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Sponsor: Sanofi **Drug substance(s):** SAR342434	**Study Identifiers:** U1111-1156-4296, NCT02294474, 2014-002844-42 **Study code:** EFC13403

Title of the study: Six-month, Randomized, Open-label, Parallel-group Comparison of the Insulin Analog SAR342434 to Humalog® in Adult Patients With Type 2 Diabetes Mellitus also Using Insulin Glargine

Study center(s): 103 active centers in 12 countries (Argentina, Chile, Colombia, Germany, Hungary, Italy, Republic of Korea, Romania, Russian Federation, Spain, Turkey, and United States)

Study period:

Date first patient enrolled: 14/Jan/2015

Date last patient completed: 16/Feb/2016

Phase of development: Phase 3

Objectives: The primary objective of this study was to demonstrate non-inferiority of SAR342434 versus Humalog in terms of changes in hemoglobin A1c (HbA1c) from baseline to Week 26 in patients with type 2 diabetes mellitus (T2DM) also using Lantus.

The secondary objectives were:

- To assess the immunogenicity of SAR342434 and Humalog in terms of positive/negative status and antibody titers at baseline and during the course of the study.
- To assess the relationship of anti-insulin antibodies with efficacy and safety.
- To assess the efficacy of SAR342434 and Humalog in terms of proportion of patients reaching target HbA1c <7.0% and <6.5%, fasting plasma glucose (FPG) and self-monitored plasma glucose (SMPG) profiles, and insulin dose.
- To assess safety of SAR342434 and Humalog.

Methodology:

Multicenter, multinational, open-label, randomized 1:1, active-controlled, 2-arm, parallel-group study comparing:

- SAR342434 + Lantus
- Humalog + Lantus.

Randomization was stratified by HbA1c obtained at the screening visit (<8.0%, ≥8.0%) and prior use of Humalog (Yes/No). The sample size (240 patients in each group) was chosen to ensure sufficient power for the primary endpoint (change in HbA1c from baseline to Week 26).

Number of patients:	Planned: 480
	Randomized: 505
	Treated: 505
Evaluated:	
	Efficacy: 505
	Safety: 505
	Anti-insulin antibody: 493

Diagnosis and criteria for inclusion: Patients with T2DM; diagnosed for at least 12 months, and have been treated with Lantus plus Humalog/Liprolog® or NovoLog®/NovoRapid® (at least 3 times daily before each meal) in the 6 months prior to screening.

Study treatments

Investigational medicinal product(s): SAR342434 (tested drug) and Humalog (control drug).

Formulation:

SAR342434 was supplied as 100 U/mL solution for subcutaneous (SC) injection in the SAR342434 SoloSTAR® disposable pen.

Humalog was supplied as 100 U/mL solution for SC injection in the Humalog KwikPen™ (EU- or US-approved Humalog comparator were used at sites depending on the countries, and were clearly identified.)

Route(s) of administration: subcutaneous injection

Dose regimen: The starting dose was a unit to unit conversion from pre-trial rapid acting insulin to either SAR342434 or Humalog.

SAR342434 or Humalog were injected SC immediately before meal intake. Occasional postprandial injection soon after meal intake could be done if deemed necessary and if allowed by the national product label for Humalog.

The dose was self-titrated to achieve a 2 hour postprandial plasma glucose in the range of 6.7-8.9 mmol/L (120-160 mg/dL) while avoiding hypoglycemia.

Noninvestigational medicinal product(s): Lantus (Insulin glargine 100U/mL)

Formulation: Lantus Insulin was supplied as 100U/mL solution in Lantus SoloSTAR disposable pen

Route(s) of administration: subcutaneous injection

Dose regimen: The starting dose of Lantus was unit to unit conversion from pre-trial insulin.

Doses of Lantus were adjusted to achieve fasting, pre-breakfast SMPG of 4.4-7.2 mmol/L (80-130 mg/dL) while avoiding hypoglycemia.

Duration of treatment: 26 weeks

Duration of observation: 28 weeks (up to 2 weeks screening + 26-week treatment + 1 day follow-up)

Criteria for evaluation:

Efficacy:

Primary endpoint: Change in HbA1c from baseline to Week 26

Secondary endpoints:

- Percentage of HbA1c responders (patients with HbA1c <7% and ≤6.5%) at Week 26;
- Change in FPG (mmol/L) from baseline to Week 26;
- Change in the mean 24-hour plasma glucose concentration (mmol/L) from baseline to Week 26 based on the 7-point SMPG profiles;
- Change in postprandial plasma glucose excursions (mmol/L) from baseline to Week 26 based on the 7-point SMPG profiles (difference between 2 hour postprandial and pre-prandial plasma glucose values at breakfast, lunch and dinner).
- Other secondary efficacy endpoints are:
  - Change in 7-point SMPG profiles per time-point from baseline to Week 26;
  - Change in 3-point SMPG profiles per time-point from baseline to Week 26.

Safety: Hypoglycemia, occurrence of adverse events particularly treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), TEAEs leading to IMP discontinuation and TEAEs leading to death, injection site reactions, hypersensitivity reactions, and weight.

Immunogenicity: Anti-insulin antibodies (AIA) status: positive or negative, AIA titer, cross-reactivity to insulin glargine, cross-reactivity to insulin glargine metabolite M1 (desArg, Arg [B31, B32]-insulin glargine) and cross-reactivity to human insulin.

Immunogenicity sampling times and bioanalytical methods: Blood samples for anti-insulin antibodies were drawn at Day 1, at Week 4, Week 12 and Week 26, and at the end-of-treatment assessments in case of premature IMP discontinuation. Samples were to be collected 8 hours after the administration of either the SAR342434 or Humalog at the earliest.

AIA were analyzed at a central laboratory blinded to the treatment group, using a validated binding assay method.

Statistical methods:

Primary analysis:

The statistical test for the primary efficacy endpoint (change in HbA1c from baseline to Week 26) was one-sided, with an alpha level of 0.025 and using a non-inferiority margin of 0.3% HbA1c.

The primary endpoint was analyzed in the intent-to-treat (ITT) population (defined as all randomized patients, irrespective of compliance with the study protocol and procedures) using a Mixed-effect Model for Repeated Measures (MMRM) approach, under the missing at random framework with treatment (SAR342434, Humalog), visit (Week 12, Week 26), treatment-by-visit interaction, randomization strata of screening HbA1c (<8%, ≥8%) and prior use of Humalog (Yes/No) as fixed categorical effects as well as, the continuous fixed covariates of baseline HbA1c value and baseline HbA1c value-by-visit interaction. All available post-baseline HbA1c data were used in the analysis (ITT estimand). The baseline value was defined as the last available value prior to the first dose administration of Investigational Medicinal Product (IMP). Difference between adjusted least - squares means (LS-means) estimates at Week 26 by treatment groups, associated standard errors and 2-sided 95% CI were estimated using adequate contrasts. Non-inferiority was demonstrated if the upper bound of the 2-sided 95% CI of the difference between SAR342434 and Humalog in the ITT population was <0.3%.

If non-inferiority of SAR342434 over Humalog was demonstrated, using a hierarchical step-down testing procedure, the inverse non-inferiority (of Humalog over SAR342434) was to be tested looking at the lower bound of the 2-sided 95% CI of the difference between SAR342434 and Humalog in the ITT population. Non-inferiority of Humalog over SAR342434 was demonstrated if the lower bound was >-0.3%.

Analysis of secondary endpoints:

All secondary efficacy endpoints were analyzed in the ITT population, using all post-baseline data available during the main 6 month period. HbA1c responders (HbA1c <7% and ≤6.5%) at Week 26 were analyzed using a logistic regression model with fixed-effect term for treatment group (SAR342434, Humalog) and randomization strata of screening HbA1c (<8%, ≥8%), prior use of Humalog (Yes, No). The change in FPG from baseline to Week 26 was analyzed using a similar MMRM model than for primary analysis. The same model was applied for the change in the mean 24-hour plasma glucose concentration (based on the 7-point SMPG profile) from baseline to Week 26, and for the change in post prandial plasma glucose excursions (difference between 2-hour post-prandial and 2-hour preprandial plasma glucose values at breakfast, lunch and dinner, based on the 7 point SMPG profile) from baseline to Week 26.

Analysis of anti-insulin antibody:

The analyses of AIA data were performed in the anti-insulin antibody population defined as all patients from the safety population with at least one AIA sample available for analysis during the 6-month on-treatment period. An AIA sample was considered as available for analysis if the sample was collected during the 6-month on-treatment period and at least 8 hours after the last administration of mealtime insulin. The number and percentage of patients with anti-SAR342434/Humalog antibody positive and antibody negative sample were summarized by treatment group and visit during the 6-month on-treatment period. The number and percentage of patients were provided by treatment group for each of the following categories: patients with treatment-induced AIAs, patients with treatment-boosted AIAs, patients with treatment-emergent AIA, patients without treatment-emergent AIA, patients with pre-existing AIAs or treatment-induced AIAs (AIA prevalence). For patients with treatment-induced and treatment-boosted AIAs, the kinetics of AIA response was further summarized using number and percentage of patients, and the peak titer was described using median, Q1 and Q3.

Summary:

Population characteristics: A total of 505 patients with T2DM were randomized to SAR342434 (n=253) or Humalog (n=252); all randomized patients were exposed to the IMP (safety population). The ITT population (efficacy population) included all 505 patients (253 on SAR342434 and 252 on Humalog).

Overall, 458 out of 505 patients (90.7%) completed the 26-week treatment. A similar number of patients in each treatment group discontinued the study treatment prematurely (SAR342434: 25 [9.9%]; Humalog 22 [8.7%]).

Demographics, baseline characteristics, and diabetes history were well-balanced between the treatment groups. The median age of the randomized population was 63.0 years and 44.3% of patients were ≥ 65 years old; 53.1% were male. Majority of patients was Caucasian (88.3%) and was either obese or overweight with a median BMI 32.3 kg/m2 and with 66.5% of patients having a BMI ≥ 30 kg/m2 at baseline. Baseline diabetes status was generally similar between the treatment groups. The median duration of diabetes prior to study start was 16.30 years and 80.8% of the patients had diabetes for ≥10 years. The mean baseline HbA1c was 8.0% for patients included in the primary analysis (patients who had a baseline and at least one post-baseline HbA1c assessment); 58.5% of the patients in the SAR342434 group and 58.7% of patients in the Humalog group had the screening HbA1c ≥8.0%. At study entry, all patients were using Lantus as basal insulin except for one patient in the Humalog group; the mean duration on Lantus prior to the study was 5.86 years. Within the past 6 months before screening, similar percentages of patients were using insulin lispro (SAR342434 group 52.6%; Humalog group 50.2%). The mean basal insulin dose prior to treatment was 0.477 U/kg in the SAR342434 group and 0.458 U/kg in the Humalog group; the mean bolus insulin dose was 0.449 U/kg in the SAR342434 group and 0.433 U/kg in the Humalog group; the mean total insulin dose was 0.927 U/kg in the SAR342434 group and 0.888 U/kg in the Humalog group.

Efficacy results: The primary objective of the study was to show non-inferiority of SAR342434 versus Humalog in the mean change in HbA1c from baseline to endpoint at Week 26, at the 0.3% non-inferiority margin. Mean HbA1c decreased similarly from baseline to Week 26 in the SAR342434 group (LS mean change -0.92%) and the Humalog group (-0.85%). The LS mean difference between the SAR342434 and the Humalog group was -0.07% (95%CI: 0.215 to 0.067). Non-inferiority of SAR342434 over Humalog was demonstrated, as the upper bound of the 2-sided 95% CI of the difference between SAR342434 and Humalog was below the prespecified non-inferiority margin of 0.3%. The inverse non-inferiority of the Humalog group over the SAR342434 group was also demonstrated as the lower bound of the 2-sided 95% CI of the difference between the SAR342434 and the Humalog was above -0.3%.

Sensitivity analyses to assess the impact of the missing data on the primary analysis showed results that were consistent with the results of the primary analysis. Mean decrease in HbA1c from baseline to Week 26 was also similar when comparing SAR342434 and Humalog US and SAR342434 and Humalog EU. The treatment-by-region-approved Humalog interaction showed no evidence of heterogeneity of treatment effect across subgroups of region-approved Humalog (p= 0.5834). Furthermore, similar decreases of HbA1c as in the overall study population and without relevant differences between the SAR342434 and Humalog groups were seen in all subgroup analyses defined by age, gender, race, ethnicity, BMI, duration of diabetes, renal function (eGFR), prior use of Humalog and geographical region.

No differences were observed between SAR342434 and Humalog for any of the secondary endpoints. Mean decrease in FPG, postprandial glucose excursions after breakfast, lunch and dinner, and mean 24-hour plasma glucose based on 7 point SMPG profiles were similar for SAR342434 and Humalog. The level of the 7-point SMPG profiles had improved similarly in both treatment groups at Week 26 compared with baseline.

Similar results were obtained for the on-treatment analysis for both primary and secondary endpoints.

Safety results: In patients with T2DM treated for 26 weeks during this study, hypoglycemia was reported by similar percentages of patients in the SAR342434 and Humalog groups, across all categories of hypoglycemia (68.4% of patients in the SAR342434 group and 74.6% of patients in the Humalog group). The event rates per patient-year of exposure were also similar in the SAR342434 and Humalog groups across the categories of hypoglycemia, except for severe hypoglycemia that was higher with SAR342434 (0.08) than with Humalog (0.03) due to 1 patient who reported 4 events and is not considered as representative of a specific risk.

The percentages of patients with any TEAEs or TEAEs leading to treatment discontinuation were similar between both treatment groups. The percentage of patients with serious TEAEs was lower in the SAR342434 group (5.5%) than in the Humalog group (10.7%). The safety profiles in terms of type of TEAEs was similar in both treatment groups with TEAEs of the

SOC Infections and Infestations being the most frequently reported events in both groups.

Death was reported for 1 patient in the SAR342434 group and 2 patients in the Humalog group. One patient in the SAR342434 group with a history of diabetic retinopathy, nephropathy, hypercholesterolemia, coronary artery disease, ischaemic cardiomyopathy, died from cardio respiratory arrest. In the Humalog group: one patient with a history of bladder cancer and colon cancer died from metastatic carcinoma of the bladder; one patient with a history of ischemic heart disease and hypertension died from cardiopulmonary failure. None of the death events was considered as related neither to the IMP nor to NIMP. One patient in the Humalog group died after the end of the study (unknown cause).

Hypersensitivity reactions were reported in 11 patients (4.3%) in the SAR342434 and 9 patients (3.6%) in the Humalog group. None of the hypersensitivity reactions led to permanent IMP discontinuation. One event in the SAR342434 group (respiratory failure during a brain surgery) was reported as SAE not related to IMP. Among those events of hypersensitivity reactions, 4 events in 4 patients in the SAR342434 group and 3 events in 2 patients in the Humalog group were adjudicated by the Allergic Reaction Assessment Committee (ARAC) as allergic reactions. The 4 events in the SAR342434 group (including seasonal allergy, dermatitis contact, allergy to arthropod bite and rhinitis allergic) were all of mild intensity and assessed by the ARAC as not related to the IMP. The 2 events of hypersensitivity (both pruritus) in one patient in the Humalog group were both of mild intensity and assessed by the ARAC as possibly related to the study medication, while the event mouth swelling (adjudicated by the ARAC as angioedema) of moderate intensity in the other patient in the Humalog group was adjudicated as not related to the study medication.

Subgroup analyses by region where Humalog was approved (US and EU) did not show any relevant treatment difference for hypoglycemia, TEAEs, serious TEAEs, and hypersensitivity reactions.

Immunogenicity results: In both treatment groups, 25% of the patients had positive AIA titers at baseline. The incidence was slightly higher in the SAR342434 group (18.8%) compared with the Humalog group (14.5%), although numerical differences are small and AIA titers were relatively low and comparable between the treatment groups The prevalence of AIA (percentage of patients with detectable AIAs at least one time point during the study) was similar in the SAR342434 and Humalog group. As expected, about 80.3 %– 96.8% of the AIAs showed cross-reactivity with human insulin and insulin glargine. Results of analyses of AIAs in subgroups defined by screening and baseline factors (age, gender, race, ethnicity, baseline BMI, baseline eGFR, randomization stratum of screening HbA1c) were consistent with the results in the overall study population. Of note, AIA analyses in the subgroups defined by region-approved Humalog were consistent with the results in the overall population. AIA incidence was slightly higher in patients treated with SAR342434 than in patients treated with Humalog in both subgroups of region-approved Humalog: treatment-emergent AIAs were reported in 21.2% of patients in the SAR342434 group compared to 16.9% of patients in the Humalog US group, and in 16.5% of patients on SAR342434 compared to 12.3% of patients on Humalog EU. In the subgroups defined by the use of Humalog prior to the study, i.e. to switching at study baseline from commercial Humalog to SAR342434 or Humalog, the results were consistent with those in the overall population. AIA incidence was similar in both treatment groups in patients pre-treated with Humalog, whereas there was a difference in patients not pre-treated with Humalog: 21.7% of patients treated with SAR342434 and 13.9% of patients treated with Humalog had treatment-emergent AIAs; patients with treatment-boosted and treatment-induced AIAs have similarly contributed to this small imbalance.

Evaluation of potential effects of treatment-emergent AIAs on the efficacy in terms of mean change of HbA1c from baseline to Week 26 or insulin dose and safety in terms of hypoglycemia, hypersensitivity reactions, injection site reactions, or general TEAEs and SAEs do not suggest an impact of treatment-emergent AIAs on clinical outcomes. In addition, there was no relationship between the maximal AIA titers and insulin doses or efficacy and safety parameters, regardless of treatment-emergent AIA status. Four cases with AIA titers increase above baseline at endpoint and potential effects on HbA1c or insulin dose, 1 case on SAR342434 and 3 on Humalog were reviewed and assessed by the ARAC. Three patients (SAR342434: 1; Humalog: 2) were considered to have decreased efficacy or increased insulin resistance. In 3 out of the 4 cases, the ARAC assessed the increase in HbA1c or increase in insulin dose as unlikely to be AIA-mediated and follow-up of AIA titers was not deemed necessary. One patient in the Humalog group was not considered to have decreased efficacy and follow-up was not considered necessary.

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