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:** NCT01676220, UTN U1111-1124-5261, EudraCT 2012-000146-35 **Study code:** EFC12347
Title of the study: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® in Insulin-naïve Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Non-insulin Antihyperglycemic Drugs with a 6-Month Safety Extension Period (EFC12347 6-months)	
Study center(s): Multicenter (197 centers in 15 countries)	
Study period: Date first patient enrolled: 31/Aug/2012 Date last patient completed: 11/Sep/2013	
Phase of development: Phase 3	
Objectives: Primary objective: To compare the efficacy of a new formulation of insulin glargine and Lantus in terms of change of hemoglobin A_{1c} (HbA_{1c}) from baseline to endpoint (scheduled at Month 6, Week 26) in patients with type 2 diabetes mellitus. Main secondary objectives: • To compare HOE901-U300 and Lantus in terms of occurrence of nocturnal hypoglycemia, change in pre-injection plasma glucose, and change in variability of pre-injection plasma glucose (later amended to variability of pre-injection plasma glucose). Further secondary objectives: • To compare HOE901-U300 and Lantus in terms of reaching target HbA_{1c} values and controlled plasma glucose (all and reaching target without hypoglycemia); • To compare HOE901-U300 and Lantus in terms of treatment satisfaction, perception of hypo- and hyperglycemia, health-related quality of life and fear of hypoglycemia in patients with type 2 diabetes mellitus; • To compare the frequency of occurrence and diurnal distribution of hypoglycemia by category of hypoglycemia (symptomatic, asymptomatic, nocturnal, severe, probable and relative); • To assess the safety and tolerability of HOE901-U300 including development of anti-insulin antibodies (AIAs).	
Methodology: The randomization was 1:1 (HOE901-U300 versus Lantus) 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} strata. The sample size (400 in each treatment arm) was chosen to ensure sufficient power for the primary endpoint (change in HbA_{1c} from baseline to endpoint) as well as to allow conclusions on the main secondary endpoint (occurrence of nocturnal hypoglycemia).	

Number of patients**:**	Planned: 800 (400 per treatment arm)
	Randomized: 878
	Treated: 873
Evaluated:	
	Efficacy: 862
	Safety: 873

Diagnosis and criteria for inclusion:

Inclusion criteria: Adult patients with type 2 diabetes mellitus inadequately controlled with non-insulin antihyperglycemic drug(s) with signed written informed consent.

Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >11% at screening; less than 1 year history of diabetes; <6 months history of treatment with non-insulin antihyperglycemic drug(s) which must be approved for combination with insulin and have been stable for 3 months; current or previous insulin use except for a maximum of 8 consecutive days (eg, acute illness, surgery) during the last year prior to screening.

Study treatments

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

Formulations: HOE901-U300 (insulin glargine 300 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution in a glass cartridge that has been assembled in a reusable pen-injector (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 injection

Dose regimen: Once daily injection in the evening, which was defined as the time period from immediately prior to the evening meal until bedtime. The injection time was fixed at the time of randomization and was to be maintained for the duration of the study.

Starting dose: The daily dose of basal insulin (HOE901-U300 or Lantus) was 0.2 U/kg body weight, rounded to the closest number divisible by 3.

The basal insulin dose was adjusted once weekly, but no more often than every 3 days, to achieve a target fasting self-measured plasma glucose (SMPG) in the target range of 4.4 to 5.6 mmol/L (80 to 100 mg/dL):

- by +6 U, if the median fasting SMPG of last 3 days was ≥7.8 mmol/L (≥140 mg/dL)
- by +3 U, if the median fasting SMPG of last 3 days was >5.6 and <7.8 mmol/L (>100 mg/dL and <140 mg/dL)
- by -3 U, if the median fasting SMPG of last 3 days was ≥3.3 and <4.4 mmol/L (≥60 mg/dL and <80 mg/dL).
- by -3 U, if the median fasting SMPG of last 3 days was <3.3 mmol/L (<60 mg/dL) or ≥2 symptomatic or 1 severe hypoglycemia in the preceding week.

Noninvestigational medicinal product(s) (if applicable): Mandatory background therapy (non-insulin antihyperglycemics approved for combination with insulin).

Patients in both treatment groups were to continue with their non-insulin antihyperglycemics approved for combination with insulin during the study on a stable dose as received prior to the study, unless safety concerns necessitated a dose reduction or discontinuation. Non-insulin antihyperglycemic drug(s) not approved in combination with insulin according to local labeling/local treatment guidelines and containing sulfonylurea, and glinides were not permitted during the study, and if used prior to the study, were discontinued at the start of the investigational medicinal product (IMP).

Rescue treatment:

If fasting plasma glucose (FPG) or HbA_{1c} measurements and/or SMPG were above the target values after the titration period (ie, after Week 12) and not improving as expected in spite of successive IMP dose titration, and no reasonable explanation existed, intensification of the treatment was to be considered by adding a non-investigational rescue therapy with the choice of the antidiabetic treatment based on the Investigator's decision.

Duration of treatment: Up to 12 months

Duration of observation: Up to 54 weeks (up to 2-week screening period + 6-month efficacy and safety period + 6-month safety extension period) + 2 to 4 days of post-treatment follow-up.

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

For all patients requiring rescue therapy during the 6-month on-treatment period, the last post-baseline efficacy measurement before the start of rescue therapy was used as the efficacy endpoint. These patients were excluded from efficacy analyses after initiation of rescue treatment. For safety endpoints, the analysis period was the main 6-month on-treatment period regardless of the use of rescue therapy.

Criteria for evaluation:

Efficacy:

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

Main secondary endpoints: incidence of patients (%) with at least one nocturnal hypoglycemia between start of Week 9 and endpoint (Month 6), indicated as severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL); change in pre-injection SMPG from baseline to endpoint (Month 6) and variability of pre-injection SMPG at endpoint (Month 6); note that change in variability could not be measured and the planned analysis was amended prior to database lock.

Other secondary efficacy endpoints included responder analyses of HbA_{1c} <7% and ≤6.5% and FPG <5.6 mmol/L and <6.7 mmol/L, changes from baseline to endpoint (Month 6) in: FPG, 8-point SMPG profiles, mean 24-hour SMPG, variability of 24-hour SMPG, daily basal insulin dose, plasma free fatty acids, C-peptide; and the requirement for rescue therapy. Treatment satisfaction and health related quality of life were assessed using Diabetes Treatment Satisfaction Questionnaires (DTSQs), EuroQol five-dimension scale (EQ-5D), and the Adult Low Blood Sugar Survey (Hypoglycemia Fear Scale – HFS II).

Safety: Hypoglycemia, occurrence of adverse events particularly treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), adverse events of special interest ([AESIs], with/without immediate notification), injection site reactions, hypersensitivity reactions, cardiovascular events, other safety information including clinical laboratory data, vital signs (including body weight), 12-lead electrocardiogram (ECG), AIAs and site of IMP administration.

Anti-insulin antibody sampling times and bioanalytical methods:

Samples for AIA assessment were to be collected at baseline, at Week 4, Week 12, Month 6, and Month 12 and in case of premature discontinuation of the study treatment. Anti-insulin antibodies were to be determined at a central laboratory using a validated AIA binding assay methodology. These data were not available for this report and will be included in the report for the 12-month analyses.

Statistical methods:

The primary efficacy endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]) was analyzed using a mixed-effects model for repeated measures (MMRM) approach with fixed categorical effects of screening HbA_{1c} (<8.0 and ≥8.0%) and randomization strata of geographical region (non-Japan; Japan), and continuous fixed covariates of baseline HbA_{1c} value and baseline HbA_{1c} value-by-visit interaction. Differences between HOE901-U300 and Lantus, with corresponding standard errors and 95% confidence intervals (CIs) were also estimated within the framework of PROC MIXED using an adequate contrast at Month 6.

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 versus Lantus. To assess non-inferiority, the upper bound of the two sided 95% CI for the difference in the mean change in HbA_{1c} from baseline to endpoint between HOE901-U300 and Lantus was compared with a predefined non inferiority margin of 0.4% HbA_{1c}. Non-inferiority would be demonstrated if the upper bound of the two-sided 95% CI of the difference between HOE901-U300 and Lantus on the modified intent-to-treat (mITT) population is <0.4%. Step 2 assessed superiority of HOE901-U300 versus Lantus only if non inferiority was demonstrated. The superiority of HOE901-U300 over Lantus was demonstrated if the upper bound of the two-sided 95% CI of the difference between HOE901-U300 and Lantus on the mITT population was <0. The test for the primary endpoint (Month 6) was performed one-sided at level α=0.025.

