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Sponsor: Sanofi **Drug substance(s):** Insulin Aspart	**Study Identifiers:** NCT03211858, U1111-1191-5775, 2017-000091-28 **Study code:** EFC15081
Title of the study: Six-month, Randomized, Open-label, Parallel-group Comparison of SAR341402 to NovoLog®/NovoRapid® in Adult Patients With Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period (EFC15081; GEMELLI 1) – (12 months data)	
Study center(s): 82 centers in 7 countries.	
Study period: Date first patient enrolled: 02/Aug/2017 Date last patient completed: 12/Jan/2019	
Phase of development: Phase III	

Objectives:

The primary objective was to demonstrate non-inferiority of SAR341402 versus NovoLog®/NovoRapid® in hemoglobin A1c (HbA1c) change from baseline to Week 26 in patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) also using Lantus®.

The secondary objectives were:

- To assess the immunogenicity of SAR341402 and NovoLog/NovoRapid in terms of positive/negative status and anti-insulin aspart antibody (AIA) titers during the course of the study.
- To assess the relationship of AIA with efficacy and safety.
- To assess the efficacy of SAR341402 and NovoLog/NovoRapid in terms of proportion of patients reaching HbA1c <7.0% and change in HbA1c, fasting plasma glucose (FPG) and self-measured plasma glucose (SMPG) profiles from baseline to Week 26 and Week 52 (only Week 52 for HbA1c).
- To assess safety of SAR341402 and NovoLog/NovoRapid.

The primary objective of the study was based on the initial main 6-month period and the results are presented in the

6-month clinical study report (CSR), as well as the results of the secondary objectives during the main 6-month period. Efficacy, safety, and immunogenicity secondary variables used to evaluate the study objectives were also measured over the 12-month period and are described in the 12-month CSR.

Methodology:

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

- SAR341402 + Lantus with
- NovoLog/NovoRapid + Lantus

Randomization was stratified by geographical region (Europe, US, Japan), by type of diabetes (T1DM, T2DM [T2DM only for US]), by HbA1c at the screening visit (<8.0%, ≥8.0%), and by prior use of NovoLog/NovoRapid (Yes, No).

Number of patients:	Planned: 580 (290 per arm) Randomized: 597 Treated: 597
Evaluated:	Efficacy: 597 Safety: 597 AIA: 590

Diagnosis and criteria for inclusion:

Patients with T1DM or with T2DM (T2DM US only) diagnosed for at least 12 months at the time of the screening visit, with 7.0% ≤HbA1c ≤10.0%, treated with multiple daily injection (MDI) regimen with:

- NovoLog/NovoRapid or insulin lispro (100 U/mL) in the last 6 months prior to screening visit AND
- Insulin glargine (100 U/mL) in the last 6 months prior to screening visit or insulin detemir (Levemir®) in the last 12 months prior to screening visit.

Study treatments:

Investigational medical products: SAR341402 (tested drug) and NovoLog/NovoRapid (control drug).

Formulation:

SAR341402 was supplied as a 100 U/mL solution in pre-filled disposable SoloSTAR® pens.

NovoLog/NovoRapid was supplied as a 100 U/mL solution in pre-filled disposable FlexPen® pens.

NovoLog (US-approved) was used in the US, and NovoRapid (EU-approved) was used in the other countries.

Route of administration: subcutaneous (SC) injection.

Dose regimen: the starting dose was a unit to unit conversion from the insulin lispro or NovoLog/NovoRapid dose used prior to the trial to either SAR341402 or NovoLog/NovoRapid, or a dose at the discretion of the investigator, taking into account the glucose control at the time of randomization.

SAR341402 or NovoLog/NovoRapid was self-administered by SC injection immediately before meal intake. Occasional postprandial injection soon after meal intake could be given if deemed necessary and if allowed by the national product label for NovoLog/NovoRapid.

The dose of either SAR341402 or NovoLog/NovoRapid was to be adjusted to achieve a 2-hour postprandial plasma glucose of <10.0 mmol/L (<180 mg/dL), while avoiding hypoglycemia. If preprandial glucose tests were used, the target range of 4.4 to 7.2 mmol/L (80 to 130 mg/dL) was recommended.

