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Sponsor / Company: Sanofi **Drug substance(s):** HOE901-U300 (insulin glargine)	**Study Identifiers:** NCT02227212, UTN U1111-1155-7309 & EudraCT 2014-001253-16 **Study code:** PDY14065
Title of the study: A Multi-center, Open-label, Single-arm, Multiple Dose Study with HOE901-U300 to Assess the Ease of Use and Safety of a New U300 Pen Injector in Insulin-Naïve Patients with T2DM	
Study center(s): 7 centers in Germany	
Study period: Date first patient enrolled: 22/Aug/2014 Date last patient completed: 20/Nov/2014	
Phase of development: Phase 3b	
Objectives: Primary Objective: To demonstrate the ease of use of the U300 pen injector in pen-naïve and insulin-naïve type 2 diabetes mellitus (T2DM) patients in a 4-week once-daily dosing regimen with HOE901-U300. Secondary Objectives: To assess in a 4-week once-daily dosing regimen with HOE901-U300 in pen-naïve and insulin-naïve T2DM patients: • The safety and usability of the U300 pen injector • The glycemic control with the U300 pen injector • The safety of HOE901-U300.	
Methodology: This was a single-arm study to evaluate the usability, safety, and overall acceptance of a new insulin pen injector with HOE901-U300 in insulin-naïve and pen-naïve T2DM patients. Patients were screened within 4 weeks prior to inclusion, and those who demonstrated proper usage of the U300 pen injector and the blood glucose meter (BGStar®) were enrolled in the study for a 4-week treatment duration. Patients visited the site at screening, baseline (Day 1), and at 1 and 4 weeks after start of treatment, then 2 weeks after the last investigational medicinal product (IMP) administration (post-treatment follow-up period). Patients had 5 mandatory telephone visits at Week -1, Day 2, Week 2, Week 3, and 2 days after the last IMP administration. No specific sample size calculation was performed for the primary and secondary analysis which was descriptive.	
Number of patients**:**	Planned: Up to 40 Randomized: 51 (8 screen failures; 3 withdrew consent before first IMP dose) Treated: 40
Evaluated:	Safety (safety population): 40

Diagnosis and criteria for inclusion:

Inclusion criteria: Patients with T2DM inadequately controlled with non-insulin, non-injectable anti-hyperglycemic drug(s) and for whom the Investigator/treating physician was to have decided that basal insulin is appropriate; signed informed consent.

Key exclusion criteria: Age <18 years; glycated hemoglobin (HbA_{1c}) <7.0% or >11% at screening; diabetes other than T2DM; history of T2DM for less than 1 year before screening; less than 6 months anti-hyperglycemic treatment before screening; initiation of new glucose-lowering medications and/or weight loss drug in the last 3 months prior to screening; previous treatment with glucagon like peptide-1 (GLP-1); patients receiving only non-insulin anti-hyperglycemic drugs not approved for combination with insulin; current or previous insulin use except for a maximum of 8 consecutive days and a total of 14 days during the last year prior to screening; unstable proliferative diabetic retinopathy or any other rapidly progressive retinopathy or macular edema likely to require treatment during the study period.

Study treatments

Investigational medicinal product(s): HOE901-U300

Formulation: HOE901-U300 (insulin glargine 300 U/mL solution) is a sterile, non-pyrogenic, clear and colorless solution in a cartridge that has been assembled in a disposable (prefilled) insulin pen (U300 pen injector). The 1.5 mL cartridge contains a total of 450 units of HOE901-U300. The device allows a dose setting of up to 80 U with minimum increment steps of 1 U.

Route(s) of administration: subcutaneous (SC) 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 baseline visit and was to be maintained for the duration of the study with a ±1-hour window.

Patients were started on a once-daily SC treatment regimen with an initial dose of 0.2 U/kg HOE901-U300 administered with the U300 pen injector. Patients were then individually uptitrated on a weekly basis (more frequently if needed but not more often than every 3 days) according to a given titration scheme based on fasting self-monitored plasma glucose (SMPG) measurements. The insulin dose was adjusted to achieve fasting SMPG in the target range of 80 to 100 mg/dL (4.4 to 5.6 mmol/L).

Noninvestigational medicinal product(s): Mandatory background non-insulin anti-hyperglycemic drugs were continued throughout the study with the dose as received prior to the study, unless safety concerns necessitated the discontinuation of the background therapy.

Duration of treatment: 4 weeks

Duration of observation: Up to 10 weeks maximum (2 to 4 weeks screening period + 4 weeks treatment period + 2 weeks post-treatment follow-up period)

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: Ease of use and overall acceptance of the U300 pen injector as evaluated by the Ease-of-Use and Ease-of-Learning Questionnaires

Secondary efficacy endpoints:

Safety and usability of the U300 pen injector as evaluated by:

- Diabetes Treatment Satisfaction Questionnaire (DTSQ): change in treatment satisfaction score and in perception of hyper- and hypoglycemia score from baseline to Week 4;
- Change in fasting plasma glucose (FPG) (mmol/L, mg/dL) from baseline to Week 4;
- Incidence (%) of Product Technical Complaints (PTCs);
- Incidence (%) of adverse events (AEs) and hypoglycemia events related to PTCs;
- Change in daily insulin dose (U and U/kg) from Day 1 to Week 4.

Safety:

- Incidence and frequency of hypoglycemia episodes;
- Adverse events;
- Injection site reactions;
- Hypersensitivity reactions;
- Clinical laboratory evaluations, vital signs, electrocardiogram (ECG).

