STATISTICAL ANALYSIS PLAN

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

SAR314102-EFC15081

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AEs:	adverse events
AIA:	anti-insulin antibody
ALP:	alkaline phosphatase
ALT:	alanine aminotransferases
ANCOVA:	analysis of covariance
ARAC:	Allergic Reaction Assessment Committee
AST:	aspartate aminotransferases
ATC:	anatomical therapeutic chemical
BMI:	body mass index
CI:	confidence interval
CLcr:	creatinine clearance
CONSORT:	consolidated standards of reporting trials
CSR:	clinical study report
DBP:	diastolic blood pressure
e-CRF:	electronic case report form
FPG:	fasting plasma glucose
GFR:	glomerular filtration rate
HbA1c:	glycosylated hemoglobin A1c
HLGT:	high level group term
HLT:	high level term
IMP:	investigational medicinal product
INR:	international normalized ratio
IRT:	interactive response technology
ITT:	intent-to-treat
KM:	Kaplan-Meier
LDL:	low-density lipoprotein
LLT:	lower level term
LPLV:	last patient last visit
LS:	least squares
MCMC:	Markov Chain Monte Carlo
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
NIMP:	non-investigational medicinal product
PCSA:	potentially clinically significant abnormality
PT:	preferred term
RBC:	red blood cell
ROW:	rest of the world
SAEs:	serious adverse events
SBP:	systolic blood pressure
SD:	standard deviation
SMPG:	self-monitored plasma glucose

SMQ:	standardized MedDRA query
SOC:	system organ class
T1DM:	type 1 diabetes mellitus
T2DM:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

This Statistical Analysis Plan (SAP) provides a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for study SAR341402 / EFC15081.

1.1 STUDY DESIGN AND RANDOMIZATION

This is a multicenter, multinational, open-label, randomized, active-controlled, 2-arm parallel group comparative Phase 3 study which will recruit outpatients with type 1 diabetes mellitus (T1DM) or with type 2 diabetes mellitus (T2DM [T2DM only for US]) of at least one year (12 months) duration and who have been on multiple daily injection (MDI) regimen using NovoLog/NovoRapid or insulin lispro 100 U/mL in the last 6 months prior to screening visit on top of insulin glargine (100 U/mL) in the last 6 months prior to screening visit or on top of Levemir (insulin detemir) in the last 12 months prior to screening visit and, comparing:

- SAR341402 in combination with insulin glargine 100 U/mL (Lantus).
- NovoLog/NovoRapid in combination with insulin glargine 100 U/mL (Lantus).

The study will comprise a 6-month treatment period followed by a 6-month safety extension period.

The study is open-label as injection devices, leaflets and other training material, and treatment kits are distinguishable from each other.

Approximately 580 patients will be randomized from approximately 84 sites. The planned n=580 patients will be randomized to the rapid-acting insulins SAR341402 or NovoLog/NovoRapid in a 1:1 ratio at the end of the screening period.

- Approximately 250 patients with T1DM will be randomized in the geographical region using NovoRapid (including Europe and Japan).
- Approximately 330 patients, including 230 with T1DM and 100 with T2DM, will be randomized in the geographical region using NovoLog (all in the US).

The number of patients with T1DM expected to be randomized in the US versus outside of the US may change owing to the recruitment potential at those regions.

Randomization will be stratified by geographical region (Europe, US, Japan), by type of diabetes (T1DM, T2DM [T2DM only for US]), by glycosylated hemoglobin A1c (HbA1c) obtained at the screening visit (<8.0%, ≥8.0%), and by prior use of NovoLog/NovoRapid (Yes, No).

The protocol-mandated background therapy is the basal insulin analogue insulin glargine, which will be continued throughout the study, including during the safety extension period.

1.2 OBJECTIVES

The primary objective will be assessed at the end of the main 6-month period, and the result will be presented in the 6-month clinical study report (CSR).

The secondary objectives will be assessed for both the main 6-month and 12-month periods, and the results will be presented respectively in the 6-month and 12-month CSR.

1.2.1 Primary objectives

The primary objective of this study is to demonstrate non-inferiority of SAR341402 versus NovoLog/NovoRapid in HbA1c change from baseline to Week 26 in patients with T1DM or T2DM also using Lantus.

1.2.2 Secondary objectives

The secondary objectives of this study are:

- To assess the immunogenicity of SAR341402 and NovoLog/NovoRapid in terms of positive/negative status and anti-insulin antibody (AIA) titers during the course of the study.
- To assess the relationship of AIAs 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-monitored 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.

1.3 DETERMINATION OF SAMPLE SIZE

The sample size calculation was performed based on the primary endpoint, change in HbA1c (%) from baseline to Week 26.

A sample size of 580 patients (290 patients per arm; approximately 480 T1DM patients [230 patients in the US using NovoLog and 250 patients in countries using NovoRapid] and 100 T2DM patients [all in the US using NovoLog]) will ensure that the upper bound of the 2-sided 95% confidence interval (CI) for the adjusted mean difference between SAR341402 and NovoLog/NovoRapid would not exceed a non-inferiority margin of 0.3% HbA1c with at least 95% power. This sample size will also ensure that the lower bound of this 2-sided 95% CI would not be below -0.3% HbA1c with at least 95% power, thus will provide at least 90% power to show both non-inferiority of SAR341402 over NovoLog/NovoRapid (primary analysis) and inverse non-inferiority of NovoLog/NovoRapid over SAR341402 (secondary analysis).

These calculations assume a common standard deviation (SD) of 1.0% and a true difference in HbA1c between the treatment groups of zero.

The non-inferiority margin of 0.3% HbA1c for the adjusted mean difference between SAR341402 and NovoLog/NovoRapid was chosen, as it is in line with recommendations by regulatory agencies including FDA, referring to a range of 0.3% to 0.4% (1), and the European Medicines Agency, suggesting the more stringent non-inferiority margin of 0.3% (2), and based on historical precedent for comparative insulin studies in which a 0.3% non-inferiority margin is often used.

An exploratory analysis of the percentage of patients with treatment-emergent AIAs (AIA incidence) will be performed to compare the immunogenicity of SAR341402 versus NovoLog/NovoRapid. The sample size of 580 patients would ensure that the 2-sided 90% CI for the adjusted risk difference between SAR341402 and NovoLog/NovoRapid would be included within the [-10%; 10%] interval with at least 68% power. This calculation assumes a true risk difference between the treatment groups of zero and a maximum AIA incidence of 30% (in previous Sanofi clinical studies performed with rapid-acting insulin analogs, AIA incidence in the range of 15-20% were observed at 6 months). The power calculations are presented in Table 1 below.

Table 1 - Power calculation based on the percentage of patients with treatment-emergent AIAs

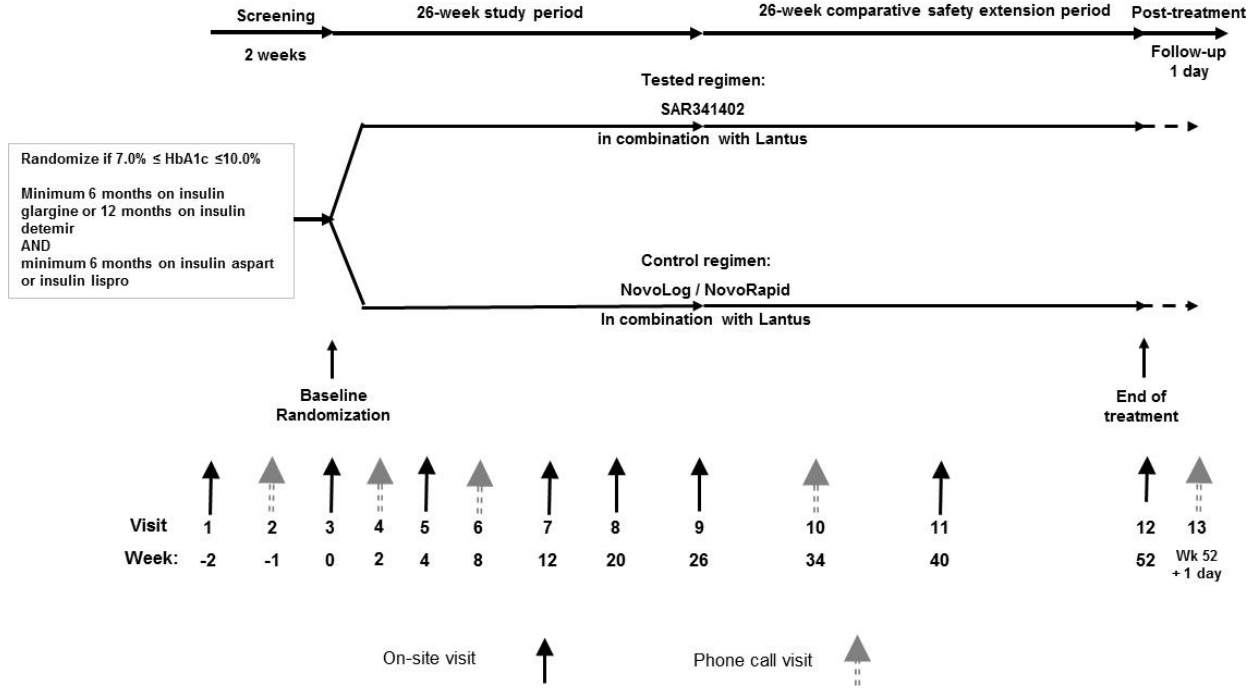
Percentage of patients with treatment-emergent AIAs	10%	20%	30%
Power for N=580 (290/arm)	97%	82%	68%

To reach this number of 580 patients randomized for the 6-month comparative efficacy and safety period, calculations were made using the nQuery Advisor® Software Version 7.0.

1.4 STUDY PLAN

The following figure describes the design of the study:

Figure 1 - Study design



The study consists of:

- A 2-week screening period, from signed informed consent to randomization.
- A 26-week treatment period, from randomization to Visit 9 (Week 26).
- A 26-week comparative safety extension period, from Visit 9 (Week 26) to the end of treatment visit (Visit 12, Week 52).
- A 1-day follow-up period with a safety telephone visit 1 day after the end of treatment visit.

In total, the study duration will be 54 weeks per patient (+ 1 day safety follow-up).

The end of treatment is at Visit 12 (Week 52) after randomization. The end of the study is a follow-up contact (Visit 13) at the time of Week 52 plus 1 day.

In case of premature permanent investigational medicinal product (IMP) discontinuation, patients will have as soon as possible a premature treatment discontinuation visit (recorded as Visit 8000 in the clinical database) with the assessments normally planned at Visit 12 (Week 52), followed by a safety follow-up (recorded as Visit 8010 in the clinical database) 1 day after.

Afterwards, the patients will remain in the study until at least Visit 9 (Week 26), and will be followed-up according to the visits and assessments as planned in the protocol (except for the 1-day safety post-treatment follow-up [Visit 13]).

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled).

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

The first patient was randomized on 14-Aug-2017. There are no planned interim analyses.

Table 2 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	02-Nov-2017	Simplification of hypoglycemia analyses	Removal of evaluation of hypoglycemia events by the time of the day from the list of planned analyses.
		Clarification of disposition presentation	Changes in planned presentation of patient disposition and in time periods of interest for extent of investigational medicinal product exposure.
		Simplification of hypoglycemia analyses	Removal of analysis of hypoglycemia events by treatment period.
3	14-Dec-2017	FDA Recommendation	Additional exploratory statistical analyses of the percentage of patients with treatment emergent AIAs were included to further compare the immunogenicity of SAR341402 versus NovoLog/NovoRapid.
			The sample size was increased from 500 to 580 in order to increase the power for meeting both the primary analysis of non-inferiority and the secondary analysis of inverse non inferiority on HbA1c, as well as to ensure reasonable power for the additional exploratory statistical analyses of AIAs.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value for efficacy variables is defined as the last available value obtained up to the date and time of randomization.

The baseline value for safety variables will be the last available value prior to the first injection of IMP (SAR341402 or NovoLog/NovoRapid). For patients randomized and not treated, the baseline value is defined as the last available value obtained up to the date and time of randomization.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

- Age (years) (calculated in the electronic case report form [e-CRF]),
- Age group (<65, ≥65 to <75, ≥75 years of age),
- Sex (Male, Female),
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, More than One Race, Unknown or Not Reported),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown /Not Reported),
- Regions (North America, Western Europe, Eastern Europe, Rest of the World [ROW]) / Countries,
- Baseline body weight (kg),
- Baseline body mass index (BMI, kg/m^2, calculated in the e-CRF),
- Baseline BMI categories (kg/m^2): <25, ≥25 to <30, ≥30 kg/m^2,
- Baseline estimated glomerular filtration rate (GFR, modification of diet in renal disease [MDRD] formula, mL/min/1.73m^2),
- Baseline estimated GFR categories (mL/min/1.73m^2): ≥90, ≥60 to <90, ≥30 to <60, <30,
- Randomization strata of geographical region (Europe, US, Japan), type of diabetes (T1DM, T2DM), screening HbA1c categories (<8%, ≥8%), and prior use of NovoLog/NovoRapid (Yes, No).

Medical and surgical history

Medical and surgical history at baseline will be coded to a "lower level term (LLT)", "preferred term (PT)", "high level term (HLT)", "high level group term (HLGT)", and associated primary "system organ class (SOC)" using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Medical history allergic and subject family history of allergy will also be recorded.

Disease characteristics at baseline

- Fasting C-peptides (nmol/L),
- Fasting C-peptides (<0.023 nmol/L, ≥0.023 to <0.42 nmol/L, ≥0.42 nmol/L),
- Type of diabetes (T1DM, T2DM),
- Duration of diabetes (years),
- Duration of diabetes (<10, ≥10 years),
- Age (years) at onset of diabetes,
- Duration of basal insulin treatment (years),
- Duration of mealtime insulin treatment in patient life (years),
- Previous basal insulin treatment:
  - Type (insulin glargine, insulin detemir),
  - Duration (years),
- Previous mealtime insulin treatment within 6 months prior to screening:
  - Type (NovoLog/NovoRapid, Humalog/Liprolog, Both NovoLog/NovoRapid and Humalog/Liprolog),
  - Duration (years),
- Diabetic complications at baseline:
  - Diabetic retinopathy (Yes, No, Unknown), including type (proliferative/non-proliferative),
  - Diabetic neuropathy (Yes, No, Unknown),
  - Diabetic nephropathy (Yes, No, Unknown),
- Family history of diabetes (Yes, No),
- History of gestational diabetes for female (Yes, No).

Any technical details related to computation, dates, and imputation for missing data are described in Section 2.5.

Baseline efficacy data

All 7-point SMPG profiles will be reported by patient in e-diary, transferred to the dedicated 7-point SMPG page in the e-CRF and reviewed by the investigator in dedicated items, or directly completed in another dedicated 7-point SMPG page in the e-CRF by the investigator. For the analyses, the investigator items will be used when available.

The following baseline efficacy data will be provided:

- HbA1c (% and mmol/mol),
- FPG (mmol/L and mg/dL),
- SMPG (mmol/L and mg/dL) from 7-point profiles measured on a 24-hour period (mean 24-hour plasma glucose concentration, postprandial plasma glucose excursions, and value at each time-point as defined in Section 2.1.3.2).

Insulin dose at baseline

All insulin doses will be reported by patient in e-diary, transferred to the dedicated mealtime insulin and basal insulin pages in the e-CRF and reviewed by the investigator in dedicated items, or directly completed in another dedicated mealtime insulin and basal insulin pages in the e-CRF by the investigator. For the analyses, the investigator items will be used when available.

The following baseline insulin doses will be provided:

- Basal insulin daily dose at baseline (U and U/kg) = median of basal insulin daily doses during the 7 days before the day of first IMP,
- Mealtime insulin daily dose at baseline (U and U/kg) = median of mealtime insulin daily doses during the 7 days before the day of first IMP,
- Total insulin daily dose at baseline (U and U/kg) = median of total insulin daily doses during the 7 days before the day of first IMP.

Any technical details related to the calculation of doses and the imputation for missing data are described in Section 2.5.3.

Smoking/alcohol habits

- Tobacco habits (never, current, former), including the average number of cigarettes per day.
- Alcohol habits (never, occasional, at least monthly, at least weekly, at least daily) including the number of daily standard drink (1 or 2, >2).

2.1.2 Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version in effect at the sponsor at the time of database lock.

- Prior medications are those the patient used within 3 months before screening and from screening to first IMP intake (not included). Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are defined as follows:
  - Concomitant medications during the main 6-month treatment period are any treatments received by the patient concomitantly to the IMP during the main 6-month period, from first injection of IMP (included) to Week 26 (Visit 9) or to the last injection of IMP + 1 day (+ 0 day for anti-diabetic medications) (included), whichever comes earlier.
  - Concomitant medications during the 12-month treatment period are any treatments received by the patient concomitantly to the IMP, from first injection of IMP (included) to the last injection of IMP + 1 day (+ 0 day for anti-diabetic medications) (included).
- A given medication can be classified both as a prior medication and as a concomitant medication.
- Post-treatment medications are those the patient took in the period running from the last injection of IMP + 2 days (+ 1 day for anti-diabetic medications) (included) to the end of the study.

Anti-diabetic medications will be identified by a list of anatomical therapeutic chemical (ATC) codes (see Appendix A).

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

HbA1c and FPG are measured in a blinded fashion at a central laboratory, for scheduled (see study flowchart in Appendix A) and unscheduled assessments.

In case of premature permanent IMP discontinuation, the process described in Section 2.5.3 will be applied to retrieve efficacy assessments performed at the end of treatment visit (Visit 8000).

Efficacy observation period

- The main 6-month randomized period for efficacy variables is defined as the time from randomization up to Week 26 (Visit 9), regardless of study treatment discontinuation.
- The 12-month randomized period for efficacy variables is defined as the time from randomization date up to Week 52 (Visit 12), regardless of study treatment discontinuation.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy variable is the change in HbA1c from baseline to Week 26 which is defined as: HbA1c value at Week 26 - HbA1c value at baseline (%). The primary efficacy variable will be derived in the intent-to-treat (ITT) population, using all HbA1c values regardless of adherence to treatment (ITT estimand). Results for the primary efficacy variable will also be presented in mmol/mol.

2.1.3.2 Secondary efficacy endpoint(s)

All secondary efficacy endpoints are calculated on the randomized periods using the ITT population.

- Change in HbA1c (%) from baseline to Week 52.

At Week 26 and Week 52:

- The percentage of patients with HbA1c <7% (HbA1c responders; Yes/No variable),
- Change from baseline in FPG (in mmol/L and mg/dL),
- Change from baseline in the mean 24-hour plasma glucose concentration, based on the 7-point SMPG profiles (in mmol/L and mg/dL),
- Change from baseline in postprandial plasma glucose excursions (difference between 2-hour postprandial and pre-prandial plasma glucose values at breakfast, lunch and dinner), based on the 7-point SMPG profiles (in mmol/L and mg/dL),
- Change from baseline in 7-point SMPG profiles per time-point (in mmol/L and mg/dL) (fasting pre-breakfast, 2 hours post-breakfast, pre-lunch, 2 hours post-lunch, pre-dinner, 2 hours post-dinner, bedtime).

The process of computation of SMPG variables is described in Section 2.5.

2.1.4 Safety endpoints

The following safety parameters will be analyzed for the main 6-month and 12-month on-treatment periods:

- Hypoglycemia (according to ADA Workgroup on Hypoglycemia) (3),
- Adverse events (AEs), serious adverse events (SAEs),
- Laboratory data,
- Injection site reactions, hypersensitivity reactions,
- Vital signs: heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP),
- Body weight.

In case of premature permanent IMP discontinuation, the process described in Section 2.5.3 will be applied to retrieve safety assessments performed at the end of treatment visit (Visit 8000).

Safety observation period

The observation period of safety data will be divided into 3 main segments:

- The pre-treatment period is defined as the time from informed consent up to the time of the first injection of IMP.
- The 12-month on-treatment period is defined as the time from the first injection of IMP up to 1 day after the last injection of IMP.
  - The main 6-month on-treatment period is defined as the time from first injection of IMP up to Week 26 (Visit 9) or up to 1 day after the last injection of IMP, whichever comes earlier.
- The post-treatment period is defined as the time starting 1 day after last injection of IMP (after the on-treatment period).

The on-study observation period is defined as the time from first injection of IMP until the end of the study (defined as the date of end of participation).

2.1.4.1 Hypoglycemia

All hypoglycemia will be reported by patient in e-diary, transferred to the dedicated hypoglycemia event page in the e-CRF and reviewed by the investigator in specific items, or directly completed in another dedicated hypoglycemia event page in the e-CRF by the investigator. For the analyses, the investigator items will be used when available.

All hypoglycemia will be categorized according to the ADA definitions (3) as described below:

- **Severe hypoglycemia:** Severe hypoglycemia will be derived as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- **Documented symptomatic hypoglycemia:** Documented symptomatic hypoglycemia will be derived as an event with symptoms of hypoglycemia and with a measured plasma glucose concentration less than or equal to 3.9 mmol/L (70 mg/dL).
- **Asymptomatic hypoglycemia:** Asymptomatic hypoglycemia will be derived as an event without symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 3.9 mmol/L (70 mg/dL).
- **Probable symptomatic hypoglycemia:** Probable symptomatic hypoglycemia will be derived as an event with symptoms of hypoglycemia and missing plasma glucose concentration.
- **Relative hypoglycemia:** Relative hypoglycemia (recently termed “pseudo-hypoglycemia”) will be derived as an event with symptoms of hypoglycemia but with a measured plasma glucose concentration greater than 3.9 mmol/L (70 mg/dL).

Any technical details to categorize hypoglycemia in case of missing hypoglycemia information are described in Section 2.5.3.

Hypoglycemia will be evaluated regardless the time of onset during the day.

In addition to the threshold of plasma glucose of less than or equal to 3.9 mmol/L (70 mg/dL), documented symptomatic hypoglycemia and asymptomatic hypoglycemia with a measured plasma glucose concentration less than 3.0 mmol/L (54 mg/dL) will also be analyzed.

Hypoglycemia observation period

- Pre-treatment hypoglycemia are events that occurred during the pre-treatment period.
- Treatment-emergent hypoglycemia are events that occurred during the on-treatment period (see Section 2.1.4).
- Post-treatment hypoglycemia are events that occurred during the post-treatment period.

2.1.4.2 Adverse events variables

All AEs and SAEs will be coded to a LLT, PT, HLT, HLGT and associated primary SOC using the version of MedDRA currently in effect at the sponsor at the time of database lock.

Adverse event observation period

The occurrence of AEs and SAEs is recorded from the time of signed informed consent until the end of the study.

- Pretreatment AEs are AEs that developed or worsened or became serious from the signed informed consent date up to first administration of IMP.
- Treatment-emergent adverse events (TEAEs) are AEs that developed or worsened or became serious during the on-treatment period.
- Posttreatment AEs are AEs that developed or worsened or became serious during the posttreatment period.

Injection site reactions and hypersensitivity reactions

If the investigator or the patient recognizes any sign related to local non-allergic reaction at the injection site, the event should be recorded in the routine AE page in the e-CRF.

Potential hypersensitivity reactions (allergic reactions or allergic-like reactions) will be entered on the AE form and the allergic reaction complementary form should be completed. An Allergic Reaction Assessment Committee (ARAC) will review all possible allergic reactions, independently from the sponsor and in a blinded way regarding the study treatment. The ARAC will review the reported cases, confirm whether or not the event is allergic in nature, and provide a diagnosis for confirmed allergic events, based on the information reported by the investigator.

For the statistical analysis, injection site and hypersensitivity reactions will be identified based on the AE forms (also based on ARAC diagnosis in order not to miss any event), using the following MedDRA codes:

- Injection site reactions will be identified using the following MedDRA searches: under HLGT "Administration site reactions" and HLTs "Administration site reactions NEC", "Injection site reactions", "Infusion site reactions" and "Application and instillation site reactions" and excluding HLTs "Implant and catheter site reactions" and "Vaccination site reactions".
- Hypersensitivity reactions will be identified using the following MedDRA searches: Angioedema standardized MedDRA query (SMQ) [Narrow], Severe cutaneous adverse reactions SMQ [Broad], Hypersensitivity SMQ [Broad and Narrow] and excluding PTs related to administration, application, injection and infusion sites. HLT "Anaphylactic Responses" are included in those SMQs.

Adverse events of special interest

Adverse events of special interest include:

- Alanine aminotransferases (ALT) increase (identified based on the ALT Increase - Associated Signs and Symptoms forms),
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/non-investigational medicinal product (NIMP),
- Symptomatic overdose with IMP/NIMP (identified based on the Overdose forms).

2.1.4.3 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period,
- Death on-treatment: deaths occurring during the on-treatment period,
- Death post-study: deaths occurring after the end of the study.

2.1.4.4 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology and clinical chemistry. Clinical laboratory values after conversion will be analyzed into international units and international units will be used in all listings and tables. Results will also be presented in conventional US units.

The following parameters will be analyzed, grouped by biological function (see study flowchart in Appendix A):

- **Hematology:**
  - Red blood cells and platelets including hemoglobin, hematocrit, red blood cells count and platelets,
  - White blood cells including white blood cell count and differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils).
- **Clinical chemistry:**
  - Serum lipids including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (in fasting condition),
  - Electrolytes including sodium, potassium,
  - Renal function including creatinine and estimated GFR (MDRD),
  - Liver function including ALT, aspartate aminotransferases (AST), alkaline phosphatase (ALP) and total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin).

Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

Vital signs include heart rate (bpm), and systolic and diastolic blood pressure (mmHg) in sitting position (see study flowchart in Appendix A).

Body weight (kg) will be presented with vital signs.

2.1.4.6 Electrocardiogram variables

Not applicable.

2.1.4.7 Immunogenicity variables

If a patient discontinues the treatment prematurely, the process described in Section 2.5.3 will be applied to retrieve immunogenicity assessments performed at the end of treatment visit (Visit 8000).

AIA assessments will be determined in a blinded fashion at a central laboratory (see study flowchart in Appendix A) using a validated anti-insulin antibody binding assay methodology. Only samples collected at least 8 hours after the last administration of mealtime insulin will be taken into account in the analysis.

Anti-insulin antibodies evaluation will consist of:

- Anti-SAR341402/ NovoLog/NovoRapid antibody positive/negative status
- Anti-SAR341402/ NovoLog/NovoRapid antibody titer
- Cross-reactivity to human insulin positive/negative status

The following definitions will be used to identify patients with a change in AIA response during the on-treatment period (see Section 2.1.4 [4]):

- Patients with treatment-induced AIAs will be defined as patients with AIAs that developed de novo (seroconversion) following the IMP administration (ie, patients with at least one positive AIA sample at any time during the on-treatment period, in those patients without pre-existing AIA or with missing sample at baseline).
- Patients with treatment-boosted AIAs will be defined as patients AIA positive at baseline that were boosted to a significant higher titer following the IMP administration (ie, patients with at least one AIA sample with at least a 4-fold increase in titers compared to baseline value at any time during the on-treatment period, in those patients with preexisting AIA). The 4-fold increase in titer corresponds to an increase of two dilution steps within the titration experiment. A single dilution difference (2-fold titer increase) is within the expected imprecision of the titration method and is therefore not considered a relevant change.

Patients with treatment-emergent AIA (Yes, No, Inconclusive) will be derived as follows:

- Patients with treatment-emergent AIAs (AIA incidence) will be defined as patients with treatment-induced or treatment-boosted AIAs.
- Patients without treatment-emergent AIAs will be defined as patients without treatment induced or treatment-boosted AIAs.
- Inconclusive patients will be defined as patients who cannot irrefutably be classified as patients without treatment-emergent AIAs. Inconclusive patients will not be included in the above categories and will be listed separately.

Treatment-emergent AIAs at last on-treatment value (Yes, No, Inconclusive) will be defined using the same definitions based on results obtained at the last on-treatment visit (ie, taking into account the closest value prior to the last dose of IMP).

The peak titer will be defined as the maximal titer observed during the on-treatment period. For patients with treatment-induced and treatment-boosted AIAs, the kinetics of AIA response will be further classified as follows:

- Transient AIA response, defined as a response detected only at one sampling time point during the on-treatment period (excluding the last sampling time point); or response detected at two or more sampling time points during the on-treatment period, where the first and last AIA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the patient's last sampling time point is AIA-negative.

- Persistent AIA response, defined as a response detected at two or more sampling time points during the on-treatment period, where the first and last AIA-positive on-treatment sample (irrespective of any negative samples in between) are separated by at least 16 weeks.
- Indeterminate AIA response, defined as a response where only the last sampling time point is positive or the last 2 sampling time points are positive but separated by a period less than 16 weeks.

2.1.5 Pharmacokinetic variables

Not applicable.

2.1.6 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.7 Quality-of-life endpoints

Not applicable.

2.1.8 Health economic endpoints

Not applicable.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as all patients who have originally met inclusion criteria and have signed the informed consent.

Randomized patients consist of all screened patients with a treatment arm allocated and recorded in the interactive response technology (IRT) database, regardless of whether the treatment was used or not.

For patient study status, the total number of patients in each of the following categories will be presented for the main 6-month period and 12-month study period separately, using a flow-chart diagram or summary tables:

- Screened patients: all patients who have originally met inclusion criteria and have signed the informed consent.
- Screen failure patients and reasons for screen failure.
- Randomized patients: all screened patients with a treatment arm allocated and recorded in the IRT database, regardless of whether the treatment was used or not.

- Safety population (as defined in Section 2.3.2, presented as treated).
- Treated but not randomized patients.
- Randomized but not treated patients.
- The ITT population (as defined in Section 2.3.1.1), analyzed as randomized.
- The per protocol population (Section 2.3.1.2), analyzed as randomized.
- The randomization strata (geographical region [Europe, US, Japan], type of diabetes [T1DM, T2DM], screening HbA1c categories [<8%, ≥8%], prior use of NovoLog/NovoRapid [Yes, No]) assigned by IRT will be summarized. The discrepancy between the strata assigned by IRT and the information reported on e-CRF will be listed for all randomized patients.
- Disposition for the main 6-month period:
  - Patients who completed the main 6-month treatment period (patients who have performed Visit 9 [Week 26] and who did not permanently discontinue treatment before Visit 9 [Week 26]),
  - Patients who permanently discontinued the IMP during the main 6-month treatment period, and the reasons for permanent treatment discontinuation,
  - Patient's decision for treatment discontinuation during the main 6-month period,
  - Patients who completed the main 6-month study period (patients who have performed Visit 9 [Week 26]),
  - Patients who prematurely discontinued the study during the main 6-month period, and the reasons for premature study discontinuation,
  - Status at last study contact of patients who prematurely discontinued the study during the main 6-month period.
- Disposition for the 12-month period:
  - Patients who completed the 12-month treatment period including 6-month extension (patients who have performed Visit 12 [Week 52] and who did not permanently discontinue treatment before Visit 12 [Week 52]),
  - Patients who permanently discontinued the IMP during the 12-month treatment period, and the reasons for permanent treatment discontinuation,
  - Patient's decision for treatment discontinuation during the 12-month period,
  - Patients who completed the 12-month study period (patients who have performed Visit 12 [Week 52]),
  - Patients who prematurely discontinued the study during the 12-month period, and the reasons for premature study discontinuation,
  - Status at last study contact.

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as the denominator divided for different treatment group.

Patients with the following deviations will be identified and described in separate listings:

- Treated but not randomized.
- Randomized but not treated.
- Randomized but not treated as randomized.

Kaplan-Meier (KM) plots/estimates of the cumulative incidence of IMP discontinuation due to any reason, or due to AE, will be provided for the main 6-month and for the 12-month on-treatment period separately. Time to treatment discontinuation will be defined as the number of days from the first dose of IMP until the day of treatment discontinuation. All completers will be considered as censored observations. The censoring time will be the number of days from the first dose of IMP until the last dosing date.

A list of patients prematurely discontinued from the treatment, along with reasons for discontinuation, will be provided.

Patients treated without being randomized will not be considered as randomized and will not be included in any population. Their safety data will be listed separately

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

All critical or major protocol deviations (including randomization and drug-dispensing irregularities, see Section 2.2.1) will be summarized by treatment group among randomized patients (number and percentages).

Additionally, the analysis populations for safety and efficacy will be summarized in a table by patient counts on the randomized population:

- Efficacy population: ITT population, Per-Protocol population,
- Safety population,
- Anti-insulin antibody population.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

The major or critical randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

- Kit dispensation without IRT transaction
- Erroneous kit dispensation
- Randomization by error
- Patient randomized twice
- Stratification error

2.3 ANALYSIS POPULATIONS

Patients who are dispensed study drug without calling the IRT or before calling the IRT are considered nonrandomized patients. They are excluded from any population for analysis, including safety. However, if these patients experienced any significant safety event, they should be documented separately in the clinical study report.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population as defined in the protocol.

2.3.1.1 Intent–to-treat population

The primary efficacy population will be the ITT population, which includes all randomized patients, irrespective of compliance with the study protocol and procedures.

Patients will be analyzed for efficacy analyses in the treatment group to which they are randomized.

2.3.1.2 Per-protocol population

The Per-Protocol population is a subset of the ITT population, which includes all randomized and exposed patients, who do not permanently discontinue IMP allocated by randomization or do not switch from treatment group during the main 6-month period, who perform week 26 and who do not present major or critical protocol deviations that could impact the analysis during the main 6-month period. The major and critical protocol deviations excluding from the per protocol population are defined as:

- Missing baseline HbA1c value.
- No Visit 9 (Week 26) HbA1c value.
- Use of any insulin other than IMP or non-IMP for 10 days or more during the main 6-month treatment period.
- T1DM patients:
  - Use of any non-insulin glucose lowering agents during the main 6-month treatment period.
- T2DM patients:
  - Use of any non-insulin glucose lowering agents (except continuation of pre-study oral antidiabetic treatments at a stable dose) during the main 6-month treatment period.
  - Use of sulfonylureas and glinides during the main 6-month treatment period.
- Use of systemic glucocorticoids greater than replacement dose for more than 10 days during the main 6-month treatment period.
- Initiation of weight loss drugs during the main 6-month treatment period.
- Wrong randomization stratum of type of diabetes (T1DM, T2DM).
- Patients who met any of the following exclusion criteria:
  - E02: HbA1c <7% or >10% at screening.
  - E08: At screening visit, body mass index (BMI) ≥35 kg/m2 in patients with T1DM and ≥40 kg/m2 in patients with T2DM.

- E18: Use of investigational drugs or prohibited therapy for this study within 3 months or 5 half-lives, whichever is longer, prior to the screening visit.
- E19: limited to the following conditions:
  - status post pancreatectomy
  - status post pancreas and/or islet cell transplantation

- Serious GCP misconduct.

2.3.2 Safety population

The safety population is defined as all randomized patients who receive at least one dose of IMP, analyzed according to the treatment actually received.

In addition:

- If a patient is dispensed IMP and is lost to follow-up without any documented evidence whether or not the patient took IMP, the patient will be considered exposed and included in the safety population.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- Non-randomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- For patients receiving more than one study treatment during the trial, the patient will be analyzed in the treatment group in which he/she has mostly taken.

2.3.3 Anti-insulin antibody population

The AIA population is defined as all patients from the safety population with at least one AIA sample available for analysis (sample collected at least 8 hours after the last administration of mealtime insulin) during the on-treatment period, analyzed according to the treatment actually received.

2.4 STATISTICAL METHODS

Continuous data will be summarized by treatment group using the number of observations available (N), mean, SD, minimum, median, and maximum.

Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from baseline) by scheduled post-baseline visits will be provided on observed cases, ie, including only patients having non-missing assessments at a specific visit. All statistical analyses

(descriptive statistics, plots, and statistical models) will be performed on visits defined using the time windows provided in Section 2.5.4.

Statistical analyses will be performed on the overall study population regardless the type of diabetes, and pooling data from the patients treated with NovoLog and NovoRapid in the comparator group. For descriptive purpose, subgroup analyses may be conducted by type of diabetes (T1DM, T2DM) and by type of comparator used (NovoLog [in US], NovoRapid [in EU and Japan]), as described in the sections below.

2.4.1 Demographics and baseline characteristics

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized.

Parameters described in Section 2.1.1 will be summarized by treatment group and in overall treatment groups using descriptive statistics.

Medical/surgical history will be summarized by primary SOC and HLT in each treatment group and overall. Events will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on incidence in the overall treatment group.

No statistical test for the between-group difference will be performed.

Demographics and baseline characteristics will also be presented according to the type of comparator (NovoLog, NovoRapid) and for T1DM patients.

2.4.2 Prior or concomitant medications

The prior, concomitant and post-treatment medications will be presented on the randomized population, separately for anti-diabetic medications and non-anti-diabetic medications. Anti-diabetic medications will be identified by a pre-defined list of ATC codes (see Appendix A).

Medications will be summarized by treatment group and overall (only for prior medications) according to the WHO-DD dictionary. Non-anti-diabetic medications will be summarized considering the first digit of the ATC class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication. Anti-diabetic medications will be presented by pharmacological class (ATC3), chemical class (ATC4), and standardized medication name.

The tables for prior medications will be sorted by decreasing frequency within the ATC categories presented based on the overall incidence across treatment groups. In case of equal frequency, alphabetical order will be used.

The tables for concomitant and post-treatment medications will be sorted by decreasing frequency within the ATC categories presented based on the incidence in the SAR341402 group. In case of equal frequency, alphabetical order will be used.

Frequency statistics including number of patients and percentage will be provided. No statistical test for the between-group difference will be performed.

The prohibited medications will be presented by prohibited medication category (as defined in protocol deviations) and standardized medication name. The following prohibited medication categories will be presented:

- Use of any insulin other than IMP or non-IMP for 10 days or more during the treatment period.
- T1DM patients:
  - Use of any non-insulin glucose lowering agents during the treatment period.
- T2DM patients:
  - Use of any non-insulin glucose lowering agents (except continuation of oral antidiabetic treatments at a stable dose) during the treatment period
  - Use of sulfonylureas during the treatment period
- Use of systemic glucocorticoids greater than replacement dose for more than 10 days during the treatment period.
- Insulin pump therapy.
- Initiation of body weight loss drugs during the treatment period.
- Any other investigational product (ie, participation in another clinical trial).

Concomitant and prohibited medications will be presented for the main 6-month and for the 12-month period separately, and for T1DM patients.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of the open-label IMP exposure and daily insulin doses (basal, mealtime, total).

The exposure will be presented overall then by subgroups defined by the randomization strata of geographical region (Europe, US, Japan), type of diabetes (T1DM, T2DM) and type of comparator (NovoLog, NovoRapid).

Observation period

The observation period for exposure data will be defined as follows:

- The main 6-month on-treatment period is defined as the time from first injection of IMP up to Week 26 (Visit 9) or up to the day of last injection of IMP, whichever comes earlier.
- The 12-month on-treatment period is defined as the time from the first injection of IMP up to the day of last injection of IMP.

The exposure parameters will be provided separately for the main 6-month on-treatment period and for the 12-month on-treatment period.

Duration of exposure

The duration of exposure will be the total number of days of administration of the open-label IMP, ignoring temporary drug discontinuation (see Section 2.5.3 for calculation in case of missing or incomplete data).

The duration of exposure to the open-label IMP will be defined as:

(Date of the last IMP administration – date of the first IMP administration) + 1

The process described in Section 2.5.3 will be applied to define the date of the last IMP administration for the main 6-month on-treatment period and 12-month on-treatment period. If this date is missing, the IMP exposure duration should be left as missing.

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). The number (n) and proportion (%) of patients exposed to the open-label IMP will be presented by specific time periods for each treatment group in the safety population.

The time periods of interest for the main 6-month on-treatment period are grouped as follows:

- Up to 4 weeks,
- >4 to 8 weeks,
- >8 to 12 weeks,
- >12 to 20 weeks,
- >20 to 25 weeks,
- >25 to 26 weeks,
- >26 weeks.

The time periods of interest for the 12-month on-treatment period are grouped as follows:

- Up to 4 weeks,
- >4 to 8 weeks,
- >8 to 12 weeks,
- >12 to 20 weeks,
- >20 to 26 weeks,
- >26 to 34 weeks,
- >34 to 40 weeks,
- >40 to 51 weeks,
- >51 to 52 weeks,
- >52 weeks.

The cumulative duration of exposure for the main 6-month on-treatment period will be described using the following time periods:

- ≥ 1 day,
- > 4 weeks,
- > 8 weeks,
- > 12 weeks,
- > 20 weeks,
- > 25 weeks,
- > 26 weeks.

The cumulative duration of exposure for the 12-month on-treatment period will be described using the following time periods:

- ≥ 1 day,
- > 4 weeks,
- > 8 weeks,
- > 12 weeks,
- > 20 weeks,
- > 26 weeks,
- > 34 weeks,
- > 40 weeks,
- > 51 weeks,
- > 52 weeks.

Daily insulin doses

The process described in Section 2.5.4 will be applied to assign visits to the insulin doses transferred from the e-diary webportal into the clinical database, and to retrieve doses in case of premature treatment discontinuation.

At baseline, the daily basal, mealtime, and total (basal plus mealtime) insulin doses (U and U/kg body weight) will be calculated as defined in Section 2.1.1. At Visit 3, daily insulin doses (basal, mealtime, and total) will be calculated as the median of daily insulin doses available in the week after the day of first IMP. At further visits, the daily insulin doses (basal, mealtime, and total) will be calculated as the median of daily insulin doses available in the week before the visit. Technical details related to the computation and handling of missing data are described in Section 2.5.

The daily insulin doses (basal, mealtime, total) will be described at baseline, during the week after the date of the first IMP administration, then at each visit, and the changes from baseline will be presented.

2.4.3.2 Compliance

Not applicable.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

2.4.4.1.1 Primary efficacy analysis

First step analysis:

The statistical test for non-inferiority assessment of SAR341402 versus NovoLog/NovoRapid on the primary efficacy endpoint (change in HbA1c from baseline to Week 26 as defined in the Section 2.1.3.1) will be one-sided, with alpha level of 0.025 and using a non-inferiority margin of 0.3% HbA1c.

The primary endpoint will be analyzed in the ITT population using all post-baseline data available during the main 6-month randomized period (ITT estimand).

The analysis for change in HbA1c should account for missing data in a fashion consistent with what the measurement would have been, had it been measured. The behavior of missing data for those patients who are off-treatment may not be the same as that of observed data for those patients who are on-treatment in the same treatment arm. Therefore, it may not be appropriate to represent the missing data from patients who do not adhere to therapy by the data from those patients on the same arm who adhere to therapy.

As a consequence, a multiple imputation approach will be used where missing data from patients who do not adhere to IMP will be represented by the data from those patients in the same treatment group who also do not adhere to IMP but have the measurement for the primary endpoint. Imputations will be performed with the MI procedure in SAS (Statistical Analysis System). Details of the proposed multiple imputation analysis in two parallel parts (according the status of the patients), are provided below:

Part1: Imputation for missing data in patients who prematurely discontinued IMP during the main 6-month randomized period:

Missing data in patients who prematurely discontinued IMP during the main 6-month randomized period will be imputed using a model estimated solely from data observed in other patients who discontinued IMP during the main 6-month randomized period but have the measurement for the primary endpoint at Week 26. Due to the anticipated small number of these latter patients, a basic imputation model will be built, including only the randomized treatment group as predictor. Missing data will be imputed using the regression method.

Part2: Imputation for missing data in patients who completed the main 6-month treatment period:

Missing data in patients who completed the main 6-month treatment period will be imputed separately, using a model estimated solely from data observed in other patients who completed the main 6-month treatment period and have the measurement for the primary endpoint at Week 26. Since in general, the missing pattern will not be monotone, a two-step approach will be used:

- Step 1: the Markov Chain Monte Carlo (MCMC) method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern. The imputation model will include the continuous fixed covariates of the baseline HbA1c value as well as the changes from baseline in HbA1c at Week 12 and Week 26.
- Step 2: using the monotone data set from step 1, missing data will be imputed using the regression method. The imputation model will include the fixed categorical effects of the treatment group, the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM) and prior use of NovoLog/NovoRapid (Yes, No), as well as the continuous fixed covariates of the baseline HbA1c value and the changes from baseline in HbA1c at Week 12 and Week 26.

Missing values will be imputed 10,000 times. Completed datasets from the two parts detailed above will be combined into a single dataset. Each completed dataset will be 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), the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM) and prior use of NovoLog/NovoRapid (Yes, No), as well as the continuous fixed covariate of baseline value. Results from the 10,000 analyses will be combined using Rubin's formula (MIANALYZE procedure in SAS).

The adjusted least squares (LS) mean of the change in HbA1c from baseline to Week 26 for each treatment group (SAR341402, NovoLog/NovoRapid) will be estimated, as well as the between-group LS mean difference of SAR341402 versus NovoLog/NovoRapid, with the corresponding standard errors and 2-sided 95% CIs. These values will be calculated using the observed proportions of patients in the randomization strata and the observed baseline mean HbA1c in the ITT population.

Non-inferiority will be demonstrated if the upper bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid on the ITT population is <0.3%.

Second step analysis:

If non-inferiority of SAR341402 over NovoLog/NovoRapid is demonstrated, using a hierarchical step-down testing procedure, the following additional analysis will be performed (not as primary objective): the inverse non-inferiority (of NovoLog/NovoRapid over SAR341402) will be 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 will be demonstrated if the lower bound is >-0.3%.

If SAR341402 is shown to be non-inferior to NovoLog/NovoRapid and NovoLog/NovoRapid non-inferior to SAR341402, similar efficacy (equivalence) of SAR341402 and NovoLog/NovoRapid will be assumed.

2.4.4.1.2 Sensitivity analysis

Sensitivity analyses will be conducted to assess the robustness of primary efficacy analysis with regard to missing data (5).

Description of missing data

The following analyses will be performed on the ITT population to explore the missing data frequency and pattern:

- As described in Section 2.2, KM plots/estimates of the cumulative incidence of IMP discontinuation will be provided by treatment group for the main 6-month period, with hazard ratio and 95% CI estimated using Cox regression model.
- Availability of HbA1c at each visit will be provided by treatment group according to the status of the patient (discontinued treatment or not).
- The number and disposition of patients with missing data will be described according to the availability for the primary efficacy analysis (Consolidated Standards of Reporting Trials [CONSORT] diagram according to missing data pattern).

- In order to explore missing data patterns for HbA1c, number and percentage of patients in each of the following categories will be presented by treatment group and patient status at Week 26 (Patient without permanent treatment discontinuation, patient with permanent treatment discontinuation):
  - Pattern 1: patients without baseline if any,
  - Pattern 2: patients with baseline but without post-baseline value during the main 6-month randomized period,
  - Pattern 3: patients with baseline and at least one post-baseline value during the main 6-month randomized period but not at Week 26,
  - Pattern 4: patients with baseline and Week 26 value during the main 6-month randomized period.
- Baseline characteristics and HbA1c values by visit will be presented by missing data pattern for each treatment group, using descriptive statistics and/or graphs.

Return to baseline analysis

To assess the robustness of primary efficacy analysis with regard to the imputation of missing data, a sensitivity analysis will be performed using a multiple imputation method that models a "return-to-baseline" for patients having missing data at Week 26.

For each patient in the SAR341402 and NovoLog/NovoRapid group in the ITT population, the missing HbA1c values at Week 26 will be imputed as equal to the patient's baseline plus an error. The error will be normally distributed with mean zero and standard deviation set equal to the estimated pooled standard deviation. No negative value will be allowed (in this case, another value will be redrawn).

Missing HbA1c values will be imputed 10,000 times to generate 10,000 datasets with complete HbA1c values at Week 26. In each dataset, the change in HbA1c from baseline to Week 26 will be derived from observed and imputed HbA1c values at Week 26. Each completed dataset will be analyzed using an ANCOVA of change from baseline to Week 26 in HbA1c (%), including the fixed categorical effects of treatment group (SAR341402, NovoLog/NovoRapid), the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM) and prior use of NovoLog/NovoRapid (Yes, No), as well as the continuous fixed covariate of baseline value. Results from the 10,000 analyses will be combined using Rubin's formula (MIANALYZE procedure in SAS).

The adjusted LS mean of the change in HbA1c from baseline to Week 26 for each treatment group (SAR341402, NovoLog/NovoRapid) will be estimated, as well as the between-group LS mean difference of SAR341402 versus NovoLog/NovoRapid, with the corresponding standard errors and 2-sided 95% CIs. These values will be calculated using the observed proportions of patients in the randomization strata and the observed baseline mean HbA1c in the ITT population.

Tipping point analysis

In order to assess the impact of missing data, a tipping-point analysis based on the pattern mixture model approach will be performed in the ITT population as described below.

The considered pattern mixture model will introduce a sensitivity parameter, δ, corresponding to the difference in mean change from baseline in HbA1c between patients with missing data and patients with observed data. Estimations will be performed using the multiple imputation approach "return-to-baseline" as described above. δ will be added to the imputed values in the SAR341402 group whereas the imputed values in the NovoLog/NovoRapid group will not change (δ = 0 corresponding to the missing at random [MAR] assumption). For each value δ will correspond an estimated LS mean in HbA1c per group and an estimated treatment effect.

To investigate how the conclusions depend on the adopted values of δ, the testing will be repeated over a range of plausible values for δ, the treatment effect being penalized by a positive value and favored by a negative value. A specific illustration on the value of the minimum penalty leading to a non-rejection of the null hypothesis (upper limit of the 95% CI of treatment effect greater than 0.3%) will be provided (6).

2.4.4.1.3 Supportive analysis

In the case the per-protocol population will represent less than 95% of the ITT population, a supportive analysis will be conducted on the per-protocol population to evaluate the robustness of the conclusion of the primary efficacy analysis when excluding the patients that may increase the chance of reaching non inferiority conclusion.

Data in the per-protocol population will be analyzed using an ANCOVA of the change in HbA1c from baseline to Week 26, including the fixed categorical effects of treatment group (SAR341402, NovoLog/NovoRapid), the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM) and prior use of NovoLog/NovoRapid (Yes, No), as well as the continuous fixed covariate of baseline value.

The adjusted LS mean of the change in HbA1c from baseline to Week 26 for each treatment group (SAR341402, NovoLog/NovoRapid) will be estimated, as well as the between-group LS mean difference of SAR341402 versus NovoLog/NovoRapid, with the corresponding standard errors and 2-sided 95% CIs. These values will be calculated using the observed proportions of patients in the randomization strata and the observed baseline mean HbA1c in the PP population.

2.4.4.1.4 Subgroup analyses

The primary efficacy endpoint will be further analyzed to examine whether the treatment effect varies in subgroups defined by the following baseline covariates:

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, More than One Race, Unknown or Not Reported),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown /Not Reported),

- Age group (<65, ≥65 to <75, ≥75 years of age),
- Sex (male, female),
- Baseline BMI (<30, ≥30 kg/m²),
- Baseline estimated GFR categories (<60, ≥60 mL/min/1.73m²),
- Randomization stratum of type of diabetes (T1DM, T2DM),
- Randomization stratum of screening HbA1c (<8.0%, ≥8.0%),
- Randomization stratum of prior use of NovoLog/NovoRapid (Yes, No),
- Type of comparator (NovoLog, NovoRapid),
- Regions (North America, Western Europe, Eastern Europe, ROW),
- Duration of diabetes (<10, ≥10 years).

The treatment effect across the subgroups defined above will be estimated for the primary efficacy variable (change in HbA1c from baseline to Week 26) in the ITT population and separately for the T1DM patients, using all post baseline HbA1c data available during the main 6-month randomized period. The same multiple imputation approach as described for primary analysis will be applied, using the 10,000 completed datasets generated for the primary analysis. Each completed dataset will be analyzed using an ANCOVA of change from baseline to Week 26 in HbA1c, including the fixed categorical effects of treatment group (SAR341402, NovoLog/NovoRapid), the randomization stratum of prior use of NovoLog/NovoRapid (Yes, No), the corresponding subgroup factor and subgroup factor-by-treatment interaction, and the continuous fixed covariate of baseline value. The randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM) will not be included in the model. Results from the 10,000 analyses will be combined using Rubin's formula (MIANALYZE procedure in SAS).

When the subgroup considered is the randomization stratum of screening HbA1c (<8.0, ≥8.0%), the baseline HbA1c value will be removed from the model.

When the subgroup considered is the randomization stratum of prior use of NovoLog/NovoRapid (Yes, No), the randomization stratum of prior use of NovoLog/NovoRapid (Yes, No) will be included only once in the model (as subgroup factor).

The adjusted LS mean of the change in HbA1c from baseline to Week 26 for each treatment group (SAR341402, NovoLog/NovoRapid) within each subgroup will be estimated, as well as the between-group LS mean difference of SAR341402 versus NovoLog/NovoRapid, with the corresponding standard errors and 2-sided 95% CIs. The significance level of the treatment-by-subgroup factor interaction will be provided for descriptive purpose. Forest plots will be provided.

Further subgroup analyses may be performed if deemed necessary for interpretation of results.

2.4.4.1.5 Additional analyses

The James-Stein (J-S) shrinkage estimator will be used to evaluate the treatment effect in each subgroup defined by type of comparator (NovoLog, NovoRapid), with a different approach (7). This estimate will be derived from the overall and subgroup treatment effect estimates in order to use all study information (including information collected in the other subgroup).

Subgroup treatment effect estimates will correspond to regular sample estimates in each subgroup obtained using a similar ANCOVA model of the primary efficacy analysis in the ITT population (see Section 2.4.4.1.1) applied to the data in each specific subgroup. For the NovoLog subgroup (US-approved comparator), the fixed categorical effect of the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM) will be replaced by the randomization strata of type of diabetes (T1DM, T2DM), and for the NovoRapid subgroup (EU-approved comparator), the fixed categorical effect of the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM) will be replaced by the randomization strata of geographical region (Europe, Japan). The overall treatment effect estimate will be obtained as a combination of the two subgroup treatment effect estimates weighted with the inverses of the variances observed in the two models.

Results (including treatment effect estimates and their 95% confidence intervals) will be presented by type of comparator and illustrated using forest plots.

Details on the estimator derivation are provided in Section 2.5.2.

2.4.4.2 Analyses of secondary efficacy endpoints

Secondary efficacy endpoints defined in Section 2.1.3.2 will be analyzed in the ITT population and separately for the T1DM patients, using all post-baseline data available during the main 6-month randomized period (for analyses at Week 26) or the 12-month randomized period (for analyses at Week 52).

2.4.4.2.1 Continuous endpoints

All continuous secondary efficacy endpoints (except for 7-point SMPG profiles per time-point) will be analyzed using a similar multiple imputation approach in two parts, as for the primary efficacy endpoint, followed by a similar ANCOVA model (as described in Section 2.4.4.1.1).

- At Week 26:
  - Missing data in patients who prematurely discontinued IMP during the main 6-month randomized period will be imputed using a model including only the treatment group as predictor (Part 1),

- Missing data in patients who completed the main 6-month treatment period will be imputed in step 1 using a model including the continuous fixed covariates of the baseline value and the change from baseline at Week 12 and Week 26, in step 2 using a model including the fixed categorical effects of the treatment group, the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8%, ≥8%) (except when analyzing the change in HbA1c) and prior use of NovoLog/NovoRapid (Yes, No), as well as the continuous fixed covariates of the baseline value and the changes from baseline at Week 12 and Week 26 (Part 2).

- At Week 52 :
  - Missing data in patients who prematurely discontinued IMP during the 12-month randomized period will be imputed using a model including only the treatment group as predictor (Part 1),
  - Missing data in patients who completed the 12-month treatment period will be imputed in step 1 using a model including the continuous fixed covariates of the baseline value as well as the changes from baseline at Week 12, Week 26, Week 40 (except for SMPG endpoints) and Week 52, in step 2 using a model including the fixed categorical effects of the treatment group, the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8%, ≥8%) (except when analyzing the change in HbA1c) and prior use of NovoLog/NovoRapid (Yes, No), as well as the continuous fixed covariates of the baseline value and the changes from baseline at Week 12, Week 26, Week 40 (except for SMPG endpoints) and Week 52 (Part 2).

For 7-point SMPG profiles per time-point, only descriptive statistics and graphs will be provided.

2.4.4.2.2 Categorical endpoints

The categorical secondary endpoint HbA1c responders (HbA1c <7%) will be analyzed using a logistic regression model with fixed-effect term for treatment, randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8%, ≥8%), and prior use of NovoLog/NovoRapid (Yes, No). If the logistic model does not converge (e.g., due to sparse data), randomization strata may be removed from the model. Patients without assessment at Week 26 (or Week 52 for the analysis at Week 52) will be considered as failure. Odds-ratios and 95% CI will be presented.

2.4.4.3 Multiplicity issues

In order to handle the multiple comparisons of the non-inferiority of SAR341402 over NovoLog/NovoRapid and then the inverse non-inferiority of NovoLog/NovoRapid over SAR341402, corresponding respectively to the primary efficacy analysis and a secondary step analysis of the primary efficacy variable, the type-I error will be controlled by the use of the sequential inferential approach. Only if non-inferiority is demonstrated, inverse non-inferiority on the mean change from baseline to Week 26 in HbA1c will be assessed. The tests for the primary endpoint (Week 26) will be performed one-sided at level $\alpha = 0.025$.

The secondary efficacy variables at Week 26 and Week 52 will be analyzed for exploratory purpose only.

2.4.4.4 Additional efficacy analysis(es)

No additional efficacy analyses are planned.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group on treated population.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately.
- The baseline value is defined as the last available value prior to the first injection of IMP. When the time of assessment is not available, the value is considered as baseline if assessment date is the date of 1st IMP intake.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests, and vital signs (PCSA criteria are provided in the ADaM metadata and in Appendix C).
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the on-treatment period by treatment group on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the last on-treatment value. The last on treatment value is defined as the value collected at the same day/time of the last dose of IMP. If this value is missing, this on-treatment value is the closest one prior to the last dose intake.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

2.4.5.1 Analyses of Hypoglycemia

All analyses of hypoglycemia will be performed on the safety population and for the T1DM patients (except for analyses monthly, by time of the day and by subgroup), separately on events occurring during the main 6-month on-treatment period and during the 12-month on-treatment period (as defined in Section 2.1.4).

Incidence of patients with at least one hypoglycemia

- Incidence of patients with at least one hypoglycemia will be presented by treatment group for any hypoglycemia and for each hypoglycemia category (as described in Section 2.1.4.1).
- For any hypoglycemia, severe and documented symptomatic hypoglycemia category, incidence of patients with at least one hypoglycemia will be compared for SAR341402 versus NovoLog/NovoRapid using a logistic regression method. The model will include fixed-effect terms for treatment group, the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8%, ≥8%), and prior use of NovoLog/NovoRapid (Yes, No). If the logistic model does not converge (e.g., due to sparse data), randomization strata may be adapted or removed from the model. Odds-ratios and 95% CIs will be displayed using forest plots.
- Incidence of patients with at least one severe hypoglycemia will be summarized by symptom.
- The number of severe hypoglycemia and the number of documented symptomatic hypoglycemia <3.0 mmol/L (54 mg/dL) per patient will be summarized by treatment group.
- For any hypoglycemia, severe and documented symptomatic hypoglycemia category, incidence of patients with at least one hypoglycemia will be summarized by time of the day. Histograms will be provided.
- For any hypoglycemia, severe and documented symptomatic hypoglycemia category, incidence of patients with at least one hypoglycemia will be presented by subgroup and compared between SAR341402 and NovoLog/NovoRapid using a similar logistic regression model as described above, with added fixed-effect terms for the subgroup and the subgroup-by-treatment interaction. When the subgroup considered will be equal (or close) to one of the randomization strata, this randomization stratum will be removed from the model. Odds-ratios and 95% CIs will be presented across subgroups using forest plots. The significance level of the subgroup-by-treatment interaction will be also provided for descriptive purpose. The following subgroups will be displayed:
  - Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, More than One Race, Unknown or Not Reported),
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown /Not Reported),
  - Age group (<65, ≥65 to <75, ≥75 years of age),
  - Sex (male, female),

- Baseline BMI (<30, ≥30 kg/m²),
- Baseline estimated GFR categories (<60, ≥60 mL/min/1.73m²),
- Randomization stratum of type of diabetes (T1DM, T2DM),
- Randomization stratum of screening HbA1c (<8%, ≥8%),
- Randomization stratum of prior use of NovoLog/NovoRapid (Yes, No),
- Type of comparator (NovoLog, NovoRapid),
- Regions (North America, Western Europe, Eastern Europe, ROW),
- Duration of diabetes (<10, ≥10 years).

The analyses of hypoglycemia by type of comparator (NovoLog, NovoRapid) will also be performed on the T1DM patients.

Further subgroup analyses may be performed if deemed necessary for interpretation of results.

Number and rate of hypoglycemia per patient-year

- Number and rate of hypoglycemia per patient-year (computed as 365.25 x [total number of episodes of hypoglycemia] / [total number of days exposed]) will be summarized by treatment group for any hypoglycemia and for each hypoglycemia category (as described in Section 2.1.4.1). Non classified hypoglycemia will be displayed.
- For any hypoglycemia, severe and documented symptomatic hypoglycemia category, incidence of patients with at least one hypoglycemia will be summarized over time using Nelson-Aalen estimates. Figures will be provided.
- For any hypoglycemia, severe and documented symptomatic hypoglycemia category, number and rate of hypoglycemia per patient-year will be presented by time of the day. Histograms will be provided.
- For any hypoglycemia, severe and documented symptomatic hypoglycemia category, number and rate of hypoglycemia per patient-year will be compared for SAR341402 versus NovoLog/NovoRapid using an overdispersed Poisson regression model with a log-link function, and the logarithm of the treatment-emergent period as offset (using PROC GENMOD). The dispersion parameter will be estimated by Pearson's chi-square statistic divided by its degrees of freedom (option SCALE=PEARSON). The model will include fixed-effect terms for treatment group and randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8%, ≥8%), and prior use of NovoLog/NovoRapid (Yes, No). If a model does not converge (eg, due to sparse data), the randomization strata may be adapted or removed from the model. Rate ratios and 95% CIs will be displayed using forest plots.

- For any hypoglycemia, severe and documented symptomatic hypoglycemia category, the number and rate of hypoglycemia per patient-year will be presented by subgroup type of comparator (NovoLog, NovoRapid) and compared between SAR341402 and NovoLog/NovoRapid using a similar overdispersed Poisson regression model as described above. If a model does not converge (eg, due to sparse data), the randomization strata may be adapted or removed from the model. Rate ratios and 95% CIs will be displayed using forest plots.

2.4.5.2 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment and posttreatment adverse events will be described separately. Analyses will be presented separately for the main 6-month and the 12-month on-treatment periods.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent, and posttreatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the SAR341402 treatment arm.

Analyses of all TEAE(s) will be generated for the safety population and for the T1DM patients (except for analyses by subgroup).

Analysis of all TEAE(s)

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE,
  - serious TEAE,
  - TEAE leading to death,
  - TEAE leading to permanent treatment discontinuation.

- All TEAEs by primary SOC, showing number (%) of patients with at least one TEAE, sorted by internationally agreed order of primary SOC.
- All TEAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one TEAE sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT.
- All TEAEs by primary SOC and PT, showing number (%) of patients with at least one TEAE, sorted by SOC internationally agreed order and decreasing incidence of PTs within SOC. This sorting order will be applied to all other tables, unless otherwise specified.
- Number (%) of patients experiencing common TEAE(s) (HLT incidence ≥2% in any treatment group) presented by primary SOC, HLT, and PT, sorted by SOC internationally agreed order. The other levels (HLT, PT) will be presented in an alphabetic order. Analysis performed overall and by subgroup. The following subgroups will be displayed:
  - Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, More than One Race, Unknown or Not Reported),
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown /Not Reported),
  - Age group (<65, ≥65 to <75, ≥75 years of age),
  - Sex (male, female),
  - Baseline BMI (<30, ≥30 kg/m²),
  - Baseline estimated GFR categories (<60, ≥60 mL/min/1.73m²),
  - Randomization stratum of type of diabetes (T1DM, T2DM),
  - Randomization stratum of screening HbA1c (<8%, ≥8%),
  - Randomization stratum of prior use of NovoLog/NovoRapid (Yes, No),
  - Type of comparator (NovoLog, NovoRapid),
  - Regions (North America, Western Europe, Eastern Europe, ROW),
  - Duration of diabetes (<10, ≥10 years).
- All TEAEs regardless of relationship and related to IMP by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one TEAE, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.
- All TEAEs by maximal severity, presented by primary SOC and PT, showing number (%) of patients with at least one TEAE by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above.

- Number (%) of patients experiencing TEAE(s) presented by Primary and Secondary SOC, HLGT, HLT, and PT, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.

Analysis of all treatment-emergent SAE(s)

- All treatment-emergent SAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one serious TEAE, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.
- All treatment-emergent SAEs regardless of relationship and related to IMP by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one treatment-emergent SAE, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.

Analysis of all TEAE(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

Analysis of TEAE(s) related to injection site reactions and hypersensitivity reactions

- All TEAEs related to injection site reactions, hypersensitivity reactions, or events confirmed as allergic reactions by ARAC, by PT, showing number (%) of patients sorted by decreasing incidence of PT in the SAR341402 group.
- All TEAEs related to injection site reactions, hypersensitivity reactions, or events confirmed as allergic reactions by ARAC, regardless of relationship and related to IMP, by PT, showing number (%) of patients sorted by decreasing incidence of PT in the SAR341402 group.
- A summary and/or listing of all events adjudicated by ARAC will be provided with the result of the adjudication.

Analysis of adverse events of special interest

- A listing of patients with symptomatic overdose with IMP/NIMP will be provided.

Analysis of pretreatment and posttreatment adverse events

- A listing of all pre-treatment and post-treatment AEs will be provided.

2.4.5.3 Deaths

The following deaths summaries will be generated on the safety population, during the main 6-month on-treatment period and for the 12-month on-treatment period separately:

- Number (%) of patients who died by study period (on-study, on-treatment, post-study) and reasons for death;

- All TEAEs leading to death (death as an outcome on the adverse event e-CRF page as reported by the investigator), by primary SOC, HLGT, HLT, and PT, showing number (%) of patients sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order;
- A listing of all deaths.

2.4.5.4 Analyses of laboratory variables

The summary statistics (including number, mean, median, standard deviation, minimum, and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time-point, last on-treatment value during the main 6-month and 12-month on-treatment periods) by treatment group. This section will be organized by biological function as specified in Section 2.1.4.4.

The incidence of PCSAs (list provided in Appendix C) at any time during the main 6-month on-treatment period and during the 12-month on-treatment period will be summarized by biological function and treatment group whatever the baseline level and according to the following baseline status categories:

- Normal/missing,
- Abnormal according to PCSA criterion or criteria.

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

Drug-induced liver injury

The liver function tests, namely AST, ALT, ALP, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter.

A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x upper limit of normal (ULN) for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Listing of possible Hy's law cases will be identified and provided by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin >2 x ULN) with ALT, AST, ALP, total bilirubin, and the following complementary parameters (if available): conjugated bilirubin and prothrombin time / international normalized ratio (INR), CPK, serum creatinine, complete blood count.

The incidence of liver-related TEAEs will be summarized by treatment group. The selection of PTs will be based on the "Hepatic disorder" SMQ.

2.4.5.5 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum, and maximum) of all vital signs variables (raw values and changes from baseline) described in Section 2.1.4.5 including body weight, will be calculated for each visit or study assessment (baseline, each post-baseline time-point, last on-treatment during the main 6-month and 12-month on-treatment periods) by treatment group.

The incidence of PCSAs at any time during the main 6-month on-treatment period and during the 12-month on-treatment period will be separately summarized by treatment group whatever the baseline level.

2.4.5.6 Analyses of electrocardiogram variables

Not applicable.

2.4.5.7 Analyses of anti-insulin antibody data

The analyses of immunogenicity data will be descriptive (no formal statistical testing) and based on the AIA population. Separate analyses will be performed for the T1DM and T2DM patients. Analyses will be presented separately for the main 6-month and the 12-month on-treatment periods.

For T1DM patients, all analyses of immunogenicity will be produced except for analyses by subgroups defined by baseline and screening factors. Analyses by type of comparator (NovoLog, NovoRapid) will be produced.

For T2DM patients, the following analyses will be produced:

- Summary of AIA response,
- Summary of AIAs by visit,
- Summary of AIA response by prior NovoLog/NovoRapid (Yes, No),
- Summary of change in HbA1c (%) from baseline to Week 26 by treatment-emergent AIA,
- Summary of change in insulin dose (mealtime, basal, total daily) from baseline to Week 26 by treatment-emergent AIA,
- Scatterplot analyses to assess the relationship between immunogenicity endpoints and efficacy/safety assessments,
- Boxplots of maximal AIA titer.

Anti-insulin antibody response

The number and percentage of patients will be 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 (AIA incidence),
- Patients without treatment-emergent AIA,
- Patients with pre-existing AIAs or treatment-induced AIAs (AIA prevalence).

For exploratory purposes, the difference between SAR341402 and NovoLog/NovoRapid in the percentage of patients with treatment-emergent AIAs (AIA incidence) will be provided with associated 2-sided 90% CI. Patients with inconclusive results will not be part of the analysis. Results will be obtained by fitting a binomial regression model with an identity-link function. The model will include fixed categorical effects for treatment, the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8%, ≥8%), and prior use of NovoLog/NovoRapid (Yes, No). The risks within each treatment group and risk difference will be provided with their 90% CIs using the adjusted LS mean estimates of the treatment effect.

For patients with treatment-induced and treatment-boosted AIAs, the kinetics of AIA response (transient, persistent, or indeterminate AIA response as defined in Section 2.1.4.7) will be further summarized using number and percentage of patients, and the peak titer will be described using median, Q1 and Q3.

Incidence of patients with treatment emergent AIA will be compared, for SAR341402 versus NovoLog/NovoRapid using a logistic regression method. The model will include fixed-effect terms for treatment group, the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8%, ≥8%), and prior use of NovoLog/NovoRapid (Yes, No). If the logistic model does not converge (e.g., due to sparse data), randomization strata may be removed from the model. Odds-ratios and 95% CIs will be displayed using forest plots.

The number and percentage of patients with treatment-induced, treatment-boosted and treatment-emergent AIAs will also be presented by visit in each treatment group using tables and/or graphs.

Boxplots of the peak AIA titer will be presented by treatment group and according to the treatment-emergent AIA status (Yes, No). These graphs will be used to identify AIA ‘outliers’, defined as peak AIA titers higher than the boxplot upper whiskers (ie, higher than 1.5 times the interquartile range above the third quartile).

Anti-insulin antibody data by visit

The number and percentage of patients with anti-SAR341402/NovoLog/NovoRapid antibody positive and antibody negative samples will be summarized by treatment group at each visit and at the last on-treatment value. The number and percentage of patients with anti-SAR341402/NovoLog/NovoRapid antibody positive sample will be displayed graphically by visit.

On the group of patients with anti-SAR341402/NovoLog/NovoRapid antibody positive sample at a given visit, anti-SAR341402/NovoLog/NovoRapid antibody titers will be summarized (using descriptive statistics by number (N), median, Q1, Q3, variation coefficient, minimum, maximum, geometric mean, SD, and 95% CI), and the number and percentage of patients with cross-reactivity to human insulin will be provided.

Boxplots of AIA titers will be presented at each visit.

The above by-visit summaries will be performed on the overall AIA population and separately for patients with treatment-induced, treatment-boosted and treatment-emergent AIAs.

Subgroup analyses

Exploratory analyses will be performed by subgroups defined by baseline and screening factors.

The following subgroups will be displayed:

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, More than One Race, Unknown or Not Reported),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown /Not Reported),
- Age group (<65, ≥65 to <75, ≥75 years of age),
- Sex (male, female),
- Baseline BMI (<30, ≥30 kg/m²),
- Baseline estimated GFR categories (<60, ≥60 mL/min/1.73m²),
- Randomization stratum of type of diabetes (T1DM, T2DM),
- Randomization stratum of screening HbA1c (<8%, ≥8%),
- Randomization stratum of prior use of NovoLog/NovoRapid (Yes, No),
- Type of comparator (NovoLog, NovoRapid),
- Regions (North America, Western Europe, Eastern Europe, ROW),
- Duration of diabetes (<10, ≥10 years),
- Anti-SAR341402/NovoLog/NovoRapid antibody status at baseline (Positive, Negative).

Further subgroup analyses may be performed if deemed necessary for interpretation of results.

Relationship between immunogenicity endpoints and efficacy/safety assessments

Subgroup analyses and scatterplots will be conducted to assess the relationship between immunogenicity endpoints and efficacy/safety assessments.

The following efficacy/safety assessments will be summarized by treatment-emergent AIA (Yes, No) and treatment-emergent AIA at last on-treatment value (Yes, No):

- Primary efficacy endpoint (change in HbA1c from baseline to Week 26) (for the main 6-month analyses) and change in HbA1c from baseline to Week 52 (for the 12-month analyses): same statistical model as described in Section 2.4.4.1.4 for subgroup analyses will be performed.
- Hypoglycemia (any, severe, documented symptomatic): the proportion of patients with at least one event will be compared between treatment groups using the same statistical model as described in Section 2.4.5.1 for hypoglycemia subgroup analyses. The number of severe hypoglycemia and the number of documented symptomatic hypoglycemia <3.0 mmol/L (54 mg/dL) per patient will also be displayed for each treatment group.
- Common TEAEs: descriptive statistics by primary SOC, HLT, and PT, showing number (%) of patients sorted by SOC internationally agreed order. The other levels (HLT, PT) will be presented in an alphabetic order.
- Serious TEAEs: descriptive statistics by primary SOC, HLGT, HLT, and PT, showing number (%) of patients sorted by SOC internationally agreed order. The other levels (HLGT, HLT and PT) will be presented in an alphabetic order.
- Injection site and hypersensitivity reactions: descriptive statistics by PT, showing number (%) of patients sorted by decreasing incidence of PT in the SAR341402 group.
- Change in daily insulin doses (basal, mealtime, total) as defined in Section 2.4.3.1.

In order to assess the impact of pre-existing antibodies that may cross-react with SAR341402, the above parameters will also be summarized by AIA status at baseline (Positive, Negative).

The relationship between the AIA titer and the efficacy and safety assessments will be explored using scatter-plots of the peak AIA titer versus the parameters below for patients from the AIA population with titer available:

- Primary efficacy endpoint (change in HbA1c from baseline to Week 26) (for the main 6-month analyses) and change in HbA1c from baseline to Week 52 (for the 12-month analyses)
- Change in total insulin dose (U/kg) from baseline to Week 26 (for the main 6-month analyses) and to Week 52 (for the 12-month analyses)
- Rate per year of treatment-emergent hypoglycemia during the on-treatment period (severe hypoglycemia, documented symptomatic < 3.0 mol/L [54 mg/dL])
- Presence/absence of treatment-emergent hypersensitivity reactions during the on-treatment period

- Presence/absence of treatment-emergent injections site reactions during the on-treatment period

The scatterplots will also be presented separately for patients with treatment-emergent AIAs.

Listings of baseline characteristics, insulin doses, HbA1c, hypoglycemia, hypersensitivity reactions, and injection site reactions will be provided for patients with treatment-emergent AIAs and high AIA titers (AIA 'outliers' as defined above).

Additionally, descriptive statistics by categories of HbA1c change from baseline to Week 26 (for the main 6-month analyses) or Week 52 (for the 12-month analyses) (<-1%, ≥-1 to ≤1%, >1%) will be performed on the number (%) of patients with or without treatment-emergent AIA and associated peak titer, and on insulin doses (basal, mealtime, total). Listings of anti-insulin antibody, insulin doses, and HbA1c data will be provided for patients with treatment-emergent AIAs and HbA1c change from baseline > 1% at Week 26 (for the 6-month analyses) or Week 52 (for the 12-month analyses).

2.5 DATA HANDLING CONVENTIONS

This section describes general rules for data handling conventions, especially for patients with missing data.

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Reference day

The reference day for the calculation of extent of exposure, time to onset and relative days is the day of the first administration of open-label IMP, denoted as Day 1.

Disease characteristics formulas

Duration of diabetes (years) = (Date of informed consent – date of diagnosis of diabetes +1)/365.25.

Age at onset of diabetes (years) = (Date [DD-MM-YYYY] of diagnosis of diabetes – date [DD-MM-YYYY] of birth +1) /365.25. In case of unavailable date of birth, only the year of the date of diabetes diagnosis and the year of the date of birth (retrieve using the age recorded at screening) will be considered in the age at onset calculation.

Duration of previous mealtime insulin treatment (years) = Duration of mealtime insulin treatment in patient life (years) = (Date of informed consent – Date of first intake of mealtime Anti-hyperglycemic therapy in patient life +1)/365.25.

Duration of basal insulin treatment (years) = (Date of informed consent – Date of first intake of Basal Anti-hyperglycemic therapy +1)/365.25

HbA1c conversion

IFCC in mmol/mol = (10.93× NGSP in %) - 23.5

Renal function formulas

Creatinine clearance (CLcr) value will be derived using the equation of Cockroft and Gault, using weight assessed at the same visit:

- For Male:

$$\text{CLcr (mL/min)} = [(140 - \text{age(years)}) \times \text{weight(kg)}] \Big/ [0.814 \times \text{serum creatinine } (\mu\text{mol/L})]$$

- For Female: result above multiplied by 0.85.

GFR will be derived using MDRD formula:

$$\text{GFR (mL/min/1.73m2)} = \left[\begin{array}{l} 175\text{x Serum Creatinine (mg/dL)}^{-1.154} \text{ x Age}^{-0.203} \text{ x 1.212 (if black)} \\ \text{x 0.742 (if female)} \end{array}\right]$$

2.5.2 Data handling conventions for efficacy variables

James-Stein shrinkage derivation for subgroup by type of comparator (7)

Overall treatment effect estimator:

$$\hat{\delta}_0 = \frac{\hat{\delta}_1 / \hat{\sigma}_1^2 + \hat{\delta}_2 / \hat{\sigma}_2^2}{1/\hat{\sigma}_1^2 + 1/\hat{\sigma}_2^2} \text{ where}$$

$\hat{\delta}_i$ is the sample difference estimator between both treatment arm obtained in subgroup i.

$\hat{\sigma}_i^2$ is the variance estimator for subgroup i.

James-Stein shrinkage estimator for subgroup i:

$$\breve{\delta}_i = \hat{c}\hat{\delta}_i + (1-\hat{c})\hat{\delta}_0 \text{ where}$$

$$c = \frac{(\delta_1 - \delta_2)^2 / (\sigma_1^2 + \sigma_2^2)}{2 + (\delta_1 - \delta_2)^2 / (\sigma_1^2 + \sigma_2^2)} \text{ assuming a common } c \text{ for all subgroups } (c_1 = c_2),$$

and by replacing δ_i with $\hat{\delta}_i$ and σ_i^2 with $\hat{\sigma}_i^2$ in the calculation of c.

For any specific c : $\text{var}(\breve{\delta}_1) = \frac{1/\sigma_1^2 + 2c/\sigma_2^2 + (1-c)^2/\sigma_2^2 + c^2\sigma_1^2/\sigma_2^4}{(1/\sigma_1^2 + 1/\sigma_2^2)^2}$

and by replacing σ_i^2 with $\hat{\sigma}_i^2$ in the calculation of the variance.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Derived variables are considered missing if the original variables required to calculate them are missing unless otherwise specified. For example, if either a baseline assessment or an endpoint assessment is missing for a particular patient, then the change from baseline at endpoint is missing. Depending upon the assessment, analyses may not include all patients in the analysis population, because certain patients in the intended population may have missing data.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, if the date of last IMP administration is missing, the exposure duration should be left as missing.

For the main 6-month on-treatment period, the date of the last IMP administration will be defined as: date of last administration reported on the end-of-treatment e-CRF page or date of Week 26 visit, whichever comes earlier. If the date of Week 26 visit is missing, the date of the last IMP administration will be defined as date of last administration reported on the end-of-treatment e-CRF page or date of randomization visit + 185 days, whichever comes earlier.

For the 12-month on-treatment period, the date of the last IMP administration will be defined as the date of last administration reported on the end-of-treatment e-CRF page.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and posttreatment medication.

Handling of adverse events/hypoglycemia with missing or partial date/time of onset

Missing or partial adverse event / hypoglycemia onset dates and times will be imputed so that if the partial event onset date/time information does not indicate that the event started prior to treatment or after the on-treatment period, the event will be classified as treatment-emergent. No imputation of event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of event resolution.

Handling of adverse events/hypoglycemia when date and time of first IMP administration is missing

When the date and time of the first IMP administration is missing, all adverse events / hypoglycemia that occurred on or after the day of randomization should be considered as treatment-emergent. The exposure duration should be kept as missing.

Handling of hypoglycemia classification when some classification items are missing

Rule for handling missing data in classification items for hypoglycemia will be provided in ADaM metadata.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category “normal/missing at baseline.”

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

Handling of missing data in the calculation of HbA1c responders

For HbA1c responders (defined by HbA1c<7%), patients without any available assessment at endpoint (Week 26 for the main 6-month period, and Week 52 for the 12-month period) will be treated as failures (non-responders) in the analysis.

Handling of missing data in the calculation of 7-point SMPG variables

For a given 7-point SMPG profile, at least 5 available measurements will be required to take the profile into account in the statistical analyses (including descriptive analyses at each time-point).

For each profile with at least 5 available measurements, the mean 24-hour plasma glucose concentration and the postprandial plasma glucose excursions will be calculated.

At a given visit, the mean 24-hour plasma glucose concentration analyzed will be the average of the mean 24-hour plasma glucose concentrations (as previously calculated) available in the week before the visit. No minimum number of available mean 24-hour plasma glucose concentrations will be required. The same will apply to the postprandial plasma glucose excursions and to the values at each time-point.

Handling of missing data in the calculation of insulin doses

The daily mealtime insulin dose will be calculated as the sum of the mealtime insulin doses collected on the same day. At least 3 available mealtime insulin doses and no more than 1 snack will be required to calculate the daily mealtime insulin dose.

The daily total insulin dose will be calculated as the sum of the daily basal and daily mealtime insulin doses. If one of the daily insulin doses is missing (basal or mealtime), the daily total insulin dose will not be calculated.

At baseline, daily insulin doses (basal, mealtime, and total) will be calculated as the median of the daily insulin doses (as previously calculated) available in the 7 days before the day of first IMP. At Visit 3, daily insulin doses (basal, mealtime, and total) will be calculated as the median of the daily insulin doses (as previously calculated) available in the 7 days after the day of first IMP. At further visits, the daily insulin doses (basal, mealtime, and total) will be calculated as the median of the daily insulin doses (as previously calculated) available in the 7 days before the visit. No minimum number of available doses will be required. For insulin doses in U/kg, if the body weight measurement is missing at a given visit, the last available measurement from previous visit will be used.

2.5.4 Windows for time points

The following process will be applied for visit re-allocation. Re-allocated visits will be used in all statistical analyses (descriptive statistics, plots, and statistical models).

No re-allocation will be performed for nominal visits already provided in the clinical database (Visit 1 to Visit 13), and for unscheduled assessments.

SMPG profiles and insulin doses

In the clinical database, SMPG profiles and insulin doses transferred from the e-diary will not be assigned to a protocol visit. For the analysis, they will be assigned to the next on-site visit actually performed by the patient after the date of data collection (Visit 3 to Visit 12, or Visit 8000).

End of treatment visit

If a patient discontinues the treatment prematurely, end of treatment (Visit 8000) assessments will be re-allocated to the next scheduled on-site visit for the patient. The next scheduled on-site visit for each patient will be determined as the next on-site visit that should be performed as per protocol, following the last visit actually performed by the patient before Visit 8000.

For a given parameter, the value will not be re-allocated in the following cases:

- If the parameter is not planned to be collected at the re-allocation visit.
- If a value is already available for the parameter at the re-allocation visit.

This process will be used to retrieve all assessments (including efficacy, safety, and immunogenicity data) performed at the end of treatment visit (Visit 8000), and will apply to insulin doses assigned to Visit 8000 following the process described above.

2.5.5 Unscheduled visits

The determination of baselines for efficacy and safety parameter variables is based on all measurements from both scheduled and unscheduled visits (measurements from the central laboratory only), as mentioned in Section 2.5.4. The determination of the last on-treatment value for safety and immunogenicity parameters is also based on all assessments from both scheduled and unscheduled visits (measurements from the central laboratory only).

Measurements from the unscheduled visits (measurements from the central laboratory only) are also considered for PCSA summary of safety parameters.

Unscheduled visit measurements are not included in the by-visit summaries.

2.5.6 Pooling of centers for statistical analyses

No pooling of centers is planned for statistical analyses. Center and country will not be included in the statistical analysis. However, the randomization stratum of geographical region (Europe, US, Japan) will be included in the models.

2.5.7 Statistical technical issues

Not Applicable.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

It is planned to lock the database approximately 4 weeks after the last patient last visit (LPLV) of the 6-month comparative efficacy and safety treatment period.

It is further planned to lock the database approximately 4 weeks after the LPLV of the 6-month safety extension phase.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS Enterprise Guide version 5.1 or higher.

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A: Anti-diabetic drug ATC codes

Appendix B: Study flowchart

Appendix C: Potentially clinically significant abnormalities criteria

Appendix A Anti-diabetic drug ATC codes

The list of ATC codes for anti-diabetic drugs is based on the WHO-DD version of September 2017. It will be updated using the version currently in effect at Sanofi at the time of database lock.

ATCNUM	ATCLEVEL	ATCTYPE
A10	2	DRUGS USED IN DIABETES
A10A	3	INSULINS AND ANALOGUES
A10AB	4	INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING
A10AC	4	INSULINS AND ANALOGUES FOR INJECTION, INTERMEDIATE-ACTING
A10AD	4	INSULINS AND ANALOGUES FOR INJECTION, INTERMEDIATE- OR LONG-ACTING COMBINED WITH FAST-ACTING
A10AE	4	INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING
A10AF	4	INSULINS AND ANALOGUES FOR INHALATION
A10B	3	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS
A10BA	4	BIGUANIDES
A10BB	4	SULFONYLUREAS
A10BC	4	SULFONAMIDES (HETEROCYCLIC)
A10BD	4	COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS
A10BF	4	ALPHA GLUCOSIDASE INHIBITORS
A10BG	4	THIAZOLIDINEDIONES
A10BH	4	DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS
A10BJ	4	GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGUES
A10BK	4	SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS
A10BX	4	OTHER BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS
A10X	3	OTHER DRUGS USED IN DIABETES
A10XA	4	ALDOSE REDUCTASE INHIBITORS

Appendix B Study flowchart

Period	Screening		Treatment period (26 weeks)							Comparative Safety Extension period (26 weeks)			Post treatment/Follow-up
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13
Week:	Wk-2	Wk-1 ☎ [a]	Wk 0 (Baseline)	Wk2 ☎ [a]	Wk4	Wk8 ☎ [a]	Wk12	Wk20	Wk26 [b] (Endpoint)	Wk34 ☎ [a]	Wk40	Wk52 [b] (End of treatment)	+1 day [c] ☎ [a]
Day (window [days])	-14	-7 (±3)	1 (±3)	14 (±3)	28 (±3)	56 (±3)	84 (±3)	140 (±3)	182 (±3)	238 (±5)	280 (±5)	364 (±5)	
Informed consent	X												
Inclusion/Exclusion criteria	X		X										
Demography, medical history, diabetes history	X												
Physical examination	X								X			X	
Vital signs [d]	X		X		X		X	X	X		X	X	
Body weight, height [e]	X		X						X			X	
12-lead ECG	X												
Dispensation of study glucometer and e-diary	X												
Training (glucometer, SMPG profiles, hypoglycemia reporting e-diary)	X		X										

Period	Screening		Treatment period (26 weeks)							Comparative Safety Extension period (26 weeks)			Post treatment/Follow-up
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13
Week:	Wk-2	Wk-1 ☎ [a]	Wk 0 (Baseline)	Wk2 ☎ [a]	Wk4	Wk8 ☎ [a]	Wk12	Wk20	Wk26 [b] (Endpoint)	Wk34 ☎ [a]	Wk40	Wk52 [b] (End of treatment)	+1 day [c] ☎ [a]
Day (window [days])	-14	-7 (±3)	1 (±3)	14 (±3)	28 (±3)	56 (±3)	84 (±3)	140 (±3)	182 (±3)	238 (±5)	280 (±5)	364 (±5)	
Training or refresher instructions on glucose meter use and routine review of diet and lifestyle counseling along with instructions on dosage self-adjustment including carbohydrate intake [f]	X	X	X	X	X	X	X	X	X	X	X	X	
Dispensation of study medication[g]			X		X		X	X	X		X		
• IMP (SAR341402 or NovoLog/NovoRapid)			X		X		X	X	X		X		
• NIMP (Lantus)			X		X		X	X	X		X		
Counting / collecting used, unused and in use pens					X		X	X	X		X	X	
Compliance check (Review of diary, returned IMP)					X		X	X	X		X	X	
IRT call	X		X		X		X	X	X		X	X	X
Visit date confirmation in e-diary web portal		X	X	X	X	X	X	X	X	X	X	X	

Period	Screening		Treatment period (26 weeks)							Comparative Safety Extension period (26 weeks)			Post treatment/Follow-up
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13
Week:	Wk-2	Wk-1 ☎ [a]	Wk 0 (Baseline)	Wk2 ☎ [a]	Wk4	Wk8 ☎ [a]	Wk12	Wk20	Wk26 [b] (Endpoint)	Wk34 ☎ [a]	Wk40	Wk52 [b] (End of treatment)	+1 day [c] ☎ [a]
Day (window [days])	-14	-7 (±3)	1 (±3)	14 (±3)	28 (±3)	56 (±3)	84 (±3)	140 (±3)	182 (±3)	238 (±5)	280 (±5)	364 (±5)	
Randomization [h]			X										
Patient to come fasting to study site	X		X				X		X		X	X	
Insulin dose collected [i]			X		X		X		X		X	X	
7-point SMPG [j]			X				X		X			X	
SMPG to support insulin dose titration [k]		X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Central laboratory													
HbA1c	X		X				X		X		X	X	
Fasting plasma glucose			X				X		X		X	X	
C-peptide (fasting)			X										
Anti-insulin antibody [l]			X		X		X		X		X	X	
Safety laboratory													
Hematology [m], Clinical chemistry [n]	X								X			X	
Lipids (fasting) [o]	X								X			X	
Hepatitis serology	X												

Period	Screening		Treatment period (26 weeks)							Comparative Safety Extension period (26 weeks)			Post treatment/Follow-up
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13
Week:	Wk-2	Wk-1 ☎ *a*	Wk 0 (Baseline)	Wk2 ☎ *a*	Wk4	Wk8 ☎ *a*	Wk12	Wk20	Wk26 *b* (Endpoint)	Wk34 ☎ *a*	Wk40	Wk52 *b* (End of treatment)	+1 day *c* ☎ *a*
Day (window [days])	-14	-7 (±3)	1 (±3)	14 (±3)	28 (±3)	56 (±3)	84 (±3)	140 (±3)	182 (±3)	238 (±5)	280 (±5)	364 (±5)	
Pregnancy test (WOCBP only) *p*	X		X				X		X		X	X	
Serum FSH and estradiol (menopausal women only)	X												
AE / SAE	To be assessed and reported (if any) throughout the study (report SAE to the sponsor within 24 hours)												X
Injection site reactions	To be assessed and reported (if any) throughout the study												X
Hypersensitivity reactions	To be assessed and reported (if any) throughout the study												X
Hypoglycemia recording	To be assessed and reported (if any) throughout the study SMPG to be performed and documented in e-diary / e-CRF in case of symptoms suggesting hypoglycemia												X

ALP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate transaminase, eGFR: estimated glomerular filtration rate, FSH: follicle stimulating hormone, IMP: investigational medicinal product, IRT: interactive response technology, NIMP: noninvestigational medicinal product, SMPG: self-measured plasma glucose, Wk: week

a Mandatory telephone visit or optional clinical visit.

b Or early termination visit. When early termination, refer to the e-CRF completion guidelines.

c Or 2 to 3 days in the event this visit falls on a weekend or holiday.

d Heart rate, blood pressure (BP). At screening visit only: determination of reference arm for BP.

e Height only at Visit 1.

f Site will provide training at screening visit and baseline visit on the correct handling including regular calibration of the glucose meter provided by the Sponsor; regular refresher instructions will be provided at each on-site visit throughout the study.

g Patients are trained on the use of IMP and NIMP pens and needles by the study staff and provided with instruction leaflets during the randomization visit.

h Randomization should be performed only after all baseline evaluations have been done.

i Mealtime and basal insulin doses are to be documented in the 7 days prior to Baseline (Visit 3) and during the first 7 days after start of IMP, and on 2 days in the weeks prior to Visit 5 (Week 4), Visit 7 (Week 12), Visit 9 (Week 26), Visit 11 (Week 40) and Visit 12 (Week 52).

j 7-point SMPGs (fasting prebreakfast, 2 hours postbreakfast, pre- and 2 hours after lunch, pre- and 2 hours after dinner, and at bedtime) are requested on at least 2 days in the week before Visit 3 (Baseline), Visit 7 (Week 12), Visit 9 (Week 26 [Endpoint]), and Visit 12 (Week 52; End of treatment), measured in a single, 24-hour period; they must be recorded into the e-diary before the visit.

k SMPG for titration oversight and supporting insulin dosing and carbohydrate intake documentation are recommended daily during the first weeks of study treatment until reaching target ranges for SMPG, and thereafter on at least 3 days each week or more frequently as requested by the investigator (as specified in titration manual):

- ➔ To assist titration of the basal insulin (Lantus): fasting (prebreakfast) SMPG.
- ➔ To assist titration of SAR341402 or NovoLog/NovoRapid: either postