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Sponsor / Company: Sanofi **Drug substance(s):** HOE901 (insulin glargine)	**Study Identifiers:** NCT01223131, UTN U1111-1116-3661 **Study code:** EFC11681
Title of the study: A 24-week, randomized, open-label, parallel group, multicenter comparison of Lantus® (insulin glargine) given once daily versus Neutral Protamine Hagedorn (NPH) insulin in children with type 1 diabetes mellitus aged at least 6 years to less than 18 years	
Study center(s): 10 centers in China	
Study period: Date first patient enrolled: 11/Feb/2011 Date last patient completed: 05/Mar/2014	
Phase of development: Phase 3	

Objectives:

Primary Objective

To assess the efficacy of insulin glargine given once daily (QD, pm dosing) on glycated hemoglobin A_{1c} (HbA_{1c}) levels over a period of 24 weeks in children with type 1 diabetes mellitus (T1DM) aged at least 6 years to less than 18 years.

Secondary Objectives

To assess the effects of insulin glargine compared to NPH insulin over 24 weeks on:

I 01. Percentage of patients reaching International Society of Pediatric and Adolescent Diabetes (ISPAD) recommended target of HbA_{1c} <7.5%,

I 02. Fasting blood glucose (FBG),

I 03. Nocturnal blood glucose (BG),

I 04. 24-hour blood glucose profile based on 8-point self-monitoring of blood glucose (SMBG) values,

I 05. Daily total insulin dose and basal insulin dose,

I 06. Rates of all hypoglycemia (including both asymptomatic and symptomatic hypoglycemia), symptomatic, asymptomatic, severe symptomatic, nocturnal, and nocturnal symptomatic hypoglycemia.

To assess the safety and tolerability of insulin glargine versus NPH insulin based on the occurrence of treatment-emergent adverse events (TEAEs).

To assess anti-insulin and anti-glargine antibody development in both groups.

To assess insulin glargine pharmacokinetics (PK) for all patients treated with insulin glargine in selected sites with approximately 45% of insulin glargine population to rule out accumulation tendency of insulin glargine after repeated dosing.

Methodology: This was an unbalanced (2:1), randomized, open-label, 2-arm parallel group, multicenter trial in children with T1DM aged at least 6 years to less than 18 years comparing the efficacy and safety of Lantus (insulin glargine) as basal insulin, given at bedtime (20:00 to 22:00) QD, versus NPH insulin dosed once daily at bedtime (20:00 to 22:00) or twice daily in the morning (before breakfast) and at bedtime (20:00 to 22:00), both given as basal plus bolus insulin regimen for 24 weeks. The study was conducted only in China.

Randomization was stratified both by baseline age (<12 years, ≥12 years) and by screening HbA_{1c} (<9%, ≥9%).

Number of patients:	Planned: 150
	Screened: 196
	Randomized: 162
	Treated: 161
Evaluated:	
	Efficacy: 161
	Safety: 161
	Pharmacokinetics: 40

Diagnosis and criteria for inclusion:

Inclusion Criteria:

Children with T1DM aged at least 6 years to less than 18 years.

Exclusion Criteria:

Diagnosis of T1DM for less than one year before participating the study,

HbA_{1c} less than 7% or greater than 12% at screening,

Patient taking oral or parenteral glucose-lowering medications other than insulin.

Study treatments

Investigational medicinal product(s): Lantus (insulin glargine, HOE901)

Formulation: Commercial insulin glargine solution (Solostar® pen devices) 100 U/mL

Route(s) of administration: Subcutaneous injection

Dose regimen:

- Lantus (insulin glargine) was given once daily at bedtime (20:00 to 22:00), at roughly the same time each day for a given patient.
- The dose of Lantus was individually titrated to achieve the following targets of metabolic control without hypoglycemia:
  - FBG between 90 and 145 mg/dL (5.0 to 8.0 mM), inclusive,
  - Bedtime BG between 120 and 180 mg/dL (6.7 to 10.0 mM), inclusive,
  - Nocturnal BG between 80 and 162 mg/dL (4.4 to 9.0 mM), inclusive, and
  - HbA_{1c} <7.5%.
- The initial Lantus dose for patients assigned to take Lantus whose prestudy regimen was based on NPH insulin was recommended to take entire daily dose of basal insulin as on the pretreatment day (reduced by 20% if NPH insulin given more than once daily), then adjusted at the discretion of the Investigator to achieve glycemic targets without an increase of hypoglycemia.

