These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** HOE901-U300 (insulin glargine)	**Study Identifiers:** NCT01683266, UTN U1111-1128-5517 & EudraCT 2012-001524-35 **Study code:** EFC12456
Title of the study: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period (EFC12456; EDITION IV)	
Study center(s): 124 active centers in 12 countries: Canada, Czech Republic, Denmark, Estonia, Finland, Hungary, Japan, Latvia, Netherlands, Romania, Sweden, and the United States of America.	
Study period: Date first patient enrolled: 12/Sep/2012 Date last patient completed: 11/Sep/2013	
Phase of development: Phase 3	

Objectives:

The primary objective was to compare the efficacy of a new formulation of insulin glargine (HOE901-U300) and Lantus (overall, regardless of the injection time) in terms of change of hemoglobin A_{1c} (HbA_{1c}) from baseline to endpoint (scheduled Month 6) in patients with type 1 diabetes mellitus (T1DM).

The secondary objectives were to compare HOE901-U300 and Lantus when given in the morning or in the evening in terms of:

- Change of HbA_{1c} from baseline to endpoint (scheduled Month 6);
- Change from baseline to endpoint (Month 6) in fasting plasma glucose (FPG), plasma glucose prior to injection of study drug, plasma glucose at 03:00 hours, mean plasma glucose (8-point profiles), glucose variability, treatment satisfaction and health related quality of life;
- Reaching target HbA_{1c} values and controlled plasma glucose (all and reaching target without hypoglycemia);
- Frequency of occurrence and diurnal distribution of hypoglycemia by category of hypoglycemia (symptomatic, asymptomatic, nocturnal, severe, probable, and relative);
- Safety and tolerability of HOE901-U300 including development of anti-insulin antibodies (AIAs) during the 12-month study period.

Methodology: The randomization was 1:1:1:1 (HOE901-U300 morning injection, HOE901-U300 evening injection, Lantus morning injection, Lantus evening injection) and was stratified according to HbA_{1c} values at screening (<8.0%; ≥8.0%) and geographical region (Non-Japan; Japan) with a minimum of 20% randomized patients per HbA_{1c} stratum. The sample size (125 in each group) was chosen to ensure sufficient power for the primary endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]).

Number of patients:	Planned: 500 (125 per treatment group) Randomized: 549 (274 patients in the HOE901-U300 overall group, 275 patients in the Lantus overall group) Treated: 549
Evaluated:	
	Efficacy: 546
	Safety: 549

Diagnosis and criteria for inclusion:

Inclusion criteria: Patients with T1DM; signed written informed consent.

Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >10% at screening; less than 1 year on basal plus mealtime insulin and self-monitoring of blood glucose (SMPG); not on stable insulin (±20% total basal insulin dose) in last 30 days prior to screening; use of premix insulins, human regular insulin as mealtime insulin and/or any glucose-lowering drugs other than basal insulin and mealtime analogue insulin in last 3 months before screening; use of insulin pump in last 6 months before screening.

Study treatments

Investigational medicinal product(s): Tested drug - HOE901-U300; Control drug - HOE901-U100 (Lantus)

Formulations: HOE901-U300 (insulin glargine 300 U/mL solution) was supplied in a disposable (prefilled) insulin pen (modified Tactipen) for subcutaneous injection. The pen-injector allowed dose setting in the range 3 to 90 U with minimum dose increments of 1.5 U. Lantus (insulin glargine 100 U/mL solution) was supplied in the marketed Solostar® (prefilled ie, disposable pen). The Solostar pen-injector allowed for a dose setting in the range of 1-80 U with minimum dose increments of 1 U.

Dilution or mixing of HOE901-U300 or Lantus with other insulins was not allowed.

Route(s) of administration: Subcutaneous injection in the left and right anterolateral or left or right posterolateral abdominal wall or thighs or upper arms. Within a given area, the injection site was changed (rotated) at each time to prevent skin reactions.

Dose regimen: Once daily (QD) injection in the morning or evening. The injection time was fixed at the time of randomization and was to be maintained for the duration of the study.

Starting dose: Patients on Lantus (once or more than QD), the starting dose was the median of the total daily basal insulin doses in the last 3 days prior to the baseline visit.

Patients on neutral protamine hagedorn (NPH) or insulin detemir QD prior to the baseline visit: the daily dose (U) of HOE901-U300 or Lantus was equal to the dose on the day prior to the baseline visit.

Patients on NPH or insulin detemir more than QD prior to the baseline visit: the daily dose of HOE901-U300 or Lantus (U) was to be 80% of the total daily NPH insulin or insulin detemir dose on the day prior to the baseline visit.

The basal insulin dose was adjusted once weekly to achieve fasting SMPG in the target range of 80 to 130 mg/dL (4.4 to 7.2 mmol/L) and while avoiding hypoglycemia.