Statistical methods: Descriptive statistics were performed for the primary and secondary usability variables. Safety analysis was based on review of individual values and descriptive statistics.

Summary: The current report presents the overall patient satisfaction and safety results with the new U300 pen injector.

Population characteristics: A total of 43 patients with T2DM inadequately controlled with non-insulin anti-hyperglycemic drug(s) were enrolled in the study to assess the usability of the U300 pen injector. Three patients withdrew before first dose of IMP and 40 patients were treated in the study. All of them were exposed to the study treatment regimen, completed the study as planned and were included in the analysis population (safety population).

The mean age of the treated patients was 66.2 years; 19 patients were male and 21 female. All subjects were Caucasian/White, the mean body mass index was 30.1 kg/m^2, and 11 (28.2%) patients had renal impairment with an estimated glomerular filtration rate <60 mL/min.

The majority of the patients had been diagnosed with T2DM ≥10 years (24/40; 60%). Mean age at onset of T2DM was 55.5 years, and the mean duration of T2DM was 10.68 years. The mean duration of prior non-insulin anti-hyperglycemic treatment was 4.32 years. Mean HbA_{1c} at baseline was 8.25%.

In the 3 months prior to enrollment, all patients received blood glucose lowering drugs, excluding insulins, most of them receiving biguanides (67.5%) or dipeptidyl peptidase-4 (DPP-4) inhibitors (37.5%).

Treatment compliance observed during the study was excellent, with all patients having a compliance of 100%.

Efficacy results: To evaluate the U300 pen injector, patients completed the ease-of-use/ease-of-learning questionnaire at Day 1, Day 7, and Week 4. Patients' ratings of ease-of-use of the pen functions during the preparation of the pen for injection and the actual injection were already high immediately after the pen training on Day 1 (post-IMP dosing) and further improved at Week 4. Immediately after the pen training, 5 out of 8 items of the ease-of-use questionnaire were rated as good or excellent by more than 80% (range: 84.6% to 97.4%) of the patients. In particular, the item "ease of use of how much insulin is remaining in the cartridge" was rated as good or excellent by only 59.0% of the patients at baseline; however, after 4 weeks of treatment with the U300 commercial pen injector, 90.0% of the patients rated this item as good or excellent. At Week 4, all the items of the ease-of-use questionnaire were rated as good or excellent by 85.0% to 97.5% of the patients. Ease-of-learning was rated as excellent or good by 89.7% and 95.0% of the patients at Day 1 and Week 4, respectively.

In an overall evaluation on Day 1 and at Week 4, 89.7% and 95% of the patients rated the overall assessment of the U300 pen injector as good or excellent, respectively. At Day 1, 100% of the patients would recommend the pen to others, compared to 97.5% at Week 4. The mean ease-of-use score was 1.56 ± 0.64 and 1.45 ± 0.55 on a scale from 1 (excellent) to 5 (very poor) at baseline and Week 4, respectively.

Satisfaction of the patients with treatment was measured by the DTSQs at baseline and Week 4. A total treatment satisfaction score range between 0 and 36 was calculated as the sum of the following single items; Item 1 ("current treatment"), Item 4 ("convenience"), Item 5 ("flexibility"), Item 6 ("understanding"), Item 7 ("recommend"), and Item 8 ("continue"), each scored on a scale from 0 (very dissatisfied) to 6 (very satisfied). The mean (standard deviation [SD]) Total Treatment Satisfaction score at baseline reflecting the treatment satisfaction with the previous anti-hyperglycemic treatment was 28.21 (5.83). Initiation of insulin treatment was not accompanied by any reduction in the treatment satisfaction as the Treatment Satisfaction score numerically increased to 29.50 (5.64) at Week 4. The perceived frequency of hyperglycemia (captured by Item 2) decreased from baseline to Week 4 in mean score from 3.62 (1.62) to 2.70 (1.86), suggesting that overall the perceived frequency of hyperglycemia decreased in the patients. The perceived frequency of hypoglycemia (captured by Item 3 of the DTSQ) was low (0.74 [1.19]) at baseline and slightly increased (1.13 [1.51]) at Week 4, suggesting that overall the perceived frequency of hypoglycemia slightly increased after initiation of insulin treatment.

Mean (SD) FPG levels decreased from baseline to Week 4 from 9.22 (1.94) mmol/L (166.08 [35.00] mg/dL) to 6.89 (2.28) mmol/L (124.15 [41.08] mg/dL). The other glycemic control parameter, pre-injection plasma glucose, also decreased from baseline to Week 4 from 11.43 (3.62) mmol/L (205.96 [65.27] mg/dL) to 9.90 (2.94) mmol/L (178.29 [52.96] mg/dL).

The changes in glycemic control were observed while the basal insulin dose was increased from 0.19 (0.03) U/kg to 0.34 (0.11) U/kg, corresponding to a mean dose of 16.82 (3.96) U at baseline and 30.15 (11.08) at Week 4.

The U300 pen injector is reliable and safe with no PTCs reported during the study.

Safety results: Overall, 7 (17.5%) patients reported a total of 16 hypoglycemic episodes (0.4 events per patient). None of these episodes was severe or serious.

No serious treatment-emergent adverse events (TEAEs) and no deaths were reported during the study, and no patient discontinued the study due to a TEAE. Treatment-emergent adverse events were reported in 11/40 (27.5%) patients. The most frequently reported TEAE was nasopharyngitis. All other TEAEs were single occurrences. There were no AEs related to PTCs.

Two injection site reactions were reported as TEAE (pain at injection site and hematoma at injection site). No further local reactions and no hypersensitivity reactions were observed during the study.

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