Reference therapy: NPH insulin

Route of administration: Subcutaneous injection

Formulation: NPH insulin 100 U/mL (Novolin® N) solution for injection

Dose regimen:

- NPH insulin was administered subcutaneously once daily at bedtime (20:00 to 22:00) or twice daily in the morning (before breakfast) and at bedtime (20:00 to 22:00). The number of the NPH insulin injections per day (once or twice daily) was at the Investigator's discretion. The number and timing of the NPH insulin injections should not be altered from the time of randomization until the end of the study, unless deemed necessary by the Investigator.
- The dose of NPH insulin was individually titrated to achieve glycemic targets as described above for Lantus.
- For patients previously treated with non-NPH insulin, the starting daily dose of NPH insulin was recommended to be the same basal insulin dose as on the pretreatment day, then adjusted at the discretion of the Investigator on an individual basis.

Noninvestigational medicinal product(NIMP): Insulin aspart

Formulation: Insulin aspart 100 U/mL (NovoRapid®) solution for injection

Route of administration: Subcutaneous injection

Dose regimen:

- Insulin aspart was given in an appropriate dose by multiple daily injections before each main meal. For mealtime dosing, bolus insulin was given according to the product labeling in China, strongly encouraged to be within 5 minutes before a meal.
- The doses of insulin aspart were adjusted to optimize glycemic control after basal insulin doses had been optimized and could be reduced as basal insulin doses are increased.
- The starting doses of insulin aspart were at the discretion of the Investigator on an individual basis.

Note: New medications or treatments for glucose-lowering other than study drug and bolus insulin were not to be started during the trial, and patients were not permitted to take other anti-hyperglycemic medications aside from basal and bolus insulins as described above.

Duration of treatment: 24 weeks

Duration of observation: 28 weeks ±7 days (up to 2 weeks screening + 1 week run-in + 24 weeks treatment + 1 week followup)

Criteria for evaluation:

Efficacy:

Primary Endpoint:

Absolute change of HbA_{1c} from baseline to Week 24.

Secondary Endpoints:

- Percentage of patients reaching ISPAD recommended target of HbA_{1c} <7.5% at Week 24,
- FBG change from baseline to Week 24,
- Nocturnal BG change from baseline to Week 24,
- Change in 24-hour blood glucose profile based on 8-point SMBG values from baseline to Week 24,
- Change in daily total insulin dose and basal insulin dose from baseline to Week 24.

Post hoc analyses:

- Change in daily bolus insulin dose from baseline to Week 24,
- Change in daily insulin (including daily total insulin, daily basal insulin, and daily bolus insulin) dose by body weight,
- Percentage of patients with 7.5% ≤HbA_{1c} ≤9% and HbA_{1c} >9% at Week 24 (according to the categorization of glycemic control in Chinese Diabetes Society's Guideline for the diagnosis and treatment of T1DM in China).

Safety:

The safety and tolerability of Lantus versus NPH insulin were assessed based on:

- Rates of all hypoglycemia (including both asymptomatic and symptomatic hypoglycemia), symptomatic, asymptomatic, severe symptomatic, nocturnal, and nocturnal symptomatic hypoglycemia during a 24-week treatment period,
- The occurrence of TEAEs,
- Other safety assessments, including laboratories, vital signs, height and weight, and physical examination findings.

Anti-insulin glargine and anti-insulin antibodies:

Anti-insulin glargine antibody (AGA) and anti-insulin antibody (AIA) status and titer were assessed at screening, Week 4, and Week 24.

Pharmacokinetics:

Insulin glargine and insulin glargine metabolite M1 and M2 concentrations in the morning 9.5 to 16.5 hours following the previous evening injection at 1, 2, and 4 weeks of treatment were assessed to rule out accumulation tendency of insulin glargine or its metabolites after repeated dosing.

Pharmacokinetic sampling times and bioanalytical methods:

Insulin glargine PK sampling was performed for patients treated with Lantus in selected sites with approximately 45% of Lantus population, consisting of a single blood (plasma) sample drawn on three occasions (in the morning 9.5 to 16.5 hours following the previous evening injection at 1, 2, and 4 weeks of treatment). Insulin glargine (parent compound) and insulin glargine metabolites M1 and M2 in plasma were determined using immunoaffinity extraction followed by liquid chromatography-tandem mass spectrometry with a lower limit of quantification (LLOQ) of 0.2 ng/mL for all 3 analytes.

Statistical methods:

The study was aimed to document the efficacy and safety for the use of Lantus (insulin glargine) or NPH but not to test a specific hypothesis.

The sample size of 150 patients (100 patients in the Lantus group and 50 patients in the NPH group) was to assess the efficacy and safety in Chinese pediatric Type 1 Diabetes population using descriptive analysis.

Analysis Population:

The primary efficacy population was modified Intention To Treat (mITT) population, which included all randomized patients who receive at least one injection of the investigational medicinal product (IMP) and have both baseline and at least one post-baseline value of any endpoint, irrespective of compliance with the study protocol and procedures.

Primary Analysis:

As a continuous efficacy parameter, the primary endpoint, absolute change of HbA_{1c} from baseline to Week 24, was analyzed using descriptive statistics (number [N], mean, standard deviation [SD], median, minimum, and maximum). For efficacy analysis, the baseline was defined as the last available value prior to the first dose injection of open-label IMP (Lantus or NPH insulin). In case of discontinuation of study drug before Week 24, HbA_{1c} was to be assessed at the time of discontinuation. The Last Observation Carried Forward (LOCF) procedure was to be used by taking this last available post-baseline on-treatment HbA_{1c} measurement as the HbA_{1c} value at Week 24.

Analysis of secondary endpoints:

Missing efficacy endpoint values for all the efficacy variables were imputed from the last available on-treatment value using the LOCF method.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) was provided by treatment for all continuous secondary endpoints using the mITT population.

Categorical secondary endpoints (eg, percentage of patients reaching ISPAD-recommended goals of HbA_{1c} <7.5% at the end of treatment visit and the incidence rate of hypoglycemia) were demonstrated by treatment.

Similarly, for the post hoc analyses, change in daily bolus insulin dose and change in daily insulin dose by body weight were analyzed using the descriptive statistics (number, mean, SD, median, minimum, and maximum), and percentages of patients with 7.5% ≤HbA_{1c} ≤9% and HbA_{1c} >9% at Week 24 were demonstrated by treatment.

Analyses of safety data:

The safety analysis was conducted on the safety population, defined as all randomized patients who did actually receive at least one dose or partial dose of study drug analyzed according to the treatment actually received.

The event rate of hypoglycemia was defined as the total number of episodes divided by the total duration from the first dose of IMP up to 24 hours after the last dose of IMP.

The incidence rate of hypoglycemia was defined as the total number of patients with at least one episode from the first dose of IMP up to 24 hours after the last dose of IMP divided by the total number of patients in the safety population.

The on-treatment period for other safety variables was defined as the time from the first dose of IMP up to 7 days after the last dose of IMP administration. The TEAEs were defined as adverse events that developed or worsened (according to the Investigator's opinion) or became serious during the on-treatment period.

Analysis of antibody variables:

The analyses of antibody data were performed based on the antibody population, defined as all randomized patients who contributed at least one valid blood sample at screening, at Week 4, or at Week 24 (the end of treatment) for AGA and AIA assessment.

Percentage of patients with AGA and AIA positive and negative status was summarized by visit for each treatment group. The percent conversions from negative to positive and positive to negative of AGA and AIA status from screening to 4 weeks and from screening to 24 weeks were summarized by treatment group.

AGA and AIA titers, as well as respective percent changes from baseline, each at nominal sampling times were listed and summarized by visit and treatment using descriptive statistics by N, mean, SD, geometric mean, coefficient of variation, standard error mean (SEM), median, minimum, and maximum.

Analyses of pharmacokinetic variables:

The PK population was defined as all randomized patients who were treated with Lantus and contributed at least the minimum required volume of plasma at Weeks 1, 2, and 4 and who had no major pharmacokinetic protocol violations.

Plasma concentrations of insulin glargine and its metabolites M1 and M2 at nominal sampling times were listed for Lantus-treated patients in the PK population and summarized by visit using descriptive statistics by N, mean, SD, geometric mean, coefficient of variation, SEM, median, interquartile ranges, minimum, and maximum.

Summary:

Population characteristics:

A total of 196 patients were screened and 162 patients with T1DM were randomized to Lantus group (n=107) or to NPH group (n=55) according to a ratio of 2:1. One patient was randomized to NPH but did not receive the study treatment.

Of the 161 treated patients, 106 patients in the Lantus group and 50 in the NPH group completed the study. Fewer patients in the Lantus group discontinued the study treatment prematurely (Lantus: 1/107, 0.9%; NPH: 4/54, 7.3%). The main reason of premature study treatment discontinuation was poor compliance to protocol (1 in the Lantus group; 3 in the NPH group).

Demographics and baseline disease characteristics were well-balanced between the treatment groups. The mean (SD) ages in the Lantus and NPH groups were 12.3 (3.2) years and 12.2 (3.5) years, respectively. The mean (SD) duration of diabetes prior to study start in the Lantus and NPH groups were 3.83 (2.93) years and 3.55 (2.25) years, respectively.