Noninvestigational medicinal product(s): Mandatory background therapy (short-acting mealtime insulin analog)

Duration of treatment: Up to 12 months

Duration of observation: Up to 54 weeks + 2 days (screening period up to 2 weeks, 6-month open-label comparative efficacy and safety treatment period, 6-month open-label comparative safety extension period, 2-day post-treatment safety follow-up)

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: Change in HbA_{1c} from baseline to endpoint (Month 6).

Secondary endpoints:

- Proportion (%) of patients with HbA_{1c} <7% at Month 6;
- Proportion (%) of patients with HbA_{1c} ≤6.5% at Month 6;
- Proportion (%) of patients with at least 1 nocturnal hypoglycemia, indicated as severe and/or confirmed by plasma glucose ≤70 mg/dL (3.9 mmol/L) from start of Week 9 to Month 6; change in pre-injection plasma glucose (mmol/L) from baseline to endpoint (Month 6);
- Change in variability of pre-injection plasma glucose from baseline to endpoint (Month 6);
- Proportion (%) of patients with FPG <100 mg/dL (5.6 mmol/L) at Month 6;
- Proportion (%) of patients with FPG ≤130 mg/dL (7.2 mmol/L) at Month 6;
- Changes from baseline to endpoint (Month 6) in: FPG; 24-hour plasma glucose; variability of 24-hour plasma glucose and;
- Change from baseline to Month 6 in 8-point SMPG profiles per time point, daily basal and daily total insulin doses; and plasma free fatty acids.

Exploratory endpoints: 5-point SMPG profiles and mean of fasting pre-breakfast SMPG

Safety: Hypoglycemia; occurrence of adverse events (AEs) particularly treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), injection site reactions, hypersensitivity reactions, cardiovascular (CV) events, and adverse events of special interest (AESIs) which included increased alanine aminotransferase (ALT), pregnancy, symptomatic/asymptomatic overdose with investigational medicinal product (IMP)/noninvestigational medicinal product. Other safety information including clinical laboratory data, vital signs (including body weight), 12-lead electrocardiogram (ECG), AIA, and site of administration.

Statistical methods: The primary efficacy endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]) was analyzed using a Mixed-effect Model with Repeated Measures (MMRM) approach with fixed categorical effect factors for randomized group (HOE901-U300 morning injection, HOE901-U300 evening injection, Lantus morning injection, Lantus evening injection), visit, randomized group-by-visit interaction, randomization strata of screening HbA_{1c} (<8.0%, ≥8.0%), randomization strata of geographical region (Non-Japan; Japan), as well as the continuous fixed covariates baseline HbA_{1c} and baseline HbA_{1c}-by-visit interaction. The differences of the estimates versus Lantus overall with the corresponding associated standard errors and 95% confidence intervals (CIs) were also calculated.

A stepwise closed testing approach was used for the primary efficacy endpoint to assess non-inferiority and superiority sequentially. Step 1 assessed non-inferiority of HOE901-U300 overall versus Lantus overall. To assess non-inferiority, the upper bound of the 2-sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 overall and Lantus overall was compared with a predefined non-inferiority margin of 0.4% HbA_{1c}. Non-inferiority was demonstrated if the upper bound of the 2-sided 95% CI of the difference between HOE901-U300 overall and Lantus overall on the modified intent-to-treat (mITT) population was <0.4%. Step 2 assessed superiority of HOE901-U300 overall versus Lantus overall only if non-inferiority was demonstrated. The superiority of HOE901-U300 overall over Lantus overall was demonstrated if the upper bound of the 2-sided 95% CI of the difference between HOE901-U300 and Lantus on the mITT population was <0 (zero). The test for the primary endpoint was performed one-sided at level α=0.025.

Safety analyses were descriptive, based on the safety population.

Summary: The current report presents the efficacy and safety results for the main 6-month on-treatment period.

Population characteristics: A total of 549 patients with T1DM were randomized: 274 patients to the HOE901-U300 overall group (136 patients to HOE901-U300 morning injection, 138 patients to HOE901-U300 evening injection) and 275 patients to the Lantus overall group (137 patients to Lantus morning injection, 138 patients to Lantus evening injection); 549 patients were exposed to the IMP (safety population). The mITT population (efficacy population) included 546 patients, HOE901-U300 (n=273) or Lantus (n=273).

Overall, a comparable number of patients in each treatment group discontinued the study prematurely (HOE901-U300 overall groups: 43/274, 15.7%; Lantus overall group 39/275, 14.2%). A total of 231 (84.3%) patients in the HOE901-U300 overall group and 236 (85.8%) in the Lantus overall group completed the main 6-month treatment period.

