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Sponsor: Sanofi **Drug substance(s):** SAR342434	**Study Identifiers:** U1111-1131-5038, NCT02273180, 2013-002945-12 **Study code:** EFC12619

Title of the study: Six-month, Randomized, Open-label, Parallel-group Comparison of SAR342434 to Humalog® in Adult Patients With Type 1 Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period (EFC12619; SORELLA 1)-6 month

Study center(s): 89 active centers in 8 countries (France, Germany, Hungary, Japan, Poland, Russia, Spain and United States)

Study period:

Date first patient enrolled: 28/Oct/2014

Date last patient completed: 22/Dec/2015

Phase of development: Phase 3

Objectives: The primary objective was to demonstrate non-inferiority of SAR342434 versus Humalog in terms of change in hemoglobin A1c (HbA1c) from baseline to Week 26 in patients with type 1 diabetes mellitus (T1DM) 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 including during the safety extension (Week 52).
- To assess the efficacy of SAR342434 and Humalog in terms of proportion of patients reaching target HbA1c < 7%, fasting plasma glucose (FPG) and Self-measured 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% versus ≥8.0%), prior use of Humalog (Y/N) and geographical region (Japan, non-Japan), with a minimum of 66 patients randomized in Japan.

Number of patients:	Planned: 480 (240 per arm)
	Randomized: 507
	Treated: 506
Evaluated:	Efficacy: 507
	Safety: 506
	Anti-insulin Antibody (AIA): 499

Diagnosis and criteria for inclusion: Patients with type 1 diabetes mellitus diagnosed for at least 12 months and treated with Lantus and Humalog/Liprolog® or NovoLog®/NovoRapid® (at least 3 times daily before each meal) in the 6 months prior to the screening visit and with 7%≤HbA1c≥10% at screening.

Study treatments

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

Formulation:

SAR342434 was supplied as a 100U/mL solution in pre-filled SAR342434 SoloSTAR disposable pen.

Humalog was supplied as a 100U/mL solution in pre-filled Humalog KwikPen® disposable pen.

Humalog US (ie, product approved, and marketed in the US) and Humalog EU (ie, product approved, and marketed in the EU) were used at sites depending on the countries.

Route(s) of administration: Subcutaneous injection

Dose regimen: The starting dose was a unit to unit conversion from the Humalog/Liprolog or NovoLog/NovoRapid dose used prior to the trial to either SAR342434 or Humalog.

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

The dose of either SAR342434 or Humalog was to be adjusted to achieve a 2-hour postprandial plasma glucose of 6.7 to 8.9 mmol/L (120 to 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 to be the same as the last dose prior to baseline visit.

Lantus was injected once daily.

Doses of Lantus were to be adjusted to achieve glycemic target for fasting, pre-prandial plasma glucose SMPG between 4.4 to 7.2 mmol/L (80 to 130 mg/dL) without hypoglycemia.

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 endpoint:

- Percentage of HbA1c responders (patients with HbA1c <7%) 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: 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) will be 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 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%), prior use of Humalog (Y/N), and geographical region (Non-Japan; Japan) as fixed categorical effects as well as, the continuous fixed covariates of baseline HbA1c value and baseline HbA1c value-by-visit interaction. All post-baseline HbA1c data available during the main 6-month period will be used (ITT estimand). The baseline value was defined as the last available value prior to the first dose administration of Investigational Medicinal Product (IMP) in the treatment period. Difference between adjusted least-square means (LS-means) estimates at Week 26 by treatment group, associated standard errors (SEs) 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 on ITT population is <0.3%.

If non-inferiority of SAR342434 was demonstrated, using a hierarchical step-down testing procedure, the inverse non-inferiority (of Humalog over SAR342434) was 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 is >-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%) 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) and geographical region (Japan, Non-Japan). 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.

Safety analyses were descriptive, based on safety population.

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 main 6-month on-treatment period. An AIA sample was considered as available for analysis if the sample was collected during the main 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 main 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: The current report presents the efficacy and safety results for the main 6-month on-treatment period.

Population characteristics:

A total of 507 patients with type 1 diabetes mellitus were randomized to SAR342434 (n=253) or to Humalog (n=254); 506 patients were exposed to IMP (safety population). All the randomized patients were included in the ITT population (efficacy population).