Non-investigational medicinal product: Lantus (insulin glargine 100 U/mL)

Formulation: Lantus was supplied as 100 U/mL solution in pre-filled disposable SoloSTAR pens.

Route of administration: SC injection

Dose regimen: The starting dose of Lantus was to be the same as the last dose of insulin glargine or insulin detemir prior to the baseline visit.

Lantus was injected once daily.

Duration of treatment: Up to 52 Weeks

Duration of observation: Up to 54 weeks (2 weeks of screening + 52 weeks of treatment + 1 day safety follow-up)

Criteria for evaluation:

Efficacy:

Primary endpoint: the primary efficacy variable (change in HbA1c from baseline to Week 26) is described in the 6-month CSR.

Secondary endpoints during the main 6-month period are described in the 6-month CSR.

Secondary endpoints during the 12-month period:

- Change in HbA1c (%) from baseline to Week 52
- Percentage of HbA1c responders (patients with HbA1c <7.0%) at Week 52;
- Change in FPG from baseline to Week 52;
- Change in the mean 24-hour plasma glucose concentration from baseline to Week 52, based on the 7-point SMPG profiles;
- Change in postprandial plasma glucose excursions from baseline to Week 52, based on the 7-point SMPG profiles (difference between 2-hour postprandial and preprandial plasma glucose values at breakfast, lunch and dinner).
- Change from baseline in 7-point SMPG profiles per time-point (fasting pre-breakfast, 2-hours post-breakfast, pre-lunch, 2 hours post-lunch, pre-dinner, 2 hours post-dinner, bedtime).

Safety: Hypoglycemia, adverse events (AE), serious adverse events (SAEs), injection site reactions, hypersensitivity reactions, vital signs, laboratory data and body weight.

Immunogenicity: AIA positive or negative status, AIA titer, cross-reactivity to human insulin (positive/negative status), and treatment-induced, treatment-boosted and treatment-emergent AIAs during the 12-month on-treatment period. To assess the potential neutralizing capacity of AIAs, the impact of AIA on safety and on glycemic control was evaluated. In addition, to support the clinical assessment, neutralizing antibodies (NAbs) were analyzed (positive or negative status and treatment-emergent NAbs during the 12-month on-treatment period).

Other criteria of interest: change in daily basal, mealtime, and total insulin dose from baseline to Week 52 (U/kg body weight).

Immunogenicity sampling times and bioanalytical methods:

Blood samples for AIAs were drawn at Day 1, Week 4, Week 12, Week 26, Week 40, Week 52, and at the end-of-treatment assessments in case of premature investigational medicinal product (IMP) discontinuation. Samples were to be collected at least 8 hours after the last administration of mealtime insulin (SAR341402 or NovoLog/NovoRapid).

Anti-insulin aspart antibodies were analyzed at a central laboratory blinded to the treatment group, using a validated binding assay method. Neutralizing antibodies were analyzed at a Sanofi laboratory from positive AIA samples, using a validated competitive ligand binding assay.

Statistical methods:

All the analyses on the 12-month data were descriptive only. No formal statistical testing was performed.

Analysis of efficacy endpoints

For the 12-month CSR, secondary efficacy endpoints were analyzed in the intent-to-treat (ITT) population (which included all randomized patients, irrespective of compliance with the study protocol and procedures) and separately for the patients with T1DM, using all post-baseline data available during the 12-month randomized period.

The change in HbA1c and FPG from baseline to Week 52 were analyzed using a multiple imputation approach in two parts ("retrieved dropout" multiple imputation, with missing data imputed separately for patients who prematurely discontinued or completed the 12-month treatment period), followed by an ANCOVA model with fixed categorical effects for treatment group (SAR341402, NovoLog/NovoRapid) and the randomization strata, as well as the continuous fixed covariate of baseline value. The same ANCOVA model was applied for the endpoints based on the 7-point SMPG profile (change in mean 24-hour plasma glucose concentration and postprandial plasma glucose excursions from baseline to Week 52), with imputation methods modified from retrieved dropout multiple imputation to return to baseline multiple imputation due to insufficient retrieve dropout data of the initially planned imputation model. Glycated hemoglobin A1c responders (HbA1c <7.0%) at Week 52 were analyzed using a logistic regression model with fixed-effect term for treatment group (SAR341402, NovoLog/NovoRapid) and the randomization strata.