Only if non-inferiority of HOE901-U300 versus Lantus had been demonstrated for the primary endpoint, would testing for superiority of HOE901-U300 over Lantus on the main secondary endpoints occur within the frame of a hierarchical testing procedure. 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 878 patients with type 2 diabetes mellitus inadequately controlled with non-insulin antihyperglycemic drug(s) were randomized to HOE901-U300 (439 patients) or to Lantus (439 patients); 873 patients were exposed to the IMP (safety population). The mITT population (efficacy population) included 862 patients.

Overall, a comparable number of patients in each treatment group discontinued the study prematurely (HOE901-U300: 62/439, 14.1%; Lantus 75/439, 17.1%). A total of 366 (83.4%) patients in the HOE901-U300 group and 350 (79.7%) in the Lantus group completed the main 6-month on-treatment period (patients who received rescue medication were excluded from the completers population).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 57.7 years; 226 of 878 (25.7%) patients were ≥65 years. Overall, 57.7% of the patients were male. A total of 685 patients (78.0%) were Caucasian. The mean body mass index (BMI) at baseline was 33.0 kg/m², and 63.6% of patients had a BMI ≥30 kg/m². The mean duration of diabetes prior to study start was 9.84 years (median: 8.5 years), the mean duration of prior treatment with non-insulin antihyperglycemic medications used within 3 months prior to randomization was 4.08 years (median: 2.54 years). The average daily basal insulin starting dose at baseline was comparable in both treatment groups (HOE901-U300: 18.34 U [0.19 U/kg]; Lantus: 18.57 U [0.19 U/kg]).

Mean HbA_{1c} at baseline was 8.49% in the HOE901-U300 group and 8.58% in the Lantus group for evaluable patients (ie, who had a baseline and at least one post-baseline HbA_{1c} assessment).

Efficacy results:

Primary endpoint: The LS mean change in HbA_{1c} from baseline to endpoint (Month 6) was -1.42% (95% CI: -1.511 to -1.326) on HOE901-U300 and -1.46% (95 % CI: -1.555 to -1.367) on Lantus. The LS mean difference between HOE901-U300 and Lantus was 0.04% (95% CI: -0.090 to 0.174). Noninferiority of HOE901-U300 over Lantus was demonstrated, as shown by the upper bound of the 95% CI (0.174%) below the prespecified noninferiority margin of 0.4%. The observed CI also supports a noninferiority margin of 0.3%. Superiority of HOE901-U300 versus Lantus was not demonstrated.

In both treatment groups, a reduction in HbA_{1c} occurred through the 6-month on-treatment period with the steepest reduction during the first 12 weeks of treatment which corresponds with mean changes in daily insulin dose.

First main secondary endpoint: The incidence of patients with at least one nocturnal hypoglycemia indicated as severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL) that occurred between 00:00 and 05:59 hours, regardless whether patient was awake or woke up because of the event, between start of Week 9 and Month 6 was 15.5% (67/432 patients) in the HOE901-U300 group and 17.4% (75/430 patients) in the Lantus group. The prespecified analysis did not demonstrate superiority of HOE901-U300 over Lantus with a relative risk of 0.89 (95% CI: 0.66 to 1.20; p=0.4536).

As the superiority of HOE901-U300 versus Lantus was not demonstrated for the first main secondary endpoint, no further tests were performed for the second and third main secondary endpoints.

Second main secondary endpoint: The interpretability of the results was limited by the high amount of missing data at baseline, however, LS mean change in average pre-injection SMPG from baseline to endpoint (Month 6) was similar in the HOE901-U300 (-2.16 mmol/L [-38.92 mg/dL]) and Lantus groups (-2.33 mmol/L [-41.89 mg/dL]).

Third main secondary endpoint: The variability of pre-injection SMPG at endpoint (Month 6) was similar in the HOE901-U300 group (18.70%) and Lantus groups (18.33%).

Other secondary efficacy endpoints:

The percentage of patients who reached HbA_{1c} <7% at Month 6 was similar between treatment groups (43.1% in the HOE901-U300 group; 42.1% in the Lantus group). The LS mean change in FPG from baseline to endpoint (Month 6) was greater in the Lantus group than in the HOE901-U300 group (LS mean difference versus Lantus was 0.39 mmol/L [95% CI: 0.100 to 0.676]; 6.99 mg/dL [95% CI: 1.800 to 12.178]).The percentages of patients in the HOE901-U300 and Lantus groups were similar for patients who reached target FPG <5.6 mmol/L (100 mg/dL) at Month 6 (26.2% and 29.5%, respectively) and for patients reaching target FPG <5.6 mmol/L (100 mg/dL) at Month 6 without experiencing any severe and/or confirmed hypoglycemia at any time (24.1% and 25.6%, respectively) or at night (25.9% and 28.1%, respectively). Comparable results between the treatment groups were also found for other secondary endpoints: change in 8-point profiles of plasma glucose, change in 24-hour average plasma glucose (based on 8-point profiles), and change in variability of 24-hour average plasma glucose (based on 8-point profiles), change in free fatty acids, and change in C-peptide.

At Month 6, the mean daily basal insulin dose was slightly higher in the HOE901-U300 group (59.37 U [0.62 U/kg]) than in the Lantus group (52.03 U [0.53 U/kg]).

Fewer patients required rescue therapy in the HOE901-U300 group (7/439, 1.6%) than in the Lantus group (15/439, 3.5%) during the main 6-month on-treatment period (based on randomized population).

The overall satisfaction of the patients with treatment in both treatment groups measured by DTSQs was good throughout the study. Health related quality of life issues remained stable with good health score on the single utility index and good perceived health status using the visual analog scale. Fear of hypoglycemia was very low at baseline and decreased further to endpoint (Month 6).

Safety results:

Overall, at least one episode of any hypoglycemia event was reported by 217 of 435 patients [49.9%] in the HOE901-U300 group and by 242 of 438 patients (55.3%) in the Lantus group.

A lower or similar percentage of patients reported hypoglycemia events in the HOE901-U300 treatment group than in the Lantus group. This was observed throughout all hypoglycemia categories and the main 6-month on-treatment study period, as well as for nocturnal hypoglycemia (occurring between 00:00 and 05:59) and daytime hypoglycemia (between 06:00 and 23:59). Results for nocturnal hypoglycemia by sleep status were consistent to those of nocturnal hypoglycemia occurring between 00:00 and 05:59. The hypoglycemia events occurring after rescue therapy initiation did not affect the overall conclusions. Hypoglycemia percentages in the subgroups defined by demographic and baseline characteristics yielded findings consistent with those in the overall study population.

Risk reduction of nocturnal severe and/or confirmed hypoglycemia (≤3.9 mmol/L [70 mg/dL]) was observed over the entire main 6-month on-treatment period in favor of HOE901-U300 versus Lantus (relative risk [RR] 0.76 [95% CI: 0.59 to 0.99]). Risk reduction of severe (any time of the day) and/or confirmed hypoglycemia <3.0 mmol/L (54 mg/dL) was observed during the main 6-month on-treatment period: 39% risk reduction in favor of HOE901-U300 (RR 0.61 [95%CI: 0.43 to 0.87]). Risk reduction was also observed for the nocturnal hypoglycemia of this category.

Descriptive analyses of events per patient-year of exposure also showed lower rates of daytime hypoglycemia in the HOE901-U300 group than in the Lantus group. For nocturnal hypoglycemia, event-rates per patient-year were similar in both treatment groups.

During the main 6-month on-treatment period severe hypoglycemia was reported in similar number of patients in both groups: 4 of 435 patients (0.9%) in the HOE901-U300 group and 4 of 438 patients (0.9%) in the Lantus group. Severe hypoglycemia occurred at a rate of 0.02 events per patient-year of exposure in each group. None of severe hypoglycemia episodes were nocturnal.

The percentages of patients with any TEAEs (HOE901-U300, 247/435 [56.8%]; Lantus, 245/438 [55.9%]) or with serious TEAEs (HOE901-U300, 24/435 [5.5%]; Lantus, 26/438 [5.9%]) were similar between both groups.

The most frequently reported serious TEAEs were from the System Organ Class Cardiac disorders (4 patients [0.9%] and 7 patients [1.6%] in the HOE901-U300 and Lantus groups, respectively). All the patients experiencing serious cardiac TEAEs suffered from preexisting, significant event-related pathology; none of the events were considered as related to the IMP or NIMP by the Investigator. Overall, the number of patients experiencing cardiac TEAEs was 10 (2.3%) in the HOE901-U300 group and 19 (4.3%) in the Lantus group.

During the main 6-month on-treatment period, 1 patient in the HOE901-U300 group had a treatment-emergent SAE with fatal outcome (atherosclerosis coronary artery, worsening of existing condition). The death was considered not related to IMP by the Investigator and the Sponsor, and was considered to be a highly probable major adverse cardiovascular event (MACE event). No further patients had SAEs with fatal outcome after completion of the main 6-month on-treatment period (during the extension period up until the cutoff of 11 September 2013). The incidence of all MACE events was similar between the groups.

An alanine transaminase (ALT) increase event observed in the HOE901-U300 group with clinically important ALT and total bilirubin increase (>3 upper limit of normal [ULN] and >2 ULN, respectively) was considered not related to the study drug. A clear clinical cause of these observations was not established. Following several weeks of interruption and rechallenge with IMP which was continuing after the end of the reporting period, no further raised liver function test disorders were reported.

A similar number of patients in both treatment groups experienced TEAEs leading to permanent treatment discontinuation (HOE901-U300: n=5 [1.1%] Lantus: n=5 [1.1%]). Hypersensitivity reactions during the main 6-month on-treatment period were reported at a similar rate in both treatment groups (HOE901-U300: n=30 [6.9%] Lantus: n=25 [5.7%]). Overall injection site reactions during the main 6-month on-treatment period showed similar rate in both treatment groups (HOE901-U300: n=17 [3.9%] and Lantus: n=21 [4.8%]).

Laboratory parameter and vital sign data as well as the assessment of ECG readings did not reveal any specific safety concerns during the main 6-month on-treatment period. The effect on body weight was neutral in both treatment groups.

Issue date: 20-May-2015

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:** NCT01676220, UTN U1111-1124-5261, EudraCT 2012-000146-35 **Study code:** EFC12347
Title of the study: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® in Insulin Naïve Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Non-Insulin Antihyperglycemic Drugs with a 6-Month Safety Extension Period (EFC12347 [12 months])	
Study center(s): Multicenter (197 centers in 15 countries)	
Study period: Date first patient enrolled: 31/Aug/2012 Date last patient completed: 26/Mar/2014	
Phase of development: Phase 3	
Objectives: Primary objective: To compare the efficacy of a new formulation of insulin glargine and Lantus in terms of change of glycated hemoglobin A_{1c} (HbA_{1c}) from baseline to endpoint (scheduled at Month 6, Week 26) in patients with type 2 diabetes mellitus (T2DM). Main secondary objectives: • To compare occurrence of nocturnal hypoglycemia; • To compare change in pre-injection plasma glucose (self-monitored plasma glucose [SMPG]); • To compare change in variability of pre-injection plasma glucose (SMPG); this was amended to variability of pre-injection SMPG as part of a statistical analysis plan (SAP) amendment dated 07 October 2013 prior to database lock. Further secondary objectives: • To compare HOE901-U300 and Lantus in terms of reaching target glycated hemoglobin (HbA_{1c}) values and controlled plasma glucose (all and reaching target without hypoglycemia); • To compare HOE901-U300 and Lantus in terms of treatment satisfaction, perception of hypo- and hyperglycemia, health status and fear of hypoglycemia; • To compare the frequency of occurrence and diurnal distribution of hypoglycemia by category of hypoglycemia (symptomatic, asymptomatic, nocturnal, severe, probable and relative); • To assess the safety and tolerability (including development of anti-insulin-antibodies [AIA]) of HOE901-U300.	
Methodology: The randomization was 1:1 (HOE901-U300 versus Lantus) and was stratified according to HbA_{1c} values at screening (<8.0%; ≥8.0%) and geographical region (non-Japan; Japan). The sample size (400 in each treatment arm) was chosen to ensure sufficient power for the primary endpoint (change in HbA_{1c} from baseline to endpoint [Month 6]) as well as to allow conclusions on the first main secondary endpoint (occurrence of nocturnal hypoglycemia) for the initial 6-month treatment period.	

Number of patients**:**	Planned: 800 (400 per treatment arm)
	Randomized: 878 (HOE901-U300: 439; Lantus: 439)
	Treated: 873
Evaluated:	
	Efficacy: 862
	Safety: 873

Diagnosis and criteria for inclusion:

Inclusion criteria: Adult patients with T2DM as defined by the World Health Organization inadequately controlled with non-insulin antihyperglycemic drug(s); signed written informed consent.