Overall, 480 patients (94.7%) completed the main 6-month treatment period. A comparable number of patients in each treatment group discontinued the study treatment prematurely (SAR342434: 15/253 [5.9%]; Humalog 11/254 [4.3%]).

Demography and baseline characteristics were well-balanced between treatment groups. The median age of the randomized population was 42.0 years and less than 10% of the population was 65 years or older. The mean body mass index (BMI) at baseline was 26.0 kg/m², with 92/507 (18.1%) patients having a BMI ≥ 30 kg/m2. The mean duration of diabetes prior to study start was 19.05 years, in 74.8% of the patients the diagnosis was known for ≥ 10 years. 60.9% of the patients had screening HbA1c ≥8.0%. At study entry, all patients were using Lantus as basal insulin, and 62.5% of the patients had used insulin lispro (Humalog/Liprolog) within the last 6 months before screening. The mean basal insulin dose prior to treatment was 0.335 U/kg, the mean bolus insulin dose was 0.360 U/kg and the mean total insulin dose 0.695 U/kg.

Mean HbA1c at baseline was similar in both treatment groups for patients included in the primary analysis (SAR342434: 8.08% and Humalog: 7.99%) (patients who had a baseline and at least one post-baseline HbA1c assessment).

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 -0.42%) and the Humalog group (-0.47%). The LS mean difference between the SAR342434 and the Humalog group was 0.06% (95% CI: -0.084 to 0.197). Non-inferiority of SAR342434 over Humalog was demonstrated, as the upper bound of the 2-sided 95% CI 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 (SAR342434: 6/253 [2.4%]; Humalog: 5/254 [2%]) 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=0.3085).

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), randomization stratum of screening HbA1c, prior use of Humalog, and geographical region. There was no evidence of heterogeneity of treatment effect across subgroups.

The small discrepancies observed between the randomization stratums of prior use of Humalog as reported in IVRS/IWRS and the actual prior use of Humalog had no effect on the results of the primary efficacy analysis.

No meaningful 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:

No meaningful differences were found in the safety and tolerability between the 2 treatment groups as well as between regions using Humalog US or Humalog EU.

In patients with T1DM 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. 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 than with Humalog, due to 1 patient who reported 119 events and is not considered as representative of a specific risk.

The percentages of patients with any TEAEs, serious TEAEs or TEAEs leading to treatment discontinuation were similar between both treatment groups. 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.

One patient in the SAR342434 group, who was a former heavy smoker, with obesity and hyperlipidemia treated with statins, died (cardiac death) during the main 6-month treatment period. The patient had no known cardiovascular disease diagnosed prior to the event. An autopsy was performed and led to the conclusion that the patient died as a result of hypertensive disease and atherosclerotic artery disease. The cardiac death was considered as not related to the IMP.

Hypersensitivity reactions were reported in 13 patients (5.2%) in the SAR342434 and 10 patients (3.9%) in the Humalog group. None was considered as serious or led to permanent IMP discontinuation. Among those events, 1 event in 1 patient in the Humalog group was adjudicated as an allergic reaction by the Allergic Reaction Assessment Committee (ARAC) versus none in the SAR342434 group. The event (urticaria) was of mild intensity, non serious, did not lead to permanent treatment discontinuation, and was assessed by the ARAC as not related to the IMP.

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 about 50% of the patients had positive AIA titers at baseline. Analysis of the AIA shows a similar response to SAR342434 and Humalog during the 6-month treatment period for median titers, and treatment-boosted and treatment-induced AIAs. Treatment-emergent AIAs were found in similar percentage of patients in both treatment groups. The prevalence, i.e. 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 87.0% - 93.7% of the AIAs showed cross-reactivity with human insulin.

Results of analyses of AIAs in subgroups defined by screening and baseline factors were consistent with the results in the overall study population. The AIA analyses in the subgroups defined by region-approved Humalog did not show differences of results of SAR342434 versus Humalog US or SAR342434 versus Humalog EU. In the subgroup defined by use of Humalog prior to the study, i.e. switching at study baseline from commercial Humalog to SAR342434 or Humalog, AIA incidence was similar between treatment groups (SAR342434 27/154 [17.5%], Humalog 19/158 [18.4%]). However, treatment boosted AIAs were found in less patients with SAR342434 (12.7%) than in patients with Humalog (17.3%), whereas treatment induced AIAs were found in more patients with SAR342434 (22.7%) than in patients with Humalog (19.5%). 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.

Issue date: 11-Dec-2017

Sponsor: Sanofi **Drug substance(s):** SAR342434	**Study Identifiers:** U1111-1131-5038, NCT02273180, 2013-002945-12 **Study code:** EFC12619

Title of the study: Six-month, Randomized, Open-label, Parallel-group Comparison of SAR342434 to Humalog® in Adult Patients With Type 1 Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period (EFC12619-12 months; SORELLA 1-12 months)

Study center(s): 89 active centers in 8 countries (France, Germany, Hungary, Japan, Poland, Russia, Spain and United States)

Study period:

Date first patient enrolled: 28/Oct/2014

Date last patient completed: 01/Jul/2016

Phase of development: Phase 3

Objectives: The primary objective was to demonstrate non-inferiority of SAR342434 versus Humalog in terms of change in hemoglobin A1c (HbA1c) from baseline to Week 26 in patients with type 1 diabetes mellitus (T1DM) 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 (AIAs) with efficacy and safety including during the safety extension (Week 52).
- To assess the efficacy of SAR342434 and Humalog in terms of proportion of patients reaching target HbA1c <7%, Fasting Plasma Glucose (FPG), and Self-measured plasma glucose (SMPG) profiles and insulin dose.
- To assess safety of SAR342434 and Humalog.

The primary objective of the study were based on the initial main 6-month on-treatment period; the results are presented in the 6 month clinical study report (CSR). Efficacy and safety variables used to evaluate the study objectives were also measured over the 12-month treatment period and are described in this 12-month results summary.

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% versus ≥8.0%), prior use of Humalog (Y/N) and geographical region (Japan, non-Japan), with a minimum of 66 patients randomized in Japan.

Number of patients**:**	Planned: 480 (240 per arm)
	Randomized: 507
	Treated: 506
Evaluated:	Efficacy: 507
	Safety: 506
	Anti-insulin antibody (AIA): 500

Diagnosis and criteria for inclusion:

Patients with T1DM diagnosed for at least 12 months and treated with Lantus and Humalog/Liprolog® or NovoLog®/NovoRapid® (at least 3 times daily before each meal) in the 6 months prior to the screening visit and with 7%≤ HbA1c ≤10% at screening.

Study treatments

Investigational medicinal products (IMP): SAR342434 (tested drug) and Humalog (control drug).

Formulation:

SAR342434 was supplied as a 100 U/mL solution in pre-filled SAR342434 SoloSTAR disposable pen.

Humalog was supplied as a 100 U/mL solution in pre-filled Humalog KwikPen® disposable pen.

Humalog US (i.e., product approved, and marketed in the US) and Humalog EU (i.e., product approved, and marketed in the EU) were used at sites depending on the countries.

Route(s) of administration: subcutaneous injection.

Dose regimen: The starting dose was a unit to unit conversion from the Humalog/Liprolog or NovoLog/NovoRapid dose used prior to the trial 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 of either SAR342434 or Humalog was to be adjusted to achieve a 2-hour postprandial plasma glucose of 6.7 to 8.9 mmol/L (120 to 160 mg/dL), while avoiding hypoglycemia.

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

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

Route(s) of administration: subcutaneous injection.

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

Lantus was injected once daily.

Doses of Lantus were to be adjusted to achieve glycemic target for fasting, pre-prandial plasma glucose SMPG between 4.4 and 7.2 mmol/L (80 and 130 mg/dL) without hypoglycemia.

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

Efficacy variables were:

- Change in HbA1c from baseline (scheduled on Day 1) to Week 52 (Month 12).
- Percentage of HbA1c responders (patients with HbA1c <7%) at Week 52.
- Change in FPG (mmol/L [mg/dL]) from baseline to Week 52.
- Change in the mean 24-hour plasma glucose concentration (mmol/L [mg/dL]) from baseline to Week 52 based on the 7-point SMPG profiles.
- Change in postprandial plasma glucose excursions (mmol/L [mg/dL]) 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 in 7-point SMPG profiles per time-point from baseline to Week 52.
- Change in 3-point SMPG profiles per time-point from baseline to Week 52.

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 body weight.