Mean (SD) HbA_{1c} at baseline was 8.87% (1.21%) in the Lantus group and 9.12% (1.29%) in the NPH group. Mean (SD) FBG at baseline was 10.38 (3.38) mmol/L in the Lantus group and 10.20 (2.75) mmol/L in the NPH group. Mean (SD) daily total insulin dose at baseline in the Lantus and NPH groups were 35.47 (14.86) and 35.81 (15.22) U, respectively. Mean (SD) daily total insulin dose by weight at baseline in the Lantus and NPH groups were 0.84 (0.23) and 0.87 (0.29) U/kg, respectively. Mean (SD) basal insulin dose at baseline in the Lantus and NPH groups were 12.35 (5.79) U and 12.89 (6.13) IU, respectively. Mean (SD) basal insulin dose by weight at baseline in the Lantus and NPH groups were 0.29 (0.09) U/kg and 0.32 (0.12) IU/kg, respectively. Mean (SD) bolus insulin dose at baseline in the Lantus and NPH groups were 23.29 (10.28) and 23.61 (11.21) U, respectively. Mean (SD) bolus insulin dose by weight at baseline in the Lantus and NPH groups were 0.55 (0.18) and 0.57 (0.23) U/kg, respectively.

Efficacy results:

Primary endpoint:

Both Lantus and NPH groups had demonstrated glycemic control in HbA_{1c} reduction from baseline (Lantus: 8.87%, NPH: 9.12%) and reached similar level of glycemic control (Lantus: 8.63%; NPH: 8.59%) at Week 24 (LOCF). Of note, the Lantus group presented with a low baseline HbA_{1c} in comparison to the NPH group.

At the end of study, Week 24 (LOCF) mean and median changes in HbA_{1c} from baseline were -0.25% and -0.50%, respectively, in the Lantus group and -0.54% and -0.40%, respectively, in the NPH group.

Secondary efficacy endpoints:

The percentage of patients reaching the ISPAD target of HbA_{1c} <7.5% at Week 24 in the Lantus group was 18.7% (20/107) and in the NPH group, 21.6% (11/51). Post hoc analyses revealed that 52.3% (56/107) of the patients in the Lantus group and 51.0% (26/51) of the patients in the NPH group had an HbA_{1c} 7.5% ≤HbA_{1c} ≤9%, while 29% (31/107) of the patients in the Lantus group and 27.4% (14/51) of the patients in the NPH group had an HbA_{1c} >9%. According to the Chinese Diabetes Society's Guideline for the diagnosis and treatment of T1DM in China, HbA_{1c} <7.5% was an indicator for optimal glycemic control in children and adolescents, and the current treatment plan should be maintained; HbA_{1c} ≥7.5% but ≤9% indicates acceptable but suboptimal glycemic control, and insulin dose titration is suggested; HbA_{1c} >9% indicates a high-risk status of the patient, and the insulin dose must be up-titrated. Therefore, the results reflected that more than 70% of the patients in both treatment groups have been controlled to an acceptable level of glucose control.

At Week 24 (LOCF), mean FBG decreased from baseline (0.76 mmol/L) in the Lantus group while increased (1.07 mmol/L) in the NPH group.

In the Lantus group, the nocturnal blood glucose (measured at 3:00 of SMBG) had remained stable throughout the study, whereas NPH was noted to be fluctuating.

In the Lantus group, the 8-point SMBG appeared less fluctuating throughout the day as compared to NPH group.

At Week 24 (LOCF), the mean daily total insulin dose was 41.69 U in the Lantus group (6.22 U [0.072 U/kg] increase from baseline) and 47.49 U in the NPH group (11.51 U [0.189 U/kg] increase from baseline). The daily basal insulin dose in the Lantus group was 14.37 U (2.03 U [0.024 U/kg] increase from baseline) whereas in the NPH group, 19.02 IU (6.10 IU [0.112 IU/kg] increase from baseline). The mean daily bolus insulin dose in the Lantus group was 27.37 U (4.07 U [0.05 U/kg] increase from baseline) whereas in the NPH group, 28.47 U (4.75 U [0.06 U/kg] increase from baseline).

Safety results:

Overall, the number of all hypoglycemia events per patient-year during the on-treatment period in the Lantus group was 68.63, whereas in the NPH group, 84.58. The number of events per patient-year for symptomatic hypoglycemia and asymptomatic hypoglycemia were 24.27 and 44.36 in the Lantus group, respectively, whereas in the NPH group, 32.32 and 52.27, respectively. Severe symptomatic hypoglycemia events in the Lantus group was 0.02 number of events per patient-year, whereas in the NPH group, 0.04. The number of events per patient-year for nocturnal hypoglycemia and nocturnal symptomatic hypoglycemia were 12.97 and 3.58 in Lantus group, respectively, whereas in the NPH group, 14.19 and 4.52, respectively.