Key exclusion criteria: Age <18 years; HbA_{1c} <7.0% or >11% at screening; T2DM less than 1 year; less than 6 months before screening with non-insulin antihyperglycemic treatment; change in dose of non-insulin antihyperglycemic treatment in the last 3 months before screening; initiation of new glucose lowering medications and/or weight loss drug in the last 3 months before screening visit and/or initiation of glucagon like peptide-1 (GLP-1) receptor agonist in the last 6 months before screening visit.

Study treatments

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

Formulations: HOE901-U300 (insulin glargine 300 U/mL solution) is a sterile, non-pyrogenic, clear, colorless solution in a glass cartridge that has been assembled in a pen injector (a modified reusable 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 injection

Dose regimen: Once daily injection in the evening, which was defined as the time period from immediately prior to the evening meal until bedtime. The injection time was fixed at the time of randomization and was to be maintained for the duration of the study.

Starting dose: The initial daily dose of basal insulin in both treatment groups (HOE901-U300 and Lantus) was 0.2 U/kg body weight, rounded to the closest number divisible by 3. The first injection of investigational medicinal product (IMP) was to be administered in the evening on the day of randomization. In both treatment groups, basal insulin doses were titrated for each patient to achieve the target fasting plasma glucose (FPG) in the range of 4.4 to 5.6 mmol/L (80 to 100 mg/dL). After reaching the target range, the insulin doses were adjusted for each patient to maintain glycemic control over the remaining study duration. No maximum doses were specified in the study protocol.

Noninvestigational medicinal product(s):

Patients were to be enrolled with background non-insulin antihyperglycemic drugs administered at the stable dose for at least 3 months prior to screening, or for glucagon-like peptide-1 (GLP-1) receptor agonist, for at least 6 months prior to screening.

The mandatory background therapy and the potential additional background new antihyperglycemic (rescue) drug were considered to be noninvestigational medicinal product (NIMP), and were to be administered according to the nationally approved label(s). Doses and combinations of background non-insulin antihyperglycemic drugs were to be kept stable throughout the study unless there was a specific safety issue related to this treatment. Dose changes of these medications were reported in source data and in the electronic case report form (eCRF).

Duration of treatment: Up to 12 months

Duration of observation: Up to 54 weeks (up to 2-week screening period + 6-month efficacy and safety period + 6-month safety + 2 days of post-treatment 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 preinjection 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, and mean plasma glucose based on 4-point SMPG profiles), daily average basal insulin doses, insulin dose by visit and other laboratory endpoints (including free fatty acids [FFA] and C-peptide). Variability of pre-injection SMPG at Month 12. Assessment of treatment satisfaction using Diabetes Treatment Satisfaction Questionnaire (DTSQs), EuroQoL-5 Dimensions (EQ-5D), and Hypoglycemia Fear Survey (HFS) variables up to Month 12. Percentage of patients under rescue therapy during the 12-month on-treatment period.

Safety: The safety analysis was based on all events of hypoglycemia (symptomatic, asymptomatic, severe, probable, relative); local tolerability at injection site, hypersensitivity reactions, adverse events of special interest (AESIs) with immediate notification (ie, increased alanine transaminase [ALT], pregnancy, symptomatic overdose with IMP/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 anti-insulin antibody (AIA) results.

Anti-insulin antibody sampling times and bioanalytical methods:

Samples for AIA assessment were collected at baseline (Visit 3), 4 weeks (Visit 7), 3 months (Visit 15), 6 months (Visit 18) and 12 months (Visit 22) 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 intent-to-treat (mITT) population. A mixed-effects model for repeated measures (MMRM) methodology was used to analyze key efficacy variables, ie, HbA_{1c}, FPG, pre-injection SMPG, and 8-point SMPG profiles.

Summaries of safety and tolerance results were presented by treatment group (HOE901-U300 or Lantus) for the 12-month on-treatment period and during the post-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 878 patients with T2DM were randomized to HOE901-U300 (439 patients) or to Lantus (439 patients); 873 patients were exposed to IMP (safety population). The mITT population (efficacy population) included 862 patients.

Overall, a comparable number of patients in each treatment group discontinued the study prematurely (HOE901-U300: 98/439, 22.3%; Lantus 124/439, 28.2%).