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 47.3 years; 55 of 549 (10.0%) patients were ≥65 years. Overall, 57.0% of the patients were male. The mean body mass index (BMI) at baseline was 27.6 kg/m². The mean duration of T1DM prior to study start was 21 years, in 78.9% of the patients the diagnosis was known for ≥10 years, 61.7% of the patients had screening HbA_{1c} ≥8.0%. Overall, 81.7% of all patients had used Lantus within the 7 days prior to randomization, 15.6% insulin detemir, and 3.0% NPH insulin. The mean basal insulin dose prior to treatment was 0.376 U/kg, the mean total insulin dose 0.719 U/kg.

Mean HbA_{1c} at baseline was similar in both treatment groups (HOE901-U300: 8.11 % and Lantus: 8.14%).

Efficacy results:

Primary efficacy endpoint: The least squares (LS) mean change in HbA_{1c} from baseline to endpoint (Month 6) was comparable in both overall treatment groups (-0.40% [95% CI: -0.501 to -0.299] in the HOE901-U300 overall group and -0.44% [95% CI: -0.543 to -0.344] in the Lantus overall group). Non-inferiority of HOE901-U300 versus Lantus overall was demonstrated with the LS mean difference in HbA_{1c} compared to Lantus overall of 0.04% (95% CI: 0.098 to 0.185) with the upper bound lower than the predefined non-inferiority margin of 0.4%. Non-inferiority would also be shown should the non-inferiority margin have been set at 0.3%. Superiority of HOE901-U300 overall versus Lantus overall was not demonstrated.

In both overall treatment groups, the mean decrease in HbA_{1c} from baseline was similar and occurred mostly during the first 12 weeks of treatment (at Week 12: HOE901-U300 overall group -0.38% and Lantus overall group -0.41%) with virtually no further decrease thereafter.

Secondary efficacy endpoints:

- Proportion (%) of patients with HbA_{1c} <7% (responder) at Month 6: The percentage of patients who reached an HbA_{1c} target <7% at Month 6 was similar in the HOE901-U300 and Lantus overall groups (16.8% and 15.0%, respectively), as was the percentage of patients who reached this target without any episode of severe or confirmed (plasma glucose <3.0 mmol/L [54 mg/dL]) hypoglycemia (6.2% and 5.9%, respectively; relative risk [RR] HOE901-U300 versus Lantus = 1.04 [95% CI: 0.56 to 1.93]) or no nocturnal (00:00 – 05:59 hours) severe or confirmed (plasma glucose <3.0 mmol/L [54 mg/dL]) hypoglycemia during the last 3 months of the main 6-month on-treatment period (11.0% in the HOE901-U300 overall group and 10.6% in the Lantus overall group (RR versus Lantus = 1.01 [95% CI: 0.64 to 1.59]).
- Proportion (%) of patients with HbA_{1c} ≤6.5% at Month 6: The percentage of patients who reached an HbA_{1c} ≤6.5% at Month 6 was similar in the HOE901-U300 and Lantus overall treatment groups (8.1% and 5.5%, respectively).
- Proportion (%) of patients with at least 1 nocturnal hypoglycemia: The incidence of patients with at least 1 severe and/or confirmed (ie, plasma glucose ≤3.9 mmol/L [70 mg/dL]) nocturnal (00:00 to 05:59 hours) hypoglycemia occurring between start of Week 9 and Month 6 was similar in the HOE901-U300 overall group and Lantus overall group (59.3% and 56.0%, respectively; RR versus Lantus = 1.06 (95%CI: 0.92 to 1.23).
- Pre-injection plasma glucose at Month 6: The LS mean change from baseline to endpoint (Month 6) in average pre-injection SMPG was similar in the overall HOE901-U300 and Lantus groups (-1.16 mmol/L [-20.97 mg/dL] and -0.82 mmol/L [-14.72 mg/dL], respectively). The LS mean difference between both overall treatment groups was -0.35 mmol/L (95% CI: -0.982 to 0.287); -6.26 mg/dL (95% CI: -17.686 to 5.168).
- The LS mean change in variability of pre-injection SMPG from baseline to Month 6 was similar in the HOE901-U300 and

Lantus overall groups (HOE901-U300 overall group -3.03% [95%CI: -6.131 to 0.066] and Lantus overall group -1.76% [95% CI: -5.014 to 1.491], respectively). The LS mean difference between HOE901-U300 and Lantus overall groups was -1.27% (95% CI: -5.735 to 3.193).

- The LS mean change in FPG from baseline to Month 6 was similar in the HOE901-U300 and Lantus overall groups (HOE901-U300 overall group -0.95 mmol/L [-17.09 mg/dL]; Lantus overall group -1.14 mmol/L [-20.54 mg/dL]. The LS mean difference between HOE901-U300 overall and Lantus overall was 0.19 mmol/L (95% CI: -0.536 to 0.919; 3.45 mg/dL [95% CI: -9.657 to 16.558]).