Over the 24-week on-treatment period, 88/107 (82.2%) patients in the Lantus group and 46/54 (85.2%) patients in the NPH group reported at least one TEAE. The most common TEAE by system organ class (SOC) was metabolism and nutrition disorders, as reported by 78 (72.9%) patients in the Lantus group and 41 (75.9%) patients in the NPH group. The second most common TEAE by SOC was infections and infestations in both treatment groups, as reported by 47 (43.9%) patients in the Lantus group and 27 (50.0%) patients in the NPH group. Common TEAEs by preferred term (PT), as reported by more than 5% of the patients in any treatment group, included hypoglycemia (Lantus: 74 [69.2%] patients versus NPH: 41 [75.9%] patients), nasopharyngitis (Lantus: 28 [26.2%] patients versus NPH: 17 [31.5%] patients), upper respiratory tract infection (Lantus: 18 [16.8%] patients versus NPH: 11 [20.4%] patients), diabetic ketoacidosis (Lantus: 2 [1.9%] patients versus NPH: 4 [7.4%] patients), and oropharyngeal pain (Lantus: 3 [2.8%] patients versus NPH: 3 [5.6%] patients).

Treatment-emergent adverse events related to the IMP were reported in 37 (34.6%) patients in the Lantus group and 24 (44.4%) patients in the NPH group. The most common TEAE related to the IMP by PT was hypoglycemia, as reported by 36 (33.6%) patients in the Lantus group and 22 (40.7%) patients in the NPH group. Other TEAEs related to the IMP included overweight, which occurred in 1 (0.9%) patient in the Lantus group and 1 (1.9%) patient in the NPH group, and dizziness, hunger, injection site swelling, and blood glucose increased, each occurring in 1 (1.9%) patient in the NPH group.

A total of 9 patients reported 10 serious TEAEs, including 4 events in 3 (2.8%) patients in the Lantus group and 6 events in 6 (11.1%) patients in the NPH group. The most common serious TEAE by SOC was metabolism and nutrition disorders, including 5 events of diabetic ketoacidosis (reported by 2 [1.9%] patients in the Lantus group and 3 [5.6%] patients in the NPH group) and 1 event of hypoglycemia (1 [1.9%] patient in the NPH group). All patients recovered from the serious TEAEs after receiving corrective treatment. One serious TEAE was considered by the Investigators as related to study treatment and led to treatment discontinuation: 1 blood glucose increased in 1 patient on NPH.

No death was observed in both treatment groups during the on-treatment period.

No patient in either treatment groups experienced ALT increase. No pregnancy was reported during the on-treatment period in either treatment groups. No symptomatic overdose with IMP/NIMP was reported in either of the treatment groups.

Overall injection site and hypersensitivity reactions during the on-treatment period reported in the Lantus group was 1/107 (0.9%), whereas in the NPH group, 4/54 (7.4%).

Antibody results:

At screening, 69.2% (74/107) and 60.7% (65/107) of the patients randomized to the Lantus group were AGA- and AIA-positive, respectively, while 69.1% (38/55) and 78.2% (43/55) of the patients in the NPH group were AIA- and AGA-positive, respectively. From screening to Week 24, in the Lantus group the incidence of patients with positive AGA and AIA status decreased, both by 4.1%. In the NPH insulin group the number of AIA-positive patients increased by 6.9% while the number of AGA-positive patients remained at the screening level. Overall, the incidence of antibody-positive patients was lower in the Lantus group compared to the NPH group at Week 24 (end of treatment). During the 24-week on-treatment period, only small changes in AGA and AIA titers were observed for both treatment groups.

Pharmacokinetic results:

Following once-daily repeated subcutaneous Lantus (insulin glargine) dosing in a subset of 40 patients, insulin glargine metabolite M1 was the principal circulating compound in plasma. Within a time interval of 9.5 to 16.5 hours following the previous evening injection mean plasma metabolite M1 concentrations were 0.855 ng/mL at Week 1, 0.760 ng/mL at Week 2, and 0.672 ng/mL at Week 4. Mean plasma concentrations of insulin glargine (parent compound) and insulin glargine metabolite M2 were below LLOQ. No accumulation of insulin glargine (parent compound) or insulin glargine metabolites M1 or M2 occurred after repeated dosing.

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