Demographics and baseline characteristics were well-balanced between the treatment groups. The mean age of the study population was 57.7 years; 226/878 (25.7%) patients were ≥65 years, and 507/878 (57.7%) of the patients were male. The majority of patients were Caucasian (685/878; 78.0%).The mean body mass index at baseline was 33.0 kg/m². The mean duration of diabetes prior to study start was 9.8 years. The duration of prior non-insulin antihyperglycemic treatment was 4.1 years. Mean HbA_{1c} at baseline was 8.54%. The mean (standard deviation [SD]) daily average basal insulin starting dose at baseline was 0.19 U/kg (0.03) body weight.

Efficacy results:

Mean HbA_{1c} decreased from baseline to endpoint (Month 12) in both treatment groups similarly; the largest decrease occurred during the first 12 weeks of treatment. During the 6-month extension period, HbA_{1c} remained stable, although mean HbA_{1c} tended to increase again, more in the Lantus group than in the HOE901-U300 group (7.13% in the HOE901-U300 group versus 7.24% in the Lantus group at Month 12). The reduction in HbA_{1c} from baseline to Month 12 was similar in both treatment groups (least squares [LS] mean difference -0.08% [95% CI: -0.227 to 0.069]; MMRM).

The other glycemic control parameters, such as FPG, fasting (prebreakfast) SMPG, pre-injection SMPG, and 24-hour average plasma glucose decreased in both treatment groups primarily during the initial 12 weeks of study treatment and tended to decrease further up to Month 6. They remained relatively stable in both treatment groups during the 6-month extension period.

Mean 8-point SMPG profiles decreased from baseline to Month 12 in both treatment groups at all time points. At Month 12, mean plasma glucose levels were comparable in both treatment groups at all time points.

The changes in glycemic control were observed while the basal insulin doses in both treatment groups were increased primarily during the first 12 weeks and to a greater extent in the HOE901-U300 group than in the Lantus group. At Month 12, the mean daily average basal insulin dose of HOE901-U300 was 64.49 U (0.67 U/kg), ie, 18% above the Lantus dose, which was 54.61 U (0.56 U/kg).

During the 12-month on-treatment period, rescue therapy, mostly rapid-acting insulin analogs, was initiated in fewer HOE901-U300 treated patients than Lantus-treated patients, although the numbers were low in both treatment groups.

The overall satisfaction of the patients with treatment in both treatment groups measured by DTSQs was good and similar throughout the study. Health related status issues remained stable in both treatment groups with good health score on the single utility index and good perceived health status using the visual analog scale. Fear of hypoglycemia was very low at baseline and decreased further to Month 12 endpoint in both treatment groups.

In summary, blood glucose control was maintained in both treatment groups during the 6-month extension period up to Month 12.

Safety results:

During the 12-month on-treatment period, hypoglycemic events of any category and at any time of day were reported by a lower percentage of patients in the HOE901-U300 group versus the Lantus group. Nocturnal hypoglycemia occurring between 00:00 and 05:59 hours showed a trend in favor of HOE901-U300. For hypoglycemia events reported any time of day, the event rates per patient-year of exposure tended to be lower in the HOE901-U300 group than in the Lantus group. Severe hypoglycemia was reported by a low and similar percentage of patients in the HOE901-U300 and Lantus groups (1.4% versus 2.1%). There were no events of severe nocturnal hypoglycemia in the HOE901-U300 group compared to 3 events in the Lantus group.

The percentages of patients with any TEAEs (274 of 435 patients [63.0%] on HOE901-U300 and 276 of 438 patients [63.0%] on Lantus) or with serious TEAEs (35 patients [8.0%] on HOE901-U300 and 39 patients [8.9%] on Lantus) were similar between both treatment groups.

One patient died during the study as a result of a TEAE (HOE901-U300 group). The death (due to a worsening of atherosclerotic heart disease) was considered not related to the IMP.

A similar number of patients in both treatment groups experienced TEAEs leading to permanent treatment discontinuation (9 patients [2.1%] on HOE901-U300 and 8 patients [1.8%] on Lantus).

Hypersensitivity reactions during the 12-month on-treatment period were reported at an identical rate in both treatment groups (41 patients [9.4%]).

A similar number of patients in both treatment groups experienced injection site reactions during the 12-month on-treatment period (20 patients [4.6%] on HOE901-U300 and 26 patients [5.9%] on Lantus).

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 consistently during the 12-month on-treatment period with a somewhat larger increase in the HOE901-U300 group compared to the Lantus group. There was no difference between the two treatment groups in terms of 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