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Sponsor: Sanofi **Drug substance(s):** HOE901	**Study Identifiers:** U1111-1168-5158 & NCT02401243 **Study code:** GLARGL07496
Title of the study: A pilot descriptive Canadian, multicenter, open-label, randomized study of two titration algorithms with insulin glargine 300 units/mL in type 2 diabetes mellitus patients	
Study center(s): 17 centers in Canada	
Study period: Date first patient enrolled: 01/Apr/2015 Date last patient completed: 17/Feb/2016	
Phase of development: Phase 3b	
Objectives: The primary objective of this study was to obtain efficacy and safety descriptive data on two different titration algorithms: the INSIGHT titration algorithm (self-titration of 1 unit/day) and the EDITION trial algorithm with insulin glargine 300 units/mL (GLA-300), when given as basal insulin in uncontrolled type 2 diabetes mellitus (T2DM) patients on basal insulin with or without non-insulin anti-hyperglycemic agents (NIAHAs) or in insulin-naïve patients. The secondary objective was to gain additional efficacy and safety data (glycated hemoglobin [A1c], fasting plasma glucose [FPG], 7-point self-monitored plasma glucose [SMPG], insulin dose, and weight) and to determine patient related outcome and health care professional (HCP) satisfaction as it pertained to each titration regimen.	
Methodology: This was a pilot descriptive Canadian, multicenter, open-label, randomized study with two titration cohorts.	
Number of patients**:** Planned: 200 Randomized: 212 Treated: 212 **Evaluated:** Efficacy: 212 Safety: 212	
Diagnosis and criteria for inclusion: ≥18 years, uncontrolled T2DM, insulin-naïve or on basal insulin.	

Study treatments

Investigational medicinal product(s): Insulin glargine 300 units/mL (GLA-300)

Formulation: 1.5 mL pre-filled pen for subcutaneous administration

Route(s) of administration: Subcutaneous

Dose regimen:

Insulin-naïve: starting dose of 0.2 units/kg.

Change from basal insulin to GLA-300:

- Same daily dose if patients had been receiving insulin glargine 100 units/mL (GLA-100).
- Same daily dose if patients had been receiving once daily (QD) detemir or normal protamine Hagedorn (NPH).
- 80% of the total daily dose if they had been receiving twice-daily detemir or NPH.

Cohort 1 titration: Self-titration by 1 unit/day and stop increasing if fasting self-monitored plasma glucose (FSMPG) was 5.6 mmol/L or below to reach a target range of 4.4 to 5.6 mmol/L.

Cohort 2 titration: Dose adjusted at least once weekly but no more often than every 3 days as per the investigator recommendation in accordance with a titration algorithm to achieve a target FSMPG in the range of 4.4 to 5.6 mmol/L.

Noninvestigational medicinal products: Blood glucose meter, test strips, lancet device, lancets, urine pregnancy test, needles, and cooling bags

Duration of treatment: 12 weeks

Duration of observation: 14 weeks + 2 days

Criteria for evaluation:

Efficacy:

Primary endpoint: Percentage of patients reaching fasting SMPG ≤5.6 mmol/L without nocturnal (midnight to 6 am) hypoglycemia (confirmed or symptomatic or severe) at 12 weeks.

Secondary endpoint(s): FSMPG change; percentage of patients reaching FSMPG ≤5.6 mmol/L; percentage of patients reaching FSMPG ≤5.6 mmol/L without nocturnal (midnight to 8 am) hypoglycemia (confirmed or symptomatic or severe); A1c and FPG change; percentage of patients reaching A1c target (A1c ≤7%); percentage of patients reaching A1c target (A1c ≤7%) without nocturnal (midnight to 6 AM and midnight to 8 AM) hypoglycemia (symptomatic or confirmed or severe); patient-related outcome (diabetes treatment satisfaction questionnaire [DTSQ]); HCP satisfaction (HCP satisfaction questionnaire).

Safety: Hypoglycemia, body weight change, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths and adverse events (AEs) leading to discontinuation.

