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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** INSULIN GLARGINE	**Study Identifiers:** U1111-1186-3400, NCT03359837 **Study code:** LANTUL07194
Title of the study: A 26-week, multi-center, open-label, randomized, parallel-group study to evaluate the efficacy and safety of two treatment regimens in patients with type 2 Diabetes after short-term intensive insulin therapy: basal insulin-based treatment versus twice-daily premixed insulin (LANTUL07194).	
Study centers: 30 centers in China	
Study period: Date first participant enrolled: 20/Jan/2018 Date last participant completed: 29/Jun/2020 Study Status: Completed	
Phase of development: Phase IV	
Objectives: **Primary objective:** • To test the hypothesis that once-daily basal insulin treatment co-administered with OADs (G+) is non-inferior to twice-daily premixed insulin treatment (PM-2) in terms of glycosylated hemoglobin A1c (HbA1c) reduction from baseline to end of study. Test for superiority is performed if non-inferiority was confirmed. **Secondary objectives:** • To assess efficacy in terms of percentage of patients achieving HbA1c <7.0% (53 mmol/mol) and HbA1c <7.0% without confirmed (BG ≤ 3.9 mmol/L) hypoglycemia. • To assess efficacy in terms of percentage of patients achieving fasting plasma glucose (FPG) target (FPG <7 mmol/L and FPG<6.1 mmol/L) and target without confirmed (BG ≤ 3.9 mmol/L) hypoglycemia. • To assess safety in terms of occurrence of hypoglycemia. • To assess daily blood glucose (BG) variation. • To assess patient satisfaction.	
Methodology: This was a multi-center, randomized, active controlled, open-label, parallel-group, prospective clinical trial.	

Number of participants:	
	Planned: 400
	Randomized: 384
	Treated: 382
Evaluated:	
	Efficacy: 367
	Safety: 382

Diagnosis and criteria for inclusion: Type 2 diabetes (T2DM) patients (18 - 70 years, HbA1c >7.5% and ≤11.0%, FPG >7.0 mmol/L, fasting C peptide >1.0 ng/mL (>0.33 nmol/L), body mass index (BMI) ≥20 kg/m^2 and <40 kg/m^2 with diabetes diagnosis between 1 and 12 years, to accept continuous treatment with stable doses of metformin (≥1 g/day, or maximum tolerated dose) and 1 or 2 oral anti-hyperglycemic drugs (OADs) for more than 8 weeks prior to screening, who were willing to start insulin treatment and intensify insulin treatment in hospital.

Study products

Investigational medicinal product(s): Insulin glargine 100 U/mL (Lantus®), insulin glulisine (Apidra®), Insulin aspart 70/30 (NovoMix®30), Sitagliptin (Januvia®), Vildagliptin (Galvus®), Repaglinide (NovoNorm®) and Acarbose (Glucobay®) were provided by the Sponsor.

Formulation: Insulin glargine100 U/mL: 100 Units/mL, solution for injection in a prefilled SoloStar® pen (3 mL)

Insulin glulisine: 100 Units/mL, solution for injection in a prefilled SoloStar® pen (3 mL)

Insulin aspart 70/30: 100 Units/mL, suspension for injection in a prefilled FlexPen®

Sitagliptin: 100 mg/tablet

Vildagliptin: 50 mg/tablet

Repaglinide: 1 mg/tablet

Acarbose: 50 mg/tablet

Route(s) of administration: Insulin glargine 100 U/mL, insulin glulisine, and Insulin aspart 70/30: subcutaneous injection; DPP-4 inhibitor (sitagliptin, vildagliptin), Repaglinide and Acarbose: oral administration

Non-investigational medicinal product(s): Previous metformin therapy was continued with the same brand, formulation, dosage and dosing frequency as before in both arms, unless for safety reason. Metformin was non-investigational medicinal product, and it was not supplied by the Sponsor.

Formulation: NA

Route(s) of administration: oral administration

Duration of treatment: 24-week period

Duration of observation: 2-week screening phase, 7-10 days run-in period, followed by 24-week treatment period

Criteria for evaluation:

Efficacy:

Primary endpoint: HbA1c change from baseline to week 24

Secondary endpoint(s): Percentage of patients achieving FPG <6.1 mmol/L, FPG <7.0 mmol/L and HbA1c <7.0% (53 mmol/mol) at week 12 and week 24; percentage of patients achieving FPG <6.1 mmol/L, FPG <7.0 mmol/L and HbA1c <7.0% (53 mmol/mol) without confirmed (BG ≤ 3.9 mmol/L) hypoglycemia at week 12 and week 24; FPG and 7-point BG change from baseline to week 12 and week 24; change of total daily insulin dose by U/day and U/kg and daily BG variation by visit up to week 24.

Safety:

Incidence of hypoglycemia, frequency of adverse events as well as abnormal standard laboratory values and vital signs and physical examination, body weight change, patient satisfaction and quality of life.

Statistical methods:

Primary Efficacy Analyses:

Both PP and ITT populations were used for the primary efficacy analyses. For primary efficacy analysis, results in PP (observed) were mainly described.

