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Sponsor / Company: Sanofi **Drug substance(s):** HOE901 (insulin glargine)	**Study Identifiers:** NCT02027753, UTN U1111-1149-1632 **Study code:** LANTUL06638
Title of the study: Efficacy and safety of treating type 2 diabetic patients with inadequate response to metformin and DPP-4 inhibitors by adding basal insulin therapy (insulin glargine)	
Study center(s): 11 centers in Korea	
Study period: Date of first patient in: 19/Dec/2013 Date of last patient out: 24/Apr/2015	
Phase of development: Phase 4	
Objectives: To investigate the percentage of patients who reached the target glycated hemoglobin (HbA_{1c}) at Week 24 after adding basal insulin therapy (insulin glargine) to dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin ± sulfonylurea.	
Study design: Open, single-arm, multicenter	
Number of patients**:** Planned: 108 Involved: 108 **Evaluated:** Efficacy: 104 Safety: 108	

Diagnosis and criteria for inclusion:

Evaluation Criteria: Patients who meet any of the following criteria are eligible for study participation:

1. Patients with type 2 diabetes mellitus (T2DM) ≥20 aged.
2. Patients who are treated with DPP- 4 inhibitor for at least 3 months before informed consent with metformin sulfonylurea inadequately controlled with HbA_{1c} ≥7.5% before study.
3. Patients who agreed with a written informed consent.

Exclusion Criteria: Patients who meet any of the following criteria are excluded from study participation:

1. Diabetes patients other than type 2 (eg, type 1 diabetes mellitus, pancreatic disease, secondary diabetes).
2. History of continuous basal insulin treatment within 3 months before screening.
3. History of diabetic acidosis (including ketoacidosis) within 1 year before screening.
4. History of myocardial infarct, stroke, or heart failure-related admission within 3 months before screening.
5. History of drug or alcoholic abuse within 6 months before screening.
6. Weight change ≥5 kg within 3 months before screening.
7. History of hypoglycemic unawareness.

8. Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg regardless of taking anti-hypertensive, or uncontrolled hypertension.

   Active malignant cancer, major systemic disease, clinically significant diabetic retinopathy, macular edema necessitating laser treatment, abnormal clinical finding from physical examination, laboratory analysis, EKG or vital sign, which can be regarded as to prevent safe completion of clinical study or to make efficacy assessment difficult by investigator or co-investigator at screening.

   Pregnant or lactating women

   Women of child bearing potential (premenopause or not surgically infertile within 3 months before screening) who match 2 conditions below:

   - Negative serum pregnancy test at screening.
   - Using medically proven effective contraceptive method.

9. Hypersensitivity to investigational drugs.

   Laboratory finding at screening:

   - Abnormal liver function: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times of upper limit of normal (ULN) range.
   - Renal insufficiency: Men with serum Cr ≥1.5 mg/dL (≥ 133μmol/L), women with serum Cr ≥1.4 mg/dL (≥124 μmol/L).

10. Use of anti-obese drug within 3 months before screening.

    Has been using drugs that can influence glucose metabolism (systemic corticosteroid, thyroid hormone) within 3 months before screening or has possibility of using these drug during the investigational period.

    Has participated in clinical studies of any investigational drugs within 3 months before screening.

11. Considered not physically or psychologically appropriate to participate in clinical study by Investigator.

    Not willing to comply with scheduled visit, self-inject insulin, or self-monitor blood glucose level.

Study treatments

Investigational medicinal product(s): Insulin glargine (Lantus)

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

Administration method:

- Insulin glargine is administered once a day (OD) at the same time.
- Time: Administration between 8:00 pm and 10:00 pm at the same time during the clinical study period is recommended.
- Initial dose: an initial dose of 0.2 U/Kg or 10 unit is recommended and it is at Investigator's decision, considering patient's weight and fasting plasma glucose (FPG) on the first day of administration.
- FPG monitoring and dose adjustment: Patients adjusted one's insulin dose under the Investigator's discretion.
- The target FPG: 70 < FPG ≤130.
- Education on Device Training: at least 2 times on the explanation on how to use insulin is conducted before administration of the investigational product.

Dose adjustment schedule: Subjects adjusted one's insulin dose once in 3 days (twice a week). Patients used the median of last 3 daily morning FPG levels (including the level on the day of dose adjustment) for dose adjustment. If there is hypoglycemia (≤7 0 m g/d L) on 3 consecutive day FPG levels, dose was adjusted according to titration algorithm.

Administration period: 24 weeks

Observation period: 28 weeks (maximum 2 weeks of screening period, 24 weeks of administering investigational products, 2 weeks of follow-up).

Criteria for evaluation:

Efficacy:

Primary Efficacy Endpoint: Percentage of patients who meet the HbA_{1c} ≤7% at Week 24.

Secondary Efficacy endpoints:

1. Percent patients with HbA_{1c} ≤7% at Week 12.
2. HbA_{1c} change rate and change at Week 12, 24 compared with screening period (visit 0).
3. Percent patients with HbA_{1c} ≤6.5% at Week 12, 24.
4. FPG, 2hr-postprandial glucose (PPG) at Week 12, 24.
5. Total daily insulin dose at Week 24
6. Fasting blood glucose (FBG) values during 3 consecutive days.
7. 7-point blood glucose value
8. Weight change at Week 24.

Safety:

1. Adverse events including hypoglycemia events (Symptomatic daytime and nocturnal hypoglycemia, asymptomatic hypoglycemia, severe hypoglycemia);
2. Adverse events;
3. Serious adverse events;
4. Overall safety including physical, and clinical examination.

Statistical methods:

In general, continuous variables are summarized in observed values, average, standard deviation, median, minimum and maximum values. Categorical variables are summarized in observed values and proportion, and denominator was determined according to analysis group.

All safety analysis was conducted in summary unless mentioned specifically, and all tests were performed at two-sided, 5% significance level.

Full analysis set (FAS) is all the population whose first efficacy analysis data can be obtained after administration of investigational product, among patients who received at least 1 round of treatment. Main analysis will be made on FAS group.

Per-protocol set (PPS): is a subpopulation of the full analysis set, with the completion according to protocol.

Per-protocol set (PPS): Included all subjects who belong to the FAS analysis, including subjects administered with investigational product without any major protocol violations. The following were considered major protocol violations:

- Lack of informed consent;
- Inclusion / exclusion criteria violations;
- Early drop-out;
- Low compliance (less than 80% of treatment compliance of oral antidiabetic [OAD]).

Primary analysis were mainly analyzed for the FAS population and analyzed for the PPS population to confirm robustness. (Main analysis will be made on FAS group, and additional analysis will be made on PPS group).

The safety set consisted of all subjects who received treatment at least once. Stratified analysis is conducted on combined treatment with sulfonylurea.

Analysis of the Primary Efficacy Endpoint

Proportion (%) and its 95% confidence interval (CI) of subjects who meet the target HbA_{1c} ≤7% at the completion of 24 week treatment and binomial test is used to test significant difference of target rate with 22%. A between-group difference was compared using a Chi-square test or Fisher's exact test.

Summary:

Combination therapy of Metformin and DPP-4 inhibitors with insulin glargine proved to be statistically significant by increasing the percentage of patients with HbA_{1c} ≤7% at Week 24 (the primary efficacy analysis endpoint), from 31.73% (33 out of 104 patients) and 33.72% (29 out of 86 patients), in FAS analysis group and PPS analysis group, respectively. In addition, FPG after treatment 24 weeks (which was the second endpoint), proved to be statistically significant by decreased the amount to 56.02±49.80mg/dL in FAS analysis group and 58.13±48.44mg/dL in PPS analysis group, compared with screening period.

The percentage of subjects reporting adverse events (AEs) for the therapy Metformin and DPP-4 inhibitors in combination with insulin glargine was 33.33% (36 out of 108 patients), and 112 cases of hypoglysemia were reported. Among the 112 cases, 92 cases (82.14%) needed oral administration of glucose, and 3 cases were severe symtomatic hypoglycemia, while all were recovered. Except for hypoglycemia, AEs occured in 43 (39.81%) subjects and they experienced the total of 86 cases of AEs. (adverse drug reactions [ADRs] in 4 subjects [3.70%], and serious adverse events [SAEs] in 8 subjects [7.41%] who experienced serious AEs [SAEs]), but they proved not to be ADRs. In subanalysis, there is no statistically significant difference between combination therapy with SU and without SU.

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