Statistical methods: The statistical hypothesis of this pilot study was to provide descriptive statistics concerning the use of two different titration algorithms. The primary analysis population was all enrolled patients (intent-to-treat [ITT] population). The 95% confidence interval (CI) for the percentage of patients in this study who achieved a FSMPG ≤5.6 mmol/L without any nocturnal hypoglycemia was calculated for each arm of the study at 12 weeks.

Descriptive statistics including mean, standard deviation, inter-quartile range and range for continuous variables and percentages for qualitative data were used for the secondary variables.

Summary:

Population characteristics: A total of 253 patients were screened, 212 were randomized (ITT population, Cohort 1: N=108, Cohort 2: N=104), and received at least one dose of study medication (safety population). Patients' median age was 62 years (23 to 90 years). More than half of the patients were male (60.4%) and the majority of patients (81.6%) were white. A total of 16 patients withdrew from the study. The most common reason for study termination was patient's request (6 patients).

Efficacy results: No difference was found between the two treatment groups for the primary endpoint of fasting SMPG ≤5.6 mmol/L without nocturnal (midnight to 6 am) hypoglycemia at 12 weeks (Cohort 1: 19.4%; Cohort 2: 18.3%).

A comparable number of patients in each cohort reached a fasting SMPG ≤5.6 mmol/L without nocturnal hypoglycemia (midnight to 8 AM) at 12 weeks (Cohort 1: 12.0%; Cohort 2: 11.5%). About one third of patients in each cohort achieved a fasting SMPG of ≤5.6 mmol/L (Cohort 1: 29.6%, Cohort 2: 27.9%). The percentages of patients achieving A1c ≤7% at Week 12 were 26.9 and 28.8% in Cohort 1 and Cohort 2, respectively. A1c ≤7% without hypoglycemia was achieved by 22.2 and 24.0% of patients in Cohort 1 and Cohort 2, respectively.

Daily basal insulin dosage increased by a mean of 26.6 U and 24.9 U in Cohort 1 and Cohort 2, respectively, corresponding to a change of 0.3 units/kg/day in both cohorts. The mean daily basal insulin dose at Week 12 was comparable in both cohorts (Cohort 1: 67.0 units/day; Cohort 2: 70.0 units/day, corresponding to a dose of 0.7 units/kg/day in both cohorts). Weight increased from baseline by a mean of 0.4 kg in Cohort 1 and 0.1 kg in Cohort 2.

No differences in the percentages of patients experiencing hypoglycemia of any category were seen between algorithms. Severe hypoglycemic events were rare (Cohort 1: N=1; Cohort 2: N=3).

Treatment satisfaction scores demonstrated a similar moderate increase in satisfaction (Cohort 1: 11.7, Cohort 2: 11.3). Both cohorts showed similar small reductions in perceived hypo- and hyperglycemia. HCPs were more satisfied with the INSIGHT algorithm and were more likely to use this algorithm compared to the EDITION algorithm. Overall, the majority of HCPs (30/35, 86%) preferred the INSIGHT over the EDITION algorithm.

Adherence to study treatment was good with patients being compliant to GLA-300 use on 94.2% and 96.1% of study days in Cohort 1 and Cohort 2, respectively.

Safety results: Thirty (30) of 108 patients (27.8%) in Cohort 1 (INSIGHT algorithm) and 32 of 104 patients (30.8%) in Cohort 2 (EDITION algorithm) experienced TEAEs. SAEs were reported for 3 out of 108 patients (2.8%) in Cohort 1 and for 4 out of 104 patients (3.8%) in Cohort 2. No deaths were reported. Three patients (2.8%) in Cohort 1 and 2 patients (1.9%) in Cohort 2 discontinued treatment permanently due to a TEAE. TEAEs leading to dose modifications (increase, decrease, interruption, frequency change, or dose decrease and frequency change) occurred in 1 patient (0.9%) in Cohort 1 and 2 patients (1.9%) in Cohort 2. Possibly treatment-related AEs were reported for 3 patients (2.8%) in Cohort 1 and 4 patients (3.8%) in Cohort 2.

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