The primary efficacy endpoint was HbA1c change from baseline to week 24. In each of the two groups, changes from baseline to week 24 were estimated through an analysis of covariance (ANCOVA) model including fixed effects for treatment, SU/glinides usage (Yes/No), and HbA1c level at screening (>9% or ≤9%) as fixed effects, baseline HbA1c as a covariate. The difference in the mean HbA1c change between the two treatment groups and 95%CI was estimated. Noninferiority was confirmed if the upper limit of the 95%CI was less than the noninferiority margin of 0.4%. The test for superiority is performed using the same model mentioned above if noninferiority was achieved. If the upper limit of the 95%CI of difference in the mean HbA1c change between two treatment groups was less than 0, the difference between the groups would be considered to be statistically significant.

Based on α=0.025 and ß=0.10, 160 patients for each group were required, making a total of 320 evaluable patients. Assuming an expected rate of 20% for non-evaluable patients, a total number of 400 patients would be randomized. Assuming an expected rate of 15% for non-evaluable patients, a total number of 377 patients would be randomized.

Secondary Efficacy Analyses:

Both PP and ITT populations were used for the secondary efficacy analyses. For secondary efficacy analyses, results in ITT (Last observation carried forward, LOCF) were mainly described.

There was no multiplicity adjustment for secondary objectives. For categorical variables, frequencies and percentages were summarized by the treatment arm. Analyses were performed to obtain a crude estimate of the difference in the percentage at each visit with 95%CI for the difference determined using the normal approximation to the binomial.

FPG change from baseline to week 12 and week 24 was analyzed using the analysis of covariance (ANCOVA) model with treatment, SU/glinides usage (Yes/No) and HbA1c level at screening (>9% or ≤9%) as fixed effects, baseline FPG as a covariate.

For total daily insulin dose descriptive analysis (including n, mean, SD, median, Q1, Q3, minimum and maximum) were provided by the treatment arm.

Change in each timepoint of 7-point BG from baseline to week 24 was modelled through the mixed model for repeated measures (MMRM), including fixed categorical effects of treatment, visit, treatment by visit interaction, and randomization strata of SU/glinides usage (Yes/No) and HbA1c level at screening (>9% or ≤9%). BG value at each visit was the dependent variable. The visit factor had 4 levels (Baseline, visit 5 [week 12], visit 6 [week 16], and visit 8 [week 24]). 1) Difference between treatment arms at each visit was tested; 2) additionally, the difference between week 12 and week 24 within the same treatment arm was also tested.

Daily BG variation included SD, coefficient of variation (CV), mean amplitude of glucose excursions (MAGE), Low Blood Glucose Index (LBGI), and High Blood Glucose Index (HBGI). Change in BG variation from baseline to week 24 was modelled through the mixed model for repeated measures (MMRM), including fixed categorical effects of treatment, visit, treatment by visit interaction, and randomization strata of SU/glinides usage (Yes/No) and HbA1c level at screening (>9% or ≤9%). BG variation at each visit was the dependent variable. The visit factor had 4 levels (Baseline, visit 5 [week 12], visit 6 [week 16], and visit 8 [week 24]). 1) Difference between treatment arms at each visit was tested; 2) additionally, the difference between week 12 and week 16, week 16 and week 24 within the same treatment arm was tested. 3) Whether the difference between treatment arms varied with time was also tested.

Safety Analyses:

Safety endpoints included:

- Incidence of hypoglycemia
- Change of body weight from baseline to week 24
- Adverse events (AEs)
- Laboratory safety variables
- Vital signs
- Physical Examination
- Patient-reported outcomes

All safety analyses were performed on the safety population.

Summary Results:

Population characteristics:

All patients were Chinese patients. Most randomized subjects (72.4%) were aged ≤ 60 years with a mean age of 54.2 years in this study. The range of weight was 48.0-116.0 kg with a mean of 73.4 kg. About 61% of patients had a BMI ≥ 25 kg/m^2 with a mean of 26.0 kg/m^2. The mean duration of diabetes was 6.8 years. All subjects received OAD treatment prior to screening and 90.4% of subjects received 2 OADs (the most commonly used OADs were metformin and sulfonylurea/nateglinide). Mean HbA1c at baseline was 8.59% (70.38 mmol/mol). Mean FPG at the beginning of the run-in period and at baseline were 10.66 mmol/L and 5.98 mmol/L, respectively.

146 (76.0%) patients in PM-2 group and 150 (78.1%) patients in G+ group were diagnosed with complications. Peripheral neuropathy (PM-2: 120, 62.5%; G+: 124, 64.6%), peripheral vascular disease (PM-2: 60, 31.3%; G+: 65, 33.9%), diabetic

nephropathy (PM-2: 64, 33.3%; G+: 57, 29.7%) and diabetic eye diseases (PM-2: 34, 17.7%; G+: 28, 14.6%) were the most common current complications.

A total of 12 patients (5 in G+, 7 in PM-2) discontinued trial treatment prematurely. 10 of 12 patients discontinued by "withdrew consent" and the other 2 patients discontinued by death (acute myocardial infarction in PM-2 and hepatic function abnormal in G+, respectively).