- Proportion (%) of patients with FPG <5.6 mmol/L (100 mg/dL): The percentage of patients who reached the target FPG <5.6 mmol/L (100 mg/dL) at Month 6 was similar in the overall HOE901-U300 overall group (9.9%) and the Lantus overall group (12.8%; RR versus Lantus overall = 0.78 [95%CI: 0.49 to 1.23]). Moreover, there was no difference between the overall treatment groups when considering the percentage of patients who reached this target without any episode of severe or confirmed (plasma glucose <3.0 mmol/L [54 mg/dL]) hypoglycemia (3.3% and 4.4%, respectively) or no nocturnal (00:00 to 05:59 hours) severe or confirmed (plasma glucose <3.0 mmol/L [54 mg/dL]) hypoglycemia during the last 3 months of the main 6-month on-treatment period (8.1% and 10.6%, respectively; RR versus Lantus overall = 0.78 [95%CI: 0.36 to 1.68] and 0.77 [95%CI: 0.46 to 1.27], respectively).

- Proportion (%) of patients with FPG <7.2 mmol/L (130 mg/dL): The percentage of patients who reached FPG <7.2 mmol/L (130 mg/dL) at Month 6 was similar in the overall HOE901-U300 overall group (25.3%) and the Lantus overall group (25.6%; RR versus Lantus overall = 0.98 [95% CI: 0.74 to 1.31]). Moreover, there was no difference between the overall treatment groups when considering the percentage of patients who reached this level without any episode of severe or confirmed (plasma glucose <3.0 mmol/L [54 mg/dL]) hypoglycemia (7.0% and 9.5%, respectively) or no nocturnal (00:00 to 05:59 hours) severe or confirmed (plasma glucose <3.0 mmol/L [54 mg/dL]) hypoglycemia during the last 3 months of the main 6 month on-treatment period (19.0% and 19.8%, respectively); RR versus Lantus overall = 0.75 [95% CI: 0.43 to 1.28] and 0.96 [95% CI: 0.68 to 1.34].

- Eight-point SMPG profile: The mean 8-point SMPG profiles of the overall treatment groups had improved at all timepoints from baseline to Month 6. In both treatment groups, similar decreases were seen from 3:00 hours to postlunch. Thereafter, the SMPG decreased to a lower level until bedtime in the Lantus overall group.

- Daily insulin doses: From baseline to Month 6, the average daily basal insulin dose increased in both overall treatment groups, mainly during the first 8 to 12 weeks of the main 6-month on-treatment period, with the steepest increase during the first 2 weeks. After Week 12, only small changes in average basal insulin dose occurred in both overall treatment groups until Month 6. The average daily basal insulin dose at Month 6 was 40.46 U (0.47 U/kg) in the HOE901-U300 overall group and 34.12 U (0.40 U/kg) in the Lantus overall group.

- The mean average daily total insulin dose at Month 6 (observed cases) was 69.56 U (0.81 U/kg) in the HOE901-U300 overall group and 60.87 U (0.73 U/kg) in the Lantus overall group.

- Free fatty acids: The LS mean change from baseline to Month 6 in plasma concentration of free fatty acids was similar in the HOE901-U300 overall (-0.06 mmol/L [95% CI: -0.11 to -0.01]; -1.73 mg/dL [95% CI: -3.13 to -0.32] and Lantus overall: -0.09 mmol/L [95% CI: -0.13 to -0.04]; -2.43 mg/dL [95% CI: -3.78 to -1.08]).

There was no difference between injection time groups for the primary and secondary endpoints.

Safety results:

No meaningful differences were found in the safety and tolerability between the 2 overall treatment groups and between HOE901-U300 morning versus evening injection, HOE901-U300 morning injection versus Lantus morning injection, and HOE901-U300 evening injection versus Lantus evening injection.

In patients with T1DM treated for 6 months during this study, hypoglycemia occurring at any time of the day or during the night (between 00:00 and 05:59 hours) was reported by similar percentage of patients and there were similar event rates per patient year of exposure in the HOE901-U300 and Lantus overall group across all categories of hypoglycemia. No differences were seen for hypoglycemia between the treatment groups and when considering morning and evening injections. During the first 8 weeks of study treatment, when most of the increase of the basal insulin dose occurred in all treatment groups, nocturnal hypoglycemia was reported by a lower percentage of patients in the HOE901-U300 overall treatment group compared with Lantus treated patients and with a clinically relevant risk reduction of 19% for documented symptomatic (≤3.9 mmol/L [70 mg/dL]) nocturnal hypoglycemia (relative risk versus Lantus 0.81, 95% CI 0.66 to 1.00) and 18% for severe and/or confirmed (≤3.9 mmol/L [70 mg/dL]) nocturnal hypoglycemia (relative risk versus Lantus 0.82, 95% CI 0.70 to 0.96).

