and <7.0 mmol/L) from baseline to week 16.
- To assess the changes in HbA1c, fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) from baseline to study end.
- To evaluate the insulin dose change from baseline to study end.
- To evaluate the body weight change from baseline to study end.
- To evaluate overall hypoglycemia, nocturnal hypoglycemia and severe hypoglycemia occurrence throughout the treatment period.
- To descriptively evaluate the safety profile.
- Subgroup analysis on efficacy (control rate, control rate without confirmed hypoglycemia, and changes in HbA1c, FPG and PPG) and safety data according to:
  - Age
  - Duration of diabetes
  - Baseline treatment (OAD)
  - Baseline HbA1c, FPG and PPG

Methodology: This was a randomized, multicenter, open-label, parallel group clinical study. After a three days run-in period where patients stopped sulfonylurea and/or glinide treatment, patients were randomized to receive basal insulin glargine 100U/mL (Gla-100) at the standard starting dose (0.2 U/kg) or a higher starting dose (0.3 U/kg). Titration of Gla-100 was based on the patients' FPG over a three-days period. Patients continued to receive their previous non-sulfonylurea or non-glinide OADs at the same dose and frequency as prior to study entry.

Number of subjects/patients**:**	Planned: 880 patients; 440 per treatment group Randomized: 892 patients; 0.2 U/kg group: 444 patients; 0.3 U/kg group: 448 patients Treated: 887 patients; 0.2 U/kg group: 444 patients; 0.3 U/kg group: 443 patients
Evaluated:	
	Efficacy: Intent to treat (ITT) population: 866 patients overall: 0.2 U/kg group: 429 patients; 0.3 U/kg group: 437 patients. Per protocol (PP) population: 814 patients overall: 0.2 U/kg group: 403 patients; 0.3 U/kg group: 411 patients Per protocol with excluded stratification error (PPES) population: 733 patients overall: 0.2 U/kg group: 361 patients; 0.3 U/kg group: 372 patients Safety: 887 patients overall: 0.2 U/kg group: 444 patients; 0.3 U/kg group: 443 patients Pharmacokinetics: Not evaluated
Diagnosis and criteria for inclusion: adult patients up to 70 years old who were overweight or obese with type 2 diabetes (T2DM) diagnosed at least 2 years previously by WHO 1999 T2DM diagnostic criteria. They must have had continuous stable doses of two to three OADs for more than three months prior to randomization including metformin with at least 1.5 g/day or at maximum tolerated dose and HbA1c over 7.5% up to 11.0% and FPG over 9.0 mmol/L.	
Study treatments **Investigational medicinal product(s):** Insulin glargine 100U/mL (Gla-100, Lantus®) Formulation: 100 U/mL, solution for injection in a pre-filled SoloStar® Route(s) of administration: Subcutaneous injection Dose regimen: Gla-100 will be administered once a day at the same time each day starting at 0.3 U/kg or 0.2 U/kg. Dose titrations will be performed, where required, at each study visit by a physician who will adjust the dose based on the median FBG level over the previous three consecutive days. If any of the FPG levels is below 4.4 mmol/L, dose adjustment will be based on the lowest level rather than the median level.	
Noninvestigational medicinal product(s): Patients continue to receive their concomitant medications at the same dose and frequency as before entry into the study.	
Duration of treatment: 16 weeks **Duration of observation:** Approximately 18 weeks	

Criteria for evaluation:

The primary endpoint was the safety endpoint of overall hypoglycemia incidence (with confirmed hypoglycemia ≤3.9 mmol/L or severe hypoglycemia) during the 16 weeks of treatment.

