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Sponsor: Sanofi **Drug substance(s):** SAR342434	**Study Identifiers:** U1111-1170-3739, NCT02603510 **Study code:** PDY13502

Title of the study: A randomized, 2×4 week, active-controlled, open-label, 2 treatment arm, 2-period cross-over study assessing the safety of SAR342434 and Humalog® used in continuous subcutaneous insulin infusion (CSII) in adult patients with type 1 diabetes mellitus (T1DM)

Study center(s): Two centers in the US

Study period:

Date first patient enrolled: 17/Nov/2015

Date last patient completed: 13/Apr/2016

Phase of development: Safety

Objectives:

The main objective of the study was to assess the safety of SAR342434 and Humalog when used in external pumps in terms of the incidence of infusion set occlusions. Infusion set occlusion is defined as failure to correct hyperglycemia (plasma glucose ≥ 16.7 mmol/L [300mg/dL]) by an insulin bolus via the insulin pump.

The secondary objectives were to assess the safety of SAR342434 and Humalog used in continuous subcutaneous insulin infusion (CSII) as determined by intervals for infusion set changes, incidence of insulin pump alarms for infusion set occlusion, patient observation of infusion set occlusions, adverse and serious adverse events including bruising at the infusion site, injection site and hypersensitivity reactions and incidence of hypoglycemic events (according to ADA Workgroup on Hypoglycemia).

Methodology: Randomized, 2×4 week, active-controlled, open-label, 2 treatment arm, 2-period cross-over study in adult male and female patients with type 1 diabetes mellitus.

Number of patients**:**	Planned: 28
	Randomized: 27
	Treated: 27
Evaluated:	Safety: 27

Diagnosis and criteria for inclusion: Male and female patients above the age of 18, with type 1 diabetes mellitus for more than 1 year. Patients needed to have at least 1 year of experience of insulin treatment, with at least 6 months of CSII treatment using an external insulin pump (either Medtronic pump with a 3 mL reservoir or Animas Vibe or OneTouch Ping). Patients were required to demonstrate compliance with self-measured plasma glucose (SMPG) four times daily during screening (≥ 75% of the four times daily SMPGs recorded in the patient diary).

Study treatments

Investigational medicinal product (1): SAR342434 (insulin lispro)

Formulation: Solution for injection containing 100 U/mL insulin lispro

Route(s) of administration: CSII via a pump

Dose regimen: Individually titrated to achieve the plasma glucose target: pre-prandial 3.9–7.2 mmol/L (70–130 mg/dL), postprandial <10.0 mmol/L (<180 mg/dL)

Investigational medicinal product (2): Humalog-U.S.

Formulation: Solution for injection containing 100 U/mL insulin lispro

Route(s) of administration: CSII via a pump

Dose regimen: Individually titrated to achieve the plasma glucose target: pre-prandial 3.9–7.2 mmol/L (70–130 mg/dL), postprandial <10.0 mmol/L (<180 mg/dL)

Duration of treatment: Two period cross-over design with each treatment period lasting 4 weeks (4 weeks of SAR342434 treatment followed by 4 weeks of Humalog or 4 weeks of Humalog treatment, followed by 4 weeks of SAR342434). Each patient used their own insulin infusion pump for the duration of the trial.

Duration of observation: For each participant, the total study duration from screening through the post-study visit was 10 weeks:

- Screening: 14 days (+7 day visit window)
- Treatment periods: 28 days for each of two treatment periods (±2 days for each visit)
- Post-study visit : 1 day after end of the second dosing period

Criteria for evaluation:

Safety: The main safety parameter was the incidence of infusion set occlusion, derived using infusion set changes due to unexplained hyperglycemia (excluding pump malfunction) recorded in the eCRF; the secondary safety parameter was the intervals for infusion set change.

Adverse events (AEs) reported by the patient or observed by the Investigator, including injection site reaction (ISR) assessments (pain, erythema, and edema) and the incidence of hypoglycemia.

Statistical methods:

Safety analysis:

The analysis population was the safety population, defined as all patients randomized and exposed to any investigational medicinal product (IMP), regardless of the amount of IMP administered.

For the main safety parameter, frequency distributions by treatment (SAR342434 versus Humalog) were provided for number and percentage of patients with at least one infusion set occlusion and also for the number of infusion set occlusion events. Without the aim of a formal hypothesis testing, the difference between SAR342434 and Humalog in the proportion of patients with at least one infusion set occlusion was provided with associated 2-sided 95% CI. The risk difference and associated 95% CI were obtained by fitting a repeated measures model using a binomial regression and an identity-link function (PROC GENMOD in Statistical Analysis System [SAS] with options DIST=BINOMIAL and LINK=IDENTITY). The model included fixed categorical effects for treatment, period and sequence. An unstructured correlation matrix was used to model within-patient error. The risk of infusion set occlusion within each treatment group and the risk difference were provided with their 95% CIs using the adjusted least squares (LS) mean estimates of the treatment effect. For secondary safety parameters, descriptive statistics for average intervals of infusion set changes were provided.

Summary:

Population characteristics: Twenty seven (27) patients were randomized into the study. Of the 27 randomized patients, 3 did not complete the study (2 in period 1 and 1 in period 2, all 3 patients in the Humalog arm); 1 was due to an SAE, 1 was based on patient's decision not to continue, and 1 was based on poor compliance and failure to return the patient diary for treatment period 2. The mean duration of type 1 diabetes was 26.58 years and the mean duration of CSII treatment was 9.44 years. Five patients used Animas insulin pumps, and 22 patients used Medtronic insulin pumps.

Safety results:

Main safety outcome: The number of patients who had at least one infusion set occlusion during the on-treatment period, defined as failure to correct hyperglycemia (plasma glucose ≥300mg/dL) by insulin bolus via the insulin pump (excluding pump malfunction) was 6/25 (24%) in the SAR342434 group and 4/27 (14.8%) in the Humalog group (risk estimate of 22.5% versus 14.6% respectively) with a risk difference for SAR342434 versus Humalog of 7.9% (95% CI [-1.90% to 17.73%]).

No period effect was detected, p=0.14.

The total number of infusion set occlusions, defined as failure to correct hyperglycemia (plasma glucose ≥300mg/dL) by insulin bolus via the insulin pump, during the on-treatment period was 14 for SAR342434 and 9 for Humalog. The number of patients with a single infusion set occlusion was 2 (8%) in the SAR342434 group and 2 (7.4%) in the Humalog group. One patient (4%) in the SAR342434 group had 2 infusion set occlusions. Two patients in the SAR342434 group (8%) and 1 patient in the Humalog group (3.7%) had 3 infusion set occlusions. One patient in the SAR342434 group (4%) and 1 patient in the Humalog group (3.7%) had more than 3 infusion set occlusions.

Secondary safety outcomes: The mean interval for infusion set change (independent of the cause of infusion set change) in days (defined as the number of days in the treatment period divided by the number of infusion set changes for patients with at least one infusion set change) was 3.09 (SD 0.97) for SAR342434 and 2.95 (SD 0.78) for Humalog. Hypoglycemia occurred in 21 (84%) patients when taking SAR342434 and in 23 (85.2%) patients when taking Humalog. There were no reports of severe hypoglycemia (the severity of the SAE of hypoglycemia was reported as unknown). There were no TEAEs of ketoacidosis reported.

Treatment emergent adverse events (TEAEs): The number of patients with any TEAE while being administered SAR342434 was 3 (12%) and while taking Humalog was 4 (14.8%). The most frequent TEAEs were upper respiratory tract infections (1 patient in SAR342434 group and 2 patients in Humalog group) and potassium imbalance (hyperkalemia, 2 patients in the Humalog group). There was 1 patient who had 3 treatment-emergent SAEs including cardiopulmonary arrest, a suspected unexpected serious adverse reaction (SUSAR), hypoglycemia and accidental overdose, all reported with a fatal outcome. These SAEs occurred on day 24 of the patient's first treatment period due to accidental overdose while taking Humalog and in the setting of normal insulin pump function. There was 1 mild TEAE of infusion site reaction, characterized as infusion site pain that occurred when being administered SAR342434. There were no hypersensitivity reactions.

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