Efficacy results:

Primary efficacy result: Comparing to PM-2, HbA1c change from baseline to week 24 in G+ was noninferior, but did not achieve superiority. The specific conclusions were based on the PP population. The results in ITT were consistent with results in the PP population for the primary efficacy endpoint.

Secondary efficacy results: the results were consistent between the PP population and ITT population. The detailed conclusions based on ITT (LOCF) were as followed:

- Comparing to baseline, mean HbA1c (%) was reduced significantly at week 12 within each treatment group (PM-2: LS mean=-1.67%, p < 0.001; G+: LS mean=-1.65%, p < 0.001). The difference in change from baseline to week 12 (LS mean=0.03%, 95% CI=-0.144, 0.200) and change from baseline to week 24 (LS mean=0.01%, 95% CI=-0.172, 0.196) between two treatments were not statistically significant.
- The difference for proportions of subjects achieving HbA1c <7.0% (53 mmol/mol) between the two treatment groups was not statistically significant at week 12 (PM-2: 53.8%; G+: 57.4%, p=0.473) and week 24 (PM-2: 56.5%; G+: 60.3%; p=0.448). The proportion of subjects achieving HbA1c <7.0% (53 mmol/mol) without confirmed (BG ≤ 3.9 mmol/L) hypoglycemia in the G+ group was significantly higher than in the PM-2 group at week 12 (PM-2: 36.6%; G+: 50.0%; p=0.009) and week 24 (PM-2: 34.4%; G+: 50.3%; p=0.002).
- The proportion of subjects achieving FPG <7.0 mmol/L in the G+ group was significantly higher than in the PM-2 group at week 12 (PM-2: 45.4%; G+: 68.1%; p<0.001) and week 24 (PM-2: 44.1%; G+: 63.8%; p<0.001). Proportion of subjects achieving FPG <7.0 mmol/L without confirmed (BG ≤ 3.9 mmol/L) hypoglycemia in the G+ group was significantly higher than in the PM-2 group at week 12 (PM-2: 33.0%; G+:59.0%; p<0.001) and week 24 (PM-2: 27.4%; G+:53.7%; p<0.001). The proportion of subjects achieving FPG <6.1 mmol/L in the G+ group was significantly higher than in the PM-2 group at week 12 (PM-2: 18.9%; G+: 38.3%; p<0.001) and week 24 (PM-2: 18.8%; G+: 33.5%; p=0.001). Proportion of subjects achieving FPG <6.1 mmol/L without confirmed (BG ≤ 3.9 mmol/L) hypoglycemia was significantly higher than in the PM-2 group at week 12 (PM-2: 11.4%; G+: 30.9%; p<0.001) and week 24 (PM-2: 9.7%; G+: 27.7%; p<0.001).
- Comparing to baseline, 7-point BG values increased at week 12 and week 24 within the same treatment, particularly post-prandial values.
- There was no statistically significant difference between treatment arms at week 24 for daily BG variation - standard deviation (SD), coefficient of variation (CV), MAGE, and HBGI. Subjects in the G+ group had lower LBGI than the PM-2 group at week 24.
- The total daily insulin dose increased by 9.4 U/day (0.12 U/kg) from baseline to week 24 in PM-2 group and by 1.7 U/day (0.02 U/kg) in G+ group.

Safety results:

During post-baseline period, most of the safety results were similar between the two treatment groups. Details were as follows:

- The percentage of subjects (34%) with non-hypoglycemia TEAEs during post-baseline period in G+ (65 subjects, 133 events) was higher than that in PM-2 (23.6%; 45 subjects and 78 events). Percentage of subjects with drug-related non-hypoglycemia TEAs to insulin aspart 70/30 was 8.4% (16 subjects and 23 events) and similar to drug-related non-hypoglycemia TEAEs to insulin glargine 100 U/mL (8.4%, 16 subjects and 33 events).

- The majority of non-hypoglycemia TEAEs during post-baseline period were mild to moderate, few subjects reported severe non-hypoglycemia TEAEs (PM-2: 1 subject, 0.5%; G+: 4 subjects, 2.1%). There were 8 serious non-hypoglycemia TEAEs in 6 subjects (3.1%) of PM-2 and 16 serious non-hypoglycemia TEAEs in 14 subjects (7.3%) of G+.
- There were 2 non-hypoglycemia TEAEs leading to discontinuation of the study drug in G+ and 1 in PM-2. One non-hypoglycemia TEAE with the outcome of death happened in each treatment (acute myocardial infarction in PM-2; hepatic function abnormal in G+).
- One subject was pregnant in PM-2 and 2 subjects had ALT increased in G+ during the post-baseline period, they were considered as Adverse event(s) of special interest (AESI).
- Comparing to PM-2, G+ had a lower percentage and events per participant-year in each hypoglycemia category. There was no severe hypoglycemia occurred.
- For weight, there was no statistically significant difference between the two treatments for change from baseline to week 24.

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