Secondary efficacy endpoints included:

- The percentage of patients who achieved an HbA1c (<7%, <6.5%, <7.5%, and without hypoglycemia) at week 16 (control rate)
- The percentage of patients who achieved a FPG target (<5.6, <6.1 and <7.0 mmol/L, and without hypoglycemia) at week 16 (control rate)
- The percentage and accumulated percentage of patients at each FPG testing (2, 6, 12 and 16 weeks) achieving the FPG target (<5.6, <6.1 and <7.0 mmol/L, and without confirmed hypoglycemia; control rate)
- The changes in HbA1c, FPG and PPG from baseline to study end and values at study end
- The percentage and accumulated percentage at each self-monitoring of blood glucose (SMBG) (1, 2, 3, 4, 5, 6, 8, 10 and 12 weeks) of patients achieving fasting blood glucose (FBG) target (<5.6, <6.1 and <7.0 mmol/L, and without confirmed hypoglycemia)
- The average of median of 3 FBG values at each SMBG
- The number of weeks required to achieve the FBG targets (<5.6, <6.1 and <7.0 mmol/L)
- Patient satisfaction and adherence (drop-out rate and the percentage of patients who can adhere to the treatment and insulin titration)
- Subgroup analysis of efficacy data (HbA1c and FPG control rate, control rate without confirmed hypoglycemia, and changes in HbA1c, FPG and average PPG) according to:
    - Age
    - Gender
    - Duration of diabetes
    - Body mass index (BMI)
    - Baseline treatment (OAD)
    - Baseline HbA1c, FPG

No pharmacokinetic sub-studies were performed.

Safety endpoints included:

- Annualized event rates of overall hypoglycemia (with confirmed hypoglycemia ≤3.9 mmol/L or severe hypoglycemia)
- Incidence and annualized event rates of nocturnal (0:00-5:59 am) hypoglycemia and symptomatic hypoglycemia
- Incidence and annualized event rates of severe hypoglycemia
- Incidence and annualized event rates of SMBG <3.0 mmol/L during the treatment period
- The insulin doses (U/day and U/kg/day) at the end of treatment
- The body weight change from baseline to study end
- Adverse events
- Subgroup analysis for overall and nocturnal hypoglycemia according to:
  - Age
  - Gender
  - Duration of diabetes
  - BMI
  - Baseline treatment (OAD)
  - Baseline HbA1c, FPG

Other safety analyses were based on reported adverse events and other safety data such as clinical laboratory data and vital signs.

Statistical methods: Primary analysis: The number and percentage of patients with confirmed or severe hypoglycemia will be tabulated by treatment arm. Analyses will be performed to obtain an estimate of the difference between groups in the percentage of patients with confirmed or severe hypoglycemia with 95% confidence interval (CI) for the difference determined using the normal approximation to the binomial. Non-inferiority is established when the confidence interval lies entirely to the left of 10%.

Summary:

Study population characteristics: 1,073 patients were screened of which 892 were included. The patients in the two treatment arms were generally well matched. Patients had a mean (SD) age of 52.5 (9.7) and were more likely to be aged under 60 years (73.4%) and be male (59.0%). 37.6% of patients had a BMI of at least 28 kg/m² and 18.7% had BMI of at least 30 kg/m². The mean (SD) duration of diabetes was 7.6 years (4.4) and 12.9% of patients had diabetes complications. Sulfonylureas or glinides were used at screening by 55.7% of patients. At screening, patients had a mean (SD) HbA1c of 8.82 (1.00)% and mean BMI of 27.8 (2.6) kg/m².

Approximately 80% of patients in both treatment groups adhered to the insulin dose titration algorithm at each visit.

Primary outcome: The estimated difference between arms in incidence of overall confirmed hypoglycemia during the study was 2.10% (95% CI -1.68% to 5.89%, ITT population) which met the non-inferiority margin required to demonstrate that a higher starting dose of Gla-100 was not associated with an increased incidence of hypoglycemia.