The percentage of patients with any TEAE (HOE901-U300 overall group, 167/274 [60.9%] patients, Lantus overall group 160/275 [58.2%] patients) or with serious TEAEs (HOE901-U300 overall group 17 [6.2%] patients, Lantus overall group 22 [8.0%] patients) were similar between both overall groups. The spectrum of TEAEs was comparable, with TEAEs of the system organ class (SOC) infections and infestations being the most frequently reported events in both groups.

During the 6-month study period, 1 patient in the HOE901-U300 group with preexisting cardiovascular disease had a TEAE with fatal outcome (severe coronary artery disease with chest pain); this was the only major adverse cardiovascular event (MACE) reported in this study. Three patients in each treatment group reported AEs leading to discontinuation of the study. Malignancy (malignant melanoma) not related to the study medication was reported in 1 patient in the Lantus group.

A similar number of patients in the HOE901-U300 and Lantus group reported hypersensitivity reactions (HOE901-U300 overall group 16 [5.8%] patients; Lantus overall group 13 [4.7%] patients). The combined number of hypersensitivity, drug hypersensitivity, generalized pruritus, rash, and erythema events was higher in the HOE901-U300 overall group compared to the Lantus overall group (HOE901-U300 overall group 9 patients; Lantus overall group zero patients). The number of injection site reactions was similar in both overall treatment groups (HOE901-U300 overall group 6 [2.2%] patients; Lantus overall group 4 [1.5%] patients). There was no difference between treatment groups in terms of the incidence of patients with AIA, AIA titer, and cross-reactivity to human insulin, nor was there any difference concerning the effect of AIA on efficacy and safety endpoints.

Issue date: 20-May-2015

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Sponsor / Company: Sanofi **Drug substance(s):** HOE901-U300 (insulin glargine)	**Study Identifiers:** NCT01683266, UTN U1111-1128-5517 & EudraCT 2012-001524-35 **Study code:** EFC12456
Title of the study: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period (EFC12456 12-months)	
Study center(s): Multicenter (124 centers in 12 countries)	
Study period: Date first patient enrolled: 12/Sep/2012 Date last patient completed: 14/Mar/2014	
Phase of development: Phase 3	
Objectives: Primary objective: To compare the efficacy of a new formulation of insulin glargine (HOE901-U300) and Lantus (overall, regardless of the injection time) in terms of change of hemoglobin A_{1c} (HbA_{1c}) from baseline to endpoint (scheduled Month 6) in patients with type 1 diabetes mellitus (T1DM). Secondary objectives were to compare HOE901-U300 and Lantus when given in the morning or in the evening in terms of: • Change of HbA_{1c} from baseline to endpoint (scheduled Month 6); • Change from baseline to endpoint (Month 6) in fasting plasma glucose (FPG), plasma glucose prior to injection of the study drug, plasma glucose at 03:00 hours, mean plasma glucose (8-point profiles), glucose variability, treatment satisfaction and health related quality of life in patients with T1DM; • Reaching target HbA_{1c} values and controlled plasma glucose (all and reaching target without hypoglycemia); • Frequency of occurrence and diurnal distribution of hypoglycemia by category of hypoglycemia (symptomatic, asymptomatic, nocturnal, severe, probable and relative); • Safety and tolerability (including development of anti-insulin antibodies [AIA]) of HOE901-U300.	
Methodology: The randomization was 1:1:1:1 (HOE901-U300 morning injection, HOE901-U300 evening injection, Lantus morning injection, Lantus evening injection) and was stratified according to HbA_{1c} values at screening (<8%; ≥8%) and geographical region (Non-Japan; Japan); for each region, there was to be a minimum of 20% randomized patients per HbA_{1c} stratum. The sample size (125 in each group) was chosen to ensure sufficient power for the primary endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]).	

Number of patients:	Planned: 500 (125 per treatment group) Randomized: 549 (274 patients in the HOE901-U300 overall group, 275 patients in the Lantus overall group) Treated: 549
Evaluated:	
	Efficacy: 547 Safety: 549

Diagnosis and criteria for inclusion:

Inclusion criteria: Patients with T1DM; signed written informed consent.

Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >10% at screening; less than 1 year on basal plus mealtime insulin and self-monitoring of blood glucose (SMPG); not on stable insulin (±20% total basal insulin dose) in last 30 days prior to screening; use of premix insulins, human regular insulin as mealtime insulin and/or any glucose-lowering drugs other than basal insulin and mealtime analogue insulin in last 3 months before screening; use of insulin pump in last 6 months before screening.

Study treatments

Investigational medicinal product(s): Tested drug - HOE901-U300; Control drug - HOE901 (Lantus)

Formulation: HOE901-U300 (insulin glargine 300 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution that was supplied in a disposable (prefilled) insulin pen (modified Tactipen®). Lantus (insulin glargine 100 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution supplied in the marketed Solostar® (prefilled ie, disposable pen).

Route of administration: Subcutaneous (SC) injection

Dose regimen: Once daily (QD) injection in the morning or evening. The injection time was fixed at the time of randomization and was to be maintained for the duration of the study.

Starting dose: Patients on Lantus: the starting dose (U) of HOE901-U300 or Lantus was equal to the median of the total daily basal insulin doses in the last 3 days prior to the baseline visit.

Patients on neutral protamine Hagedorn (NPH) or insulin detemir QD prior to the baseline visit: the starting dose (U) of HOE901-U300 or Lantus was equal to the NPH or insulin detemir dose on the day prior to the baseline visit.

Patients on NPH or insulin detemir more than QD prior to the baseline visit: the starting dose (U) of HOE901-U300 or Lantus was to be equal to 80% of the total daily NPH or insulin detemir dose on the day prior to the baseline visit.

The basal insulin dose was adjusted once weekly to achieve fasting SMPG in the target range of 80 to 130 mg/dL (4.4 to 7.2 mmol/L).

Noninvestigational medicinal product(s): Mandatory background therapy – short-acting mealtime insulin analog.

Mealtime insulin doses were to be adjusted to optimize glycemic control after basal insulin had been optimized. Doses could be reduced as basal insulin doses were increased. Patients in both treatment groups were to continue with their mealtime insulin analog during the study.

Duration of treatment: Up to 12 months

Duration of observation: Up to 54 weeks + 2 days (screening period up to 2 weeks, 6-month open-label comparative efficacy and safety treatment period, 6-month open-label comparative safety extension period, 2-day post-treatment safety follow-up).

The analysis period for efficacy and safety was the main 6-month on-treatment period and a 12-month on-treatment period.

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: Change in HbA_{1c} from baseline to Month 12.

Other efficacy endpoints: Change from baseline to Month 12 for the following: FPG, SMPG (including pre-injection SMPG, variability of pre-injection SMPG, 8-point SMPG profiles, mean 24-hour plasma glucose and variability of 24-hour plasma glucose based on 8-point SMPG profiles, fasting (prebreakfast) SMPG, 5-point SMPG profiles), daily average insulin doses (including basal, mealtime and total insulin, and ratio of basal to total insulin), plasma free fatty acids (FFA); assessment of treatment satisfaction using Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs), health status using EuroQol five-dimension scale (EQ-5D) and fear of hypoglycemia using hypoglycemia fear survey (HFS) up to Month 12.

Safety: The safety analysis was based on all events of hypoglycemia (symptomatic, asymptomatic, severe, probable, relative); local tolerability at injection site, hypersensitivity reactions, cardiovascular events (including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), adverse events of special interest (AESIs) with immediate notification (ie, alanine aminotransferase [ALT] increase, pregnancy, symptomatic overdose with investigational medicinal product [IMP]/noninvestigational medicinal product [NIMP]); AESIs without immediate notification (ie, asymptomatic overdose with IMP/NIMP); other adverse events (AEs) or serious adverse events (SAEs); other safety information including: clinical laboratory data, vital signs including body weight, 12-lead electrocardiogram (ECG), and AIA results.

Anti-insulin antibody sampling times and bioanalytical methods: Samples for AIA assessment were collected at baseline (Visit 3), Week 4 (Visit 7), Week 12 (Visit 11), Month 6 (Visit 14), Month 12 (Visit 18), and in case of premature discontinuation from the study treatment. Anti-insulin antibodies were determined at a centralized laboratory using a validated AIA binding assay methodology.

Statistical methods: Descriptive statistics on the 12-month on-treatment period were provided for HbA_{1c} and other efficacy endpoints for the modified intention to treat (mITT) population. A mixed-effects model for repeated measures (MMRM) methodology was used to analyze change from baseline to Month 12 endpoint on key efficacy variables (ie, HbA_{1c}, FPG, pre-injection SMPG [average and variability], and 24-hour 8-point SMPG profile [average and variability]).

Summaries of safety and tolerance results were presented by treatment groups (HOE901-U300 or Lantus) for the 12-month on-treatment period for the safety population. Unless otherwise specified, the analysis of the safety variables is descriptive and no systematic testing was planned.

Summary: The current report presents the efficacy and safety results for the 12-month on-treatment period.

Population characteristics: A total of 549 patients with T1DM were randomized to HOE901-U300 (274 patients; morning injection: 136, evening injection: 138) or to Lantus (275 patients; morning injection: 137, evening injection: 138); all patients were exposed to IMP (safety population). The mITT population (efficacy population) included 547 patients.

Overall, a comparable percentage of patients in each treatment group discontinued the study prematurely (HOE901-U300 overall group: 55/274, 20.1%; Lantus overall group: 50/275, 18.2%).

Demographics and baseline characteristics were well-balanced between the overall groups. The mean age of the study population was 47 years; 55/549 (10.0%) patients were ≥65 years. 313/549 (57.0%) of the patients were males. The majority of patients were Caucasian (467/549; 85.1%). The mean body mass index (BMI) at baseline was 27.6 kg/m^2. The mean duration of diabetes prior to study start was 21.0 years and the median total daily insulin dose was 0.667 U/kg body weight. Mean HbA_{1c} at baseline was 8.12%.

Efficacy results:

Mean HbA_{1c} decreased similarly from baseline to the Month 12 endpoint in both overall groups (Least squares [LS] mean difference of HOE901-U300 overall versus Lantus overall in change from baseline to Month 12 endpoint: 0.02% [95% confidence interval {CI}: -0.134 to 0.173]; MMRM), with the largest decrease occurring between baseline and Week 12. During the 6-month safety extension period, HbA_{1c} increased again and in a similar manner in both overall groups, but remained below the values observed at baseline (Month 12, HOE901-U300 overall: 7.86% [1.03]; Lantus overall: 7.86% [0.84]). When comparing HOE901-U300 and Lantus in the morning injection groups and evening injection groups during the 6-month safety extension period, glycemic control was maintained in both treatment groups similarly as shown by similar changes of HbA_{1c} at Month 12. However, at Month 12, a significantly larger decrease in HbA_{1c} was observed in the HOE901-U300 morning group than in the HOE901-U300 evening group (LS mean differences in change from baseline: -0.25% [95% CI: -0.472 to -0.036]).

Other parameters of glycemic control such as FPG, pre-injection SMPG, 24-hour average plasma glucose based on 8-point SMPG profile, variability of 24-hour average plasma glucose, and average prebreakfast SMPG improved similarly in both overall groups primarily during the initial 12 weeks of study treatment. Fasting plasma glucose, pre-injection SMPG, 24-hour average plasma glucose and average prebreakfast SMPG remained stable during the 6-month safety extension period. The change from baseline to Month 12 in 24-hour average plasma glucose was similar between both overall groups (LS mean difference HOE901-U300 overall versus Lantus overall: 0.12 mmol/L [95% CI: -0.338 to 0.582]; MMRM). Variability of average plasma glucose decreased similarly in both overall groups during the 6-month safety extension period. At Month 12, mean 8-point SMPG profiles had improved similarly in both treatment groups at all time points.

These changes in glycemic control were observed while mean daily average basal insulin doses increased in both overall groups, mainly during the first 12 weeks with only small further changes thereafter until Month 12. From baseline to Month 12, the mean daily average basal insulin dose increased by 14.87 U (0.165 U/kg) in the HOE901-U300 overall group and by 8.63 U (0.093 U/kg) in the Lantus overall group. At Month 12, the mean daily average basal insulin dose was 41.89 U (0.482 U/kg) in the HOE901-U300 overall group, ie, 19.3% (U/kg) above that in Lantus overall group (34.44 U [0.404 U/kg]). During the 12 month on-treatment period, in the morning groups, both the mean daily HOE901-U300 and Lantus doses were substantially increased, with a greater increase of the HOE901-U300 dose. In the evening groups, the HOE901-U300 dose was increased, while there was only a small increase in the Lantus group.

The mean daily average mealtime insulin doses increased in the first 4 weeks in both overall groups and remained relatively stable thereafter. From baseline to Month 12, the mean daily average mealtime insulin dose increased by 4.15 U (0.046 U/kg) in the HOE901-U300 overall group and by 2.15 U (0.021 U/kg) in the Lantus overall group. At Month 12, the mean daily average mealtime insulin dose was 30.73 U (0.361 U/kg) in the HOE901-U300 overall group and 26.78 U (0.322 U/kg) in the Lantus overall group. In the morning groups, mealtime insulin doses were increased in the HOE901-U300 group, while only small adjustments were done in the Lantus group. In the evening groups, the mealtime insulin dose increase was small and larger in the Lantus group than in the HOE901-U300 group.

As a result of the changes in basal and mealtime doses, at Month 12, mean daily average total insulin dose was 16.0% (U/kg) higher in the HOE901-U300 overall group (72.28 U [0.841 U/kg]) than in the Lantus overall group (60.85 U [0.725 U/kg]), and was driven by the differences in basal insulin dose increase. The mean daily average total insulin dose (U/kg) was 6.5% higher in the HOE901-U300 morning group compared to the HOE901-U300 evening group; in the morning groups, it was 15.6% higher with HOE901-U300 compared to Lantus; and in the evening groups, it was 16.8% higher with HOE901-U300 compared to Lantus.

During the 12-month on-treatment period and across treatment groups, a minimal and not clinically meaningful improvement in treatment satisfaction (DTSQs), health status (EQ 5D scores) and fear of hypoglycemia (HFS) was observed.