Analysis of safety endpoints

Safety analyses during the 12-month on-treatment period were based on the safety population (defined as all randomized patients who receive at least one dose of IMP, regardless of the amount of treatment administered).

Analysis of anti-insulin aspart antibody response:

Immunogenicity analyses during the 12-month on-treatment period were descriptive (no formal statistical testing), based on the AIA population (defined as all patients from the safety population with at least one AIA sample available for analysis during the on-treatment period). The analysis focused on the change in AIA response observed following the IMP administration:

- Patients with treatment-induced AIAs were defined as patients with AIAs that developed de novo (seroconversion) following the IMP administration;
- Patients with treatment-boosted AIAs were defined as patients with pre-existing AIAs that were boosted to a significant higher titer following the IMP administration (at least 4-fold increase in titer values);
- Patients with treatment-emergent AIAs (AIA incidence) were defined as patients with treatment-induced or treatment-boosted AIAs.

Analysis of neutralizing antibody response:

The analyses of NAb data were based on the AIA population. The analysis focused on the change in NAb response observed following the IMP administration. Patients with treatment-emergent NAb (NAb incidence) were defined, for the 12-month analyses, as patients with treatment-emergent AIA and with at least one positive NAb sample during the 12-month on-treatment period.

Summary:

The current report presents the efficacy, safety, and immunogenicity results for the 12-month treatment period.

Population characteristics:

A total of 597 patients were randomized and treated, 301 in the SAR341402 group and 296 in the NovoLog/NovoRapid group. All randomized patients were included in the ITT population (efficacy population) and all patients received the IMP (safety population). Immunogenicity analyses were performed on the AIA population, which included, for the 12-month analyses, 590 patients (298 in the SAR341402 group and 292 in the NovoLog/NovoRapid group).

Overall, 527 patients (88.3 %) in the randomized population completed the 12-month treatment period. A similar number of patients in each treatment group discontinued the study treatment prematurely (SAR341402: 37/301 [12.3%]; NovoLog/NovoRapid: 33/296 [11.1%]).

Demography and baseline characteristics were balanced between the 2 treatment groups. The median age of the randomized population was 49.0 years (patients with T1DM: 45.0 years; patients with T2DM: 64.0 years) and 16.6% of the patients were ≥65 years; 59.6% of the patients were males; 83.2% (497/597) of the patients had T1DM and 16.8% (100/597) had T2DM (US only); the median duration of diabetes prior to study start was 17.2 years (in the overall population, as well as in the subgroups of patients with T1DM or with T2DM), and in 77.7% of the patients the diagnosis was known for ≥10 years; mean HbA1c at baseline was 8.00% in the SAR341402 group and 7.94% in the NovoLog/NovoRapid group; 52.9% (316/597) of the patients were in the randomization stratum of screening HbA1c ≥8.0%.

At baseline, daily basal and mealtime insulin doses (U/kg) were similar in the SAR341402 and NovoLog/NovoRapid groups.

Subgroup analyses by randomization stratum of prior use of NovoLog/NovoRapid for demographic and baseline characteristics as well as daily insulin doses at baseline did not reveal any noteworthy differences between the 2 treatment groups, regardless if patients were using commercial NovoLog/NovoRapid or Humalog/Liprolog prior to the study. In addition, there were no relevant changes in mealtime insulin doses from baseline to Day 1, ie, from commercial pre-study insulin to the first doses of IMP, in either treatment group and regardless of commercial insulin received before the study, including for patients pre-treated with commercial NovoLog/NovoRapid and switching to SAR341402 at randomization (mean change [SE]: -0.000 U/kg [0.073]) or remaining on NovoLog/NovoRapid at randomization (mean change [SE]: -0.003 U/kg [0.071]).

Efficacy results:

Mean HbA1c decreased similarly from baseline to Week 52 in the SAR341402 group (LS mean change: -0.25%) and the NovoLog/NovoRapid group (-0.26%). The LS mean difference between the SAR341402 and the NovoLog/NovoRapid group was 0.01% (95% CI: -0.146 to 0.173%).

No relevant differences between SAR341402 and NovoLog/NovoRapid were seen in subgroup analyses defined by randomization stratum of type of diabetes, type of comparator, prior use of NovoLog/NovoRapid, regions, race, ethnicity, age group, sex, baseline body mass index (BMI), baseline renal function (eGFR), randomization stratum of screening HbA1c, and duration of diabetes. There was no evidence of heterogeneity of treatment effect across any of the subgroups. In particular, the mean decrease in HbA1c from baseline to Week 52 was similar between SAR341402 and NovoLog/NovoRapid regardless the type of diabetes; the decrease in HbA1c was, as expected, more pronounced in patients with T2DM as compared to patients with T1DM. It was also similar between SAR341402 and NovoLog, as well as between SAR341402 and NovoRapid.

In patients using commercial NovoLog/NovoRapid prior to the study (as per randomization stratum), the decrease in HbA1c from baseline to Week 52 was generally similar in patients switching to SAR341402 at randomization (LS mean change [SE]: -0.28% [0.065]) compared to those continuing with NovoLog/NovoRapid in the comparator group (LS mean change [SE]: -0.26% [0.069]). In patients using commercial Humalog/Liprolog (prior to the study (as per randomization stratum), the decreases in HbA1c from baseline to Week 52 were also similar for patients switching from insulin lispro to SAR341402 (LS mean change [SE]: -0.19% [0.091]) or to the comparator NovoLog/NovoRapid (LS mean change [SE]: -0.26% [0.087]).

No clinically meaningful differences were observed between SAR341402 and NovoLog/NovoRapid for any of the other secondary endpoints, including the assessment of HbA1c responders, FPG, and SMPG derived data.

Efficacy evaluation in the subgroup of patients with T1DM, who represented the vast majority of the study population, also showed similar results with SAR341402 and NovoLog/NovoRapid and were generally consistent with those for the overall population.

Safety results:

Hypoglycemia

During the 12-month on-treatment period, in the 2 treatment groups, almost all the patients had at least one episode of hypoglycemia regardless of the category: 98.0% in both groups (295/301 patients in the SAR341402 group and 290/296 patients in the NovoLog/NovoRapid group).

Hypoglycemia was reported by similar percentages of patients in the SAR341402 and NovoLog/NovoRapid groups for all categories of hypoglycemia (any, severe, documented symptomatic and asymptomatic), with no meaningful difference in the event rates per patient-year of exposure. Severe hypoglycemia was reported by 6.0% of patients in the SAR341402 group and 4.7% of patients in the NovoLog/NovoRapid group.

Hypoglycemia analyses by various subgroups did not show any clinically meaningful differences between SAR341402 and NovoLog/NovoRapid. Subgroup analyses by randomization stratum of prior use of NovoLog/NovoRapid did not reveal any noteworthy differences between SAR341402 and NovoLog/NovoRapid. The percentages of patients reporting hypoglycemia of any category were similar between treatment groups, regardless if patients were using commercial NovoLog/NovoRapid or insulin lispro prior to the study. In patients pre-treated with NovoLog/NovoRapid hypoglycemia (any category) was reported by 99.0 % of patients in the SAR341402 group and by 97.9 % of patients in the NovoLog/NovoRapid group; severe hypoglycemia was reported by 5.2 % of patients in the SAR341402 group and by 4.8 % of patients in the NovoLog/NovoRapid group.

Adverse event

The reported TEAEs were generally similar between the 2 treatment groups and consistent with established safety profile of insulin products. A total of 184/301 (61.1%) patients in the SAR341402 group and 168/296 (56.8%) in the NovoLog/NovoRapid group reported TEAEs during the 12-month on-treatment period.

Serious TEAEs were reported in 36 patients (12.0%) in the SAR341402 group and in 29 patients (9.8%) in the NovoLog/NovoRapid group. Serious TEAEs were distributed over a variety of System Organ Classes (SOC) without any clustering by Preferred Term (PT).

Six deaths occurred during the 12-month study period, one in the SAR341402 group and 5 in the NovoLog/NovoRapid group. Three deaths occurred while the patients were on-treatment: in the SAR341402 group, one patient who had not been compliant with his antidiabetic therapy was found dead at home; the death was attributed to diabetic ketoacidosis but the results of the autopsy were not disclosed; in the NovoLog/NovoRapid group, one patient died from a TEAE of sudden death possibly due to multiorgan failure (with no further details available) and the other one from a TEAE of cardiac arrest likely due to sepsis. The 3 other deaths occurred post-treatment, all in the NovoLog/NovoRapid group: one patient died from a post-treatment AE of hypovolemic shock while being hospitalized following a TEAE of myocardial infarction that led to treatment discontinuation and peptic ulcer hemorrhage (the patient did not recover from these two events at the time of death); another patient died from a post-treatment AE of sepsis ; the third patient died from prolymphocytic leukemia (a TEAE that started during the main 6-month study period). None of these events were considered related to the study drug.

The incidence of TEAEs leading to permanent treatment discontinuation was low and similar in the 2 treatment groups (SAR341402: 2.0% [6 patients]; NovoLog/NovoRapid: 1.4% [4 patients]).

Hypersensitivity reactions (identified by customized MedDRA query [CMQ]) were reported by similar and low percentages of patients in the 2 treatment groups (SAR341402: 5.6%; NovoLog/NovoRapid: 7.1%). Two events of hypersensitivity reactions (pneumonitis in the SAR341402 group and acute respiratory failure in the NovoLog/NovoRapid group) were considered as serious and occurred in one patient in each treatment group (one event per patient). They were considered as not related to IMP by the Investigator. Other hypersensitivity reactions were all considered as non-serious, but they were considered by the Investigator as related to IMP in 2 patients (0.7%) in the SAR341402 group (dermatitis allergic and pruritus generalized; 1 patient each) and in 1 patient (0.3%) in the NovoLog/NovoRapid group (urticaria). Treatment-emergent AEs of hypersensitivity reaction resulted in permanent IMP discontinuation in 2 patients in the SAR341402 group (dermatitis allergic and urticaria, 1 patient each) and in 1 patient in the NovoLog/NovoRapid group (urticaria). Twenty-three (23) events of hypersensitivity reactions were adjudicated as allergic reactions by the ARAC (10 events reported in 9 patients in the SAR341402 group; 13 events reported in 13 patients in the NovoLog/NovoRapid group). Only 2/23 events were considered by the ARAC as related to IMP (one event of urticaria in each treatment group). Both of those events led to permanent IMP discontinuation.

Treatment-emergent AEs of injection site reaction were reported in a low and similar percentage of patients in the SAR341402 group (0.7% [2 patients]) and in the NovoLog/NovoRapid group (1.4% [4 patients]). None of the events were considered related to SAR341402, whereas events were reported by the Investigator as related to NovoLog/NovoRapid in 3 out of 4 patients.

Subgroup analyses by type of comparator did not show any relevant treatment difference for TEAEs between SAR341402 and NovoLog and between SAR341402 and NovoRapid. The incidence of TEAEs in patients using commercial NovoLog/NovoRapid prior to the study (as per randomization stratum) was similar in the 2 treatment groups (SAR341402: 59.9% [115/192 patients]; NovoLog/NovoRapid: 58.0% [109/188 patients]). In patients using commercial Humalog/Liprolog prior to the study (as per randomization stratum) the incidence of TEAEs was higher in the SAR341402 group (63.3% [69/109 patients]) than in the NovoLog/NovoRapid group (54.6% [59/108 patients]). This difference was mainly driven by the SOCs infections and infestations and nervous system disorders.

In patients with T1DM, as in the overall population, no meaningful differences were found in the general safety between the 2 treatment groups.

Immunogenicity results:

Analysis of the AIAs showed overall a similar response to SAR341402 and NovoLog/NovoRapid during the 12-month treatment period for median titers, treatment-boosted and treatment-induced AIAs. The percentage of patients who had positive AIA titers at baseline was comparable between the 2 groups (SAR341402: 35.3%; NovoLog/NovoRapid: 36.7%). The percentages of patients with treatment-emergent AIAs (ie, treatment-boosted or treatment-induced AIAs) during the 12-month on-treatment period were also similar in both groups (SAR341402: 25.5% [76/298]; NovoLog/NovoRapid: 29.1% [85/292]).

Evaluation of potential effects of treatment-emergent AIAs on the efficacy in terms of mean change in HbA1c from baseline to Week 52 or in insulin dose and safety in terms of hypoglycemia, hypersensitivity reactions, injection site reactions, or common TEAEs and serious TEAEs did 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. There was also no relationship between the maximal AIA titers and insulin doses or efficacy and safety parameters for patients with treatment-emergent AIAs.

Results of analyses of AIAs in subgroups defined by baseline and screening factors, in particular for type of diabetes, type of comparator, and prior use of NovoLog/NovoRapid, showed similar responses for SAR341402 and NovoLog/NovoRapid and were thus generally consistent with the results in the overall study population. Differences observed in some subgroups were numerically small, and the small number of patients should be taken into consideration when assessing the data.

In particular in patients using commercial NovoLog/NovoRapid prior to the study (as per randomization stratum) and switching to SAR341402 or continuing with the comparator NovoLog/NovoRapid, the percentage of patients AIA positive at baseline was similar between the 2 groups (SAR341402: 38.2% [68/178 patients]; NovoLog/NovoRapid: 38.7% [65/168 patients]). Treatment-emergent AIAs were found in 21.5% (41/191) of the patients in the SAR341402 group and 27.6% (51/185) of the patients in the NovoLog/NovoRapid group.

In patients using commercial Humalog/Liprolog prior to the study (as per randomization stratum), ie, switching from insulin lispro to SAR341402 or the comparator NovoLog/NovoRapid, the percentage of patients AIA positive at baseline was similar between the 2 groups (SAR341402: 29.8% [28/94 patients]; NovoLog/NovoRapid: 33.3% [33/99 patients]). Treatment-emergent AIAs were found in a similar percentage of patients in the 2 groups (SAR341402: 32.7% [35/107 patients]; NovoLog/NovoRapid: 31.8% [34/107 patients]).

The analyses of the NAb data for the 12-month treatment period showed that the percentage of patients who had detectable NAbs at baseline was low and similar in the 2 treatment groups (4.0% in the SAR341402 group versus 4.1% in the NovoLog/NovoRapid group). No clinically meaningful difference was observed between the 2 groups in terms of NAb response. In patients with treatment-emergent NAbs, no impact on HbA1c or on the needs in insulin doses was observed, neither in the overall population nor in any subgroup.

Other criteria of interest: insulin doses

Basal and mealtime insulin doses remained almost unchanged during the 12-month treatment period in the 2 treatment groups.

Subgroup analyses by randomization stratum of prior use of NovoLog/NovoRapid did not reveal any noteworthy differences between SAR341402 and NovoLog/NovoRapid. The change from baseline to Week 52 in basal and mealtime insulin dose was similar between treatment groups, regardless if patients were using commercial NovoLog/NovoRapid or Humalog/Liprolog prior to the study. In patients pre-treated with commercial NovoLog/NovoRapid (as per randomization stratum) the mean change (SE) in mealtime insulin dose from baseline to Week 52 was -0.000 (0.156) U/kg in the SAR341402 group compared to 0.015 (0.132) U/kg in the NovoLog/NovoRapid group. In patients pre-treated with Humalog/Liprolog (as per randomization stratum) the mean change (SE) was -0.001 (0.147) U/kg in the SAR341402 group and -0.001 (0.105) U/kg in the NovoLog/NovoRapid treatment group.

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