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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) – (6 months data)	
Study center(s): 82 centers in 7 countries.	
Study period: Date first subject enrolled: 02/Aug/2017 Date last subject completed: 16/Jul/2018	
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.

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 obtained at the screening visit (<8.0%, ≥8.0%), and by prior use of NovoLog/NovoRapid (Yes, No).

Number of subjects:	Planned: 580 (290 per arm) Randomized: 597 Treated: 597
Evaluated:	Efficacy: 597 Safety: 597 AIA: 588

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 product: 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.

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: change in HbA1c from baseline to Week 26.

Secondary endpoints:

- Percentage of HbA1c responders (patients with HbA1c <7.0%) at Week 26;
- Change in FPG from baseline to Week 26;
- Change in the mean 24-hour plasma glucose concentration from baseline to Week 26, based on the 7-point SMPG profiles;
- Change in postprandial plasma glucose excursions from baseline to Week 26, 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 main 6-month on-treatment period.

Other criteria of interest: change in daily basal, mealtime, and total insulin dose from baseline to Week 26 (U/kg body weight).

Immunogenicity sampling times and bioanalytical methods:

Blood samples for AIAs were drawn at Day 1, Week 4, Week 12 and Week 26, 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.

Statistical methods:

Primary efficacy analysis:

The statistical test for the primary efficacy endpoint (change in HbA1c from baseline to Week 26) was one-sided, with 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 all post-baseline data available during the main 6-month randomized period (ITT estimand).

A multiple imputation approach in two parts was used with missing data imputed separately for patients who prematurely discontinued IMP during the main 6-month randomized period and patients who completed the main 6-month treatment period.

Data obtained after the imputations were analyzed using an analysis of covariance (ANCOVA) of the change in HbA1c from baseline to Week 26, including the fixed categorical effects of treatment group (SAR341402, NovoLog/NovoRapid), randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8.0%, ≥8.0%), and prior use of NovoLog/NovoRapid (Yes, No), as well as the continuous fixed covariate of baseline value. The adjusted least squares mean (LS mean) of the change in HbA1c from baseline to Week 26 for each treatment group (SAR341402, NovoLog/NovoRapid) was estimated, as well as the between-group LS mean difference of SAR341402 versus NovoLog/NovoRapid, with the corresponding standard errors and 2-sided 95% confidence intervals (CIs).

Non-inferiority was demonstrated if the upper bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid on ITT population was <0.3%. If non-inferiority of SAR341402 over NovoLog/NovoRapid was demonstrated, using a hierarchical step-down testing procedure, the following additional analysis was performed (not as primary objective): the inverse non-inferiority (of NovoLog/NovoRapid over SAR341402) was tested looking at the lower bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid in the ITT population. Non-inferiority of NovoLog/NovoRapid over SAR341402 was demonstrated if the lower bound was >-0.3%. If SAR341402 was shown to be non-inferior to NovoLog/NovoRapid and NovoLog/NovoRapid non-inferior to SAR341402, similar efficacy (statistical equivalence) of SAR341402 and NovoLog/NovoRapid was assumed.

Analysis of secondary endpoints:

Secondary efficacy endpoints were analyzed in the ITT population and separately for the patients with T1DM, using all post-baseline data available during the main 6-month randomized period. The change in FPG from baseline to Week 26 was analyzed using a similar multiple imputation approach in two parts, as for the primary efficacy endpoint, followed by a similar ANCOVA model. The same ANCOVA model was applied for the analyses based on the 7-point SMPG profile (change in mean 24-hour plasma glucose concentration and postprandial plasma glucose excursions from baseline to Week 26), 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 26 were analyzed using a logistic regression model with fixed-effect term for treatment group (SAR341402, NovoLog/NovoRapid) and the randomization strata.

Safety analyses during the main 6-month on-treatment period were descriptive, 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 main 6-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.

Summary:

The current report presents the efficacy and safety results for the main 6-month on-treatment period. Results for the 12-month study period (main 6-month study period and 6-month safety extension period) will be presented in a separate report.

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).

Overall, 553 patients (92.6 %) in the randomized population completed the main 6-month treatment period. A similar number of patients in each treatment group discontinued the study treatment prematurely (SAR341402: 22/301 [7.3%]; NovoLog/NovoRapid: 22/296 [7.4%]).

Demography and baseline characteristics were well-balanced between the 2 treatment groups. The median age of the randomized population was 49 years (patients with T1DM: 45 years; patients with T2DM: 64 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 mean duration of diabetes prior to study start was 19.5 years (patients with T1DM: 19.6 years; patients

with T2DM:18.9 years), 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%.

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:

The non-inferiority of SAR341402 versus NovoLog/NovoRapid in change in HbA1c from baseline to Week 26 was demonstrated, as the upper bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid (95% CI: -0.192 to 0.039) was below the pre-specified non-inferiority margin of 0.3%. Mean HbA1c decreased similarly from baseline to Week 26 in the SAR341402 group (LS mean change: -0.38%) and the NovoLog/NovoRapid group (-0.30%). The LS mean difference between the two treatment groups was -0.08% (95% CI: -0.192 to 0.039).

The inverse non-inferiority of NovoLog/NovoRapid over the SAR341402 group was tested as a second step analysis and was also demonstrated as the lower bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/Novorapid was above -0.3%. Efficacy of SAR341402 on change in HbA1c from baseline to Week 26 is therefore similar to that of NovoLog/NovoRapid.

Sensitivity analyses to assess the impact of the missing HbA1c data at Week 26 (SAR341402: 18/301 patients [6.0%]; NovoLog/NovoRapid: 18/296 patients [6.1%]) on the primary analysis showed results that were consistent with the results of the primary analysis.

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 26 was similar between SAR341402 and NovoLog/NovoRapid regardless of the type of diabetes. Results by type of comparator showed that the decrease in HbA1c from baseline to Week 26 was similar between SAR341402 and NovoLog, as well as between SAR341402 and NovoRapid. In patients who used commercial NovoLog/NovoRapid prior to the study (as per randomization stratum), results showed that changes in HbA1c from baseline to Week 26 were similar in patients who had switched from NovoLog/NovoRapid to SAR341402 at randomization (LS mean change [SE]: -0.37% [0.052]) compared with patients who had continued NovoLog/NovoRapid (LS mean change [SE]: -0.33% [0.052]). In patients using commercial Humalog/Liprolog prior to the study (as per randomization stratum), the decreases in HbA1c from baseline to Week 26 were also similar for patients switching from insulin lispro to SAR341402 (LS mean change [SE]: -0.39% [0.070]) or to the comparator NovoLog/NovoRapid (LS mean change [SE]: -0.24% [0.067]).

No clinically meaningful differences were observed between SAR341402 and NovoLog/NovoRapid for any of the secondary endpoints, including the assessment of HbA1c responders, FPG, and SMPG parameters (including postprandial plasma glucose excursions).

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 main 6-month on-treatment period, in the 2 treatment groups, the majority of patients had at least one event of hypoglycemia regardless of the category: 96.7% (291/301 patients) in the SAR341402 group and 96.3% (285/296 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 4.0% of patients in the SAR341402 group and 3.4% of patients in the NovoLog/NovoRapid group.

Subgroup analyses by type of comparator did not show any relevant difference for hypoglycemia between SAR341402 and NovoLog or 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 NovoLog/NovoRapid or insulin lispro prior to the study. In patients pre-treated with NovoLog/NovoRapid any hypoglycemia was reported by 97.4 % of patients in the SAR341402 group and by 95.2 % of patients in the NovoLog/NovoRapid group. Severe hypoglycemia was reported by 3.1 % of patients in the SAR341402 group and by 3.7 % of patients in the NovoLog/NovoRapid group.

Adverse events

The safety profiles in terms of type of TEAEs and frequency of occurrence were generally similar between the SAR341402 and the NovoLog/NovRapid groups. A total of 156/301 (51.8%) patients in the SAR341402 group and 146/296 (49.3%) in the NovoLog/NovoRapid group reported TEAEs during the main 6-month on-treatment period.