Safety results:

During the 12-month on-treatment period, the percentage of patients with at least 1 hypoglycemia event of any category was similar in both overall groups for both hypoglycemia with onset at any time of day (HOE901-U300 overall: 95.3%; Lantus overall: 94.9%), for nocturnal hypoglycemia with onset between 00:00 and 05:59 hours (HOE901-U300 overall: 73.4%; Lantus overall: 74.9%) and during daytime with onset between 06:00 and 23:59 hours (HOE901-U300 overall: 94.9%; Lantus overall: 94.2%). The percentage of patients with nocturnal hypoglycemia defined by sleep status were similar between the HOE901-U300 and Lantus overall groups (66.4% versus 64.0%) for all categories of hypoglycemia and similar or lower, depending of the category of hypoglycemia, than the percentages of patients reporting nocturnal hypoglycemia defined by

onset between 00:00 and 05:59 hours. In the injection groups, the percentage of patients with at least 1 hypoglycemia event was similar for any category of hypoglycemia events with onset at any time of the day, during nighttime (00:00 to 05:59 hours) and during daytime (06:00 to 23:59 hours).

The event rates per patient-year of exposure for hypoglycemia events reported at any time of the day were higher in the HOE901-U300 overall group (77.26) than in the Lantus overall group (69.99) during the 12-month on-treatment period and during the 6-month safety extension period, although the majority of these events were reported during the main study 6-month on-treatment period. The difference between both overall groups was primarily due to higher event rates per patient-year of exposure for hypoglycemia reported during the daytime (06:00 to 23:59 hours).

During the 12-month on-treatment period, the event rates per patient-year of exposure of nocturnal hypoglycemia (00:00 to 05:59 hours) were similar in the HOE901-U300 (8.30) and Lantus (8.86) overall groups and within the HOE901-U300 and Lantus morning and evening groups, while the rates of hypoglycemia were higher for events occurring during daytime in the HOE901-U300 overall group (68.94) compared to the Lantus overall group (61.09).

Severe hypoglycemia was reported in 25 patients (9.1%) in the HOE901-U300 overall group and 31 patients (11.3%) in the Lantus overall group. There were no differences related to the time of injection (morning or evening).

One patient (0.4%) in the HOE901-U300 overall group died during the study period due to a serious treatment-emergent adverse event (TEAE) of coronary artery disease. This death was considered not to be related to the study drug by the Investigator. There was no death reported in the Lantus overall group.

The percentage of patients with any TEAEs (HOE901-U300 overall: 198/274 patients [72.3%]; Lantus overall: 187/275 patients [68.0%]) or with serious TEAEs (HOE901-U300 overall: 27/274 patients [9.9%]; Lantus overall: 26/275 patients [9.5%]) during the 12-month on-treatment period was similar in both overall groups. The percentage of patients experiencing any TEAEs was higher in the HOE901-U300 evening group (75.5%) compared with the other injection groups (67.6% to 68.9%). This difference was mainly due to a higher percentage of TEAEs from the system organ class (SOC) Infections and Infestations in the HOE901-U300 evening group. The percentage of patients experiencing serious TEAEs was similar in the 4 injection groups (8.8% to 10.8%).

A similar proportion of patients in each overall group experienced TEAEs leading to permanent treatment discontinuation (HOE901-U300 overall: 1.8%; Lantus overall: 1.5%). Serious cardiac TEAEs (SOC Cardiac Disorders) were reported by 2 patients (0.7%) in the HOE901-U300 overall group and by 1 patient (0.4%) in the Lantus overall group. Hypersensitivity reactions were reported in 25 patients (9.1%) in the HOE901-U300 overall group and 21 patients (7.6%) in the Lantus overall group. Injection site reactions were rare in both overall groups (HOE901-U300 overall: 8 patients [2.9%], Lantus overall: 4 patients [1.5%]).

The laboratory parameters and vital sign data, as well as the assessment of ECG readings did not reveal any specific safety concerns during the 12-month on-treatment period.

The percentage of AIA-positive patients increased similarly in the HOE901-U300 and Lantus overall groups during the 12-month on-treatment period; there was no difference between both overall groups in terms of AIA status, AIA titer and cross-reactivity with human insulin nor was there any difference between both overall groups concerning the effect of AIA on efficacy and safety endpoints. However, there was a higher incidence of hypoglycemia events of any category in AIA-positive patients compared to AIA-negative patients in the HOE901-U300 overall group (97.0% [230/237] of AIA-positive patients and 82.8% [24/29] of AIA-negative patients) and in the Lantus overall group (96.2% [226/235] of AIA-positive and 91.4% [32/35] of AIA-negative patients). Nocturnal hypoglycemia events of any category were reported more frequently in AIA-positive patients compared with AIA-negative patients in both overall treatment groups (HOE901-U300 overall: 77.2% [183/237] and 58.6% [17/29] of patients, respectively; Lantus overall: 77.4% [182/235] and 68.6% [24/35], respectively).

Overall, no new safety signals were detected in this study in relation to insulin glargine, regardless of the formulation used.

Issue date: 20-May-2015