Secondary safety results: There were no statistically significant differences between the 0.2 U/kg and 0.3 U/kg treatment arms in the incidence of symptomatic hypoglycemia (7.0% vs 9.8%, p=0.128, ITT population) and nocturnal hypoglycemia (1.2% vs 2.7%, p=0.102, ITT population). There were no events of severe hypoglycemia or hypoglycemia with FBG <3.0 mmol/L reported during the study. The annualized event rates of symptomatic hypoglycemia were similar between the treatment arms (33.5/100 patient-year exposure vs 48.3/100 patient-year exposure, p=0.059). A slight imbalance was observed in annualized event rates of nocturnal hypoglycemia between 0.2 U/kg and 0.3 U/kg treatment arms (4.5/100 patient-year vs 12.4/100 patient-year, p=0.031); however, there was no statistically significant difference between the arms (4.5/100 patient-year vs 8.8/100 patient-year, p=0.176), when one patient in the 0.3 U/kg arm, who experienced five events of nocturnal hypoglycemia over five nights, was removed from the analysis.

Secondary efficacy results: Approximately 40% of patients achieved an HbA1c <7.0% and approximately 55% achieved FPG <7.0 mmol/L at the end of the study. There were no statistically significant differences between the 0.2 U/kg and 0.3 U/kg treatment arms (HbA1c <7.0%: 40.0% vs 40.7%, p=0.538; FPG < 7.0 mmol/L: 53.6% vs 55.4%, p=0.492; ITT population). At week 2 and week 6 a larger proportion of patients in the 0.3 U/kg arm had met the FPG targets than in the 0.2 U/kg arm; however, there was no statistical difference between the arms at week 16. There were no differences in PPG between the treatment arms during the study; mean (SD) change from baseline to week 16 for 0.3 U/kg vs 0.2 U/kg arm was: -3.15 mmol/L (2.82) vs -3.39 (2.91), p=0.401. More than 90% of patients met the FBG target of < 7.0 mmol/L measured by SMBG at week 12, with no difference between the treatment arms (0.3 U/kg 93.6% vs 0.2 U/kg 93.6%, p=0.834). Patients in the 0.3 U/kg arm met the FBG targets earlier in the study than those in the 0.2 U/kg arm (FBG <7.0 mmol/L mean (SD): 2.7 weeks (2.4 weeks) vs 3.6 weeks (2.6 weeks), p<0.001). There was no difference in patient satisfaction and quality of life between the two treatment arms.

Safety results: Gla-100 was titrated to a mean (SD) of 0.36 (0.13) U/kg/day in the 0.2 U/kg arm and 0.40 (0.13) U/kg/day in the 0.3 U/kg arm by week 16.

There was no significant difference in incidence of treatment emergent adverse events (TEAEs) between the treatment groups. The number of patients experiencing any TEAE was higher in the 0.2 U/kg group than the 0.3 U/kg group. Serious adverse events (SAEs) were experienced by 11 patients in both treatment groups. There were no deaths during the study.

There were 11 patients who experienced TEAEs considered possibly related to study insulin, five in the 0.2 U/kg group (constipation, 2 patients; insomnia, 1 patient; jaundice, 1 patient; injection site pain, 1 patient; overdose, 1 patient), and six in the 0.3 U/kg group (hypersensitivity, constipation, liver injury, asthenia, injection site swelling, alanine aminotransferase increased).

Safety narratives are provided for all SAEs, AESI and AEs that led to withdrawal of study treatment.

Table: Overview of adverse event profile: treatment emergent adverse events (safety population)

	0.2 U/kg N=444		0.3 U/kg N=443		
Overview of Treatment emergent adverse events	**Incidence (%)**	**Events (rate)**	**Incidence (%)**	**Events (rate)**	**P values**
Any TEAE	81 (18.2%)	135 (30.4%)	69 (15.6%)	99 (22.3%)	0.2893
Any treatment emergent serious AEs	11 (2.5%)	13 (2.9%)	11 (2.5%)	11 (2.5%)	0.9957
Any TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Any TEAE leading to permanent treatment discontinuation	0 (0.0%)	0 (0.0%)	3 (0.7%)	3 (0.7%)	
Any possibly related TEAE	5 (1.1%)	6 (1.4%)	6 (1.4%)	6 (1.4%)	0.7587
Possibly related treatment emergent serious AEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Possibly related TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Possibly related TEAE leading to permanent treatment discontinuation	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	

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