Serious TEAEs were reported in 25 patients (8.3%) in the SAR341402 group and in 18 patients (6.1%) in the NovoLog/NovoRapid group. Serious TEAEs were distributed over a variety of System Organ Classes (SOC) without any clustering by Preferred Term (PT).

Two deaths occurred during the main 6-month study period, both in the NovoLog/NovoRapid group. One patient died from a TEAE of sudden death possibly due to multiorgan failure, with no further details available. The other patient died from a post-treatment AE of hypovolemic shock while being hospitalized following a TEAE of myocardial infarction that lead to treatment discontinuation and peptic ulcer hemorrhage. The patient did not recover from these two events at the time of death. Two additional deaths were reported after the main 6-month study period, one in each treatment group. 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: 1.7% [5 patients]; NovoLog/NovoRapid: 1.0% [3 patients]).

Hypersensitivity reactions were reported by similar and low percentages of patients (3.7%) in the 2 treatment groups. None of them was considered as serious, but they were considered as related to the IMP by the Investigator in 2 (0.7%) patients in the SAR341402 group and in 1 (0.3%) patient in the NovoLog/NovoRapid group. Treatment-emergent AEs of hypersensitivity reaction resulted in permanent IMP discontinuation in 2 patients in the SAR341402 group and in 1 patient in the NovoLog/NovoRapid group. Fourteen (14) events of hypersensitivity reactions were adjudicated as allergic reactions by the ARAC (6 events reported in 5 patients in the SAR341402 group; 8 events reported in 8 patients in the NovoLog/NovoRapid group). Only 2/14 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/NovoRapid. In patients using commercial NovoLog/NovoRapid prior to the study (as per randomization stratum) the incidence of TEAEs was similar in the 2 treatment groups (SAR341402: 47.9% [92/192 patients]; NovoLog/NovoRapid: 50.0% [94/188 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 (58.7% [64/109 patients]) than in the NovoLog/NovoRapid group (48.1% [52/108 patients]). This difference was mostly 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 safety and tolerability between the 2 treatment groups.

Immunogenicity results:

Analysis of the AIAs showed overall a similar response to SAR341402 and NovoLog/NovoRapid during the 6-month treatment period for median titers, treatment-boosted and treatment-induced AIAs. Similar percentages of patients in the 2 groups had positive AIA titers at baseline (SAR341402: 35.3%; NovoLog/NovoRapid: 36.7%). The percentages of patients with treatment-emergent AIAs (ie, treatment-boosted or treatment-induced AIAs) during the main 6-month on-treatment period were also similar in both groups (SAR341402: 16.9% [50/296]; NovoLog/NovoRapid: 20.5% [60/292]).

Evaluation of potential effects of treatment-emergent AIAs on the efficacy in terms of mean change in HbA1c from baseline to Week 26 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), the percentage of patients AIA positive at baseline was similar between SAR341402 and NovoLog/NovoRapid (SAR341402: 38.2% [68/178 patients]; NovoLog/NovoRapid: 38.7% [65/168 patients]). Treatment-emergent AIAs were found in 12.6% [24/191] of the patients in the SAR341402 group and 20.0% [37/185 patients] of the patients in the NovoLog/NovoRapid group.

In patients using commercial Humalog/Liprolog prior to the study (as per randomization stratum) 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: 24.8% [26/105 patients]; NovoLog/NovoRapid: 21.5% [23/107 patients]).

Other criteria of interest: insulin doses

Only small changes in daily basal and mealtime insulin dose (U/kg) were observed over the main 6-month treatment period with no relevant difference between 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 26 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 the mean change (SE) in mealtime insulin dose from baseline to Week 26 was -0.009 (0.133) U/kg in the SAR341402 group compared to 0.019 (0.114) U/kg in the NovoLog/NovoRapid group. In patients pre-treated with Humalog/Liprolog the mean change (SE) was -0.015 (0.133) U/kg in the SAR341402 group and -0.003 (0.121) U/kg in the NovoLog/NovoRapid treatment group.

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