Immunogenicity: 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 AIAs were drawn on Day 1, at Week 4, Week 12, Week 26, Week 40, Week 52, and at the end-of-treatment assessments in case of premature IMP discontinuation. Samples were to be collected at the earliest 8 hours after the administration of SAR342434 or Humalog.

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

Statistical methods:

The primary efficacy variable, which was change in HbA1c from baseline to Week 26, was analyzed and presented in the 6-month CSR.

Efficacy endpoints during the 12-month period were analyzed on the intent-to-treat (ITT) population (defined as all randomized patients, irrespective of compliance with the study protocol and procedures). All analyses for the 12-month study period were descriptive (no formal statistical testing). For HbA1c, FPG, and 7-point SMPG endpoints (mean 24-hour plasma glucose concentration and postprandial plasma glucose excursions), the change from baseline to Week 52 was analyzed using a mixed-effect model for repeated measures (MMRM) approach, under the missing at random (MAR) framework and carried out via Statistical Analysis System (SAS) PROC MIXED with an adequate contrast at Visit 11 (Week 52). The model included the fixed categorical effects of randomization strata of screening HbA1c (<8.0, ≥8.0%), prior use of Humalog (Yes, No) and geographical region (Japan, Non-Japan), treatment group (SAR342434, Humalog), visit (Week 12, Week 26, Week 40, Week 52), and treatment-by-visit interaction, as well as, the continuous fixed covariates of baseline value and baseline value-by-visit interaction for the corresponding endpoint. Difference between adjusted least-square means (LS-means) estimates at Week 52 by treatment group, associated standard errors (SEs) and 2-sided 95% confidence interval (CI) were estimated using adequate contrasts.

Safety analyses were descriptive, based on the safety population.

The analyses of AIA data were performed on the AIA population defined as all patients from the safety population with at least one AIA sample available for analysis during the 12-month on-treatment period. An AIA sample was considered as available for analysis if the sample was collected during the 12-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 12-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 AIAs, 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.

In order to assess the relationship between immunogenicity and efficacy assessments, change in HbA1c from baseline to Week 52 was summarized by treatment-emergent AIA (Yes, No) and treatment-emergent AIA at last on treatment value (Yes, No). The following safety data was also summarized descriptively by treatment-emergent AIA (Yes, No) and AIA incidence at last on-treatment value (Yes, No): hypoglycemia (any, severe, documented symptomatic, and severe and/or confirmed, regardless of the time of onset during the day), common TEAEs and SAEs, injection site and hypersensitivity reactions.

Summary: The current report presents the efficacy and safety results for the 12-month treatment period

Population characteristics: A total of 507 patients with T1DM were randomized to SAR342434 (n=253) or to Humalog (n=254); 506 patients were exposed to IMP (safety population). All the randomized patients were included in the ITT population (efficacy population).

Overall, 461 patients (90.9%) completed the 12-month treatment period. A comparable number of patients in each treatment group discontinued the study treatment prematurely (SAR342434: 26/253 [10.3%]; Humalog 19/254 [7.5%]).

Demography and baseline characteristics were well-balanced between treatment groups. The median age of the randomized population was 42.0 years and less than 10% of the population was 65 years or older. The mean body mass index (BMI) at baseline was 26.0 kg/m², with 92/507 (18.1%) patients having a BMI ≥30 kg/m^2. The median duration of diabetes prior to study start was 16.40 years, in 74.8% of the patients the diagnosis was known for ≥10 years. 60.9% of the patients had screening HbA1c ≥8.0%. Mean HbA1c at baseline was 8.03%. At study entry, all patients were using Lantus as basal insulin, and 62.5% of the patients had used insulin lispro (Humalog/Liprolog) within the last 6 months before screening. At baseline, the mean basal insulin dose was 0.335 U/kg, the mean mealtime insulin dose was 0.360 U/kg and the mean total insulin dose 0.695 U/kg.

Insulin doses: Mealtime, basal and total insulin doses were generally similar between SAR342434 and Humalog with small changes during the study. The mean ratio of average daily basal insulin dose over total insulin dose before randomization, was the same at baseline in each treatment group (0.49) and remained unchanged at Week 52 (SAR342434 group: 0.48; Humalog group: 0.49).

Efficacy results: Mean HbA1c decreased similarly from baseline to Week 52 in the SAR342434 group (LS mean change -0.22%) and the Humalog group (-0.30%). The LS mean difference between the SAR342434 and the Humalog group was 0.07% (95% CI: -0.084 to 0.232). During the 6-month extension period HbA1c increased but remained lower than baseline in both treatment groups while insulin doses remained practically unchanged.

No meaningful differences were observed between SAR342434 and Humalog for any of the other efficacy endpoints. Mean changes 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 52 compared with baseline.

Similar results were obtained for the on-treatment analysis.

Safety results: No meaningful differences were found in the safety between the 2 treatment groups.

In patients with T1DM treated for 52 weeks during this study, hypoglycemia was reported by similar percentages of patients in the SAR342434 and Humalog groups, across all categories of hypoglycemia. 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 than with Humalog, due to 1 patient who reported 122 events and is not considered as representative of a specific risk.

The percentages of patients with any TEAEs, serious TEAEs or TEAEs leading to treatment discontinuation were similar between both treatment groups. The safety profiles in terms of type of TEAEs were similar in both treatment groups with TEAEs of the SOC infections and infestations being the most frequently reported events in both groups.

One patient in the SAR342434 group died (cardiac death) during the main 6-month treatment period. The cardiac death was considered as not related to the IMP. No death was reported in the 6-month extension period.

Hypersensitivity reactions were reported in 15 patients (6.0%) in the SAR342434 and 16 patients (6.3%) in the Humalog group. None was considered as serious or led to permanent IMP discontinuation. Among those events, 2 events in 2 patients in the Humalog group were adjudicated as allergic reactions by the Allergic Reaction Assessment Committee (ARAC) versus none in the SAR342434 group. Both events (urticaria and rhinitis allergic [hypersensitivity as per ARAC diagnosis]) were of mild intensity, non serious, did not lead to permanent treatment discontinuation, and were assessed by the ARAC as not related to the IMP.

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. Other subgroup analyses by prior use of Humalog, age, gender, BMI and HbA1c at screening did not show notable treatment difference for these safety assessments.

Immunogenicity results: In both treatment groups, about 50% of the patients had positive AIA titers at baseline. Analysis of the AIA shows a similar response to SAR342434 and Humalog during the 12-month treatment period for median titers, and treatment-boosted and treatment-induced AIAs.

Treatment-emergent AIAs were found in similar percentage of patients in both treatment groups. The prevalence, i.e., percentage of patients with detectable AIAs at least one time point during the study was similar in the SAR342434 and Humalog group. As expected, AIAs were cross-reactive to human insulin and insulin glargine in more than about 80-90% of the patients and to the insulin glargine metabolite M1 in more than 70% of the patients.

Results of analyses of AIAs in subgroups defined by screening and baseline factors were consistent with the results in the overall study population, showing similar results in the SAR342434 and Humalog groups. In the subgroup defined by regions using Humalog US, AIA incidence was quite similar between treatment groups (SAR342434 29/137 [21.2%], Humalog US 32/139 [23.0%]). However, treatment-boosted AIAs were found in fewer patients with SAR342434 (14.3%) than in patients with Humalog US (23.8%), while treatment-induced AIAs were found in 27.0% of patients with SAR342434 as compared with 22.4% of patients with Humalog US. In the subgroup defined by regions using Humalog EU, AIA incidence, treatment-boosted AIAs and treatment-induced AIAs were all similar in the 2 treatment groups. In the subgroup defined by use of Humalog prior to the study, i.e., switching at study baseline from commercial Humalog to SAR342434 or Humalog, AIA incidence was similar between treatment groups (SAR342434 34/155 [21.9%], Humalog 36/158 [22.8%]). However, treatment-boosted AIAs were found in less patients with SAR342434 (15.0%) than in patients with Humalog (23.5%), whereas treatment induced AIAs were found in more patients with SAR342434 (29.3%) than in patients with Humalog (22.1%).

Evaluation of potential effects of treatment-emergent AIAs on the efficacy in terms of mean change of HbA1c from baseline to Week 52 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.

Five patients in the SAR342434 group and 7 patients in the Humalog group had AIA titers increased at Week 52 compared with baseline and concomitant increase of HbA1c or insulin dose or an ongoing hypersensitivity or SAE. These cases were reviewed by the ARAC; follow up of AIA was not deemed necessary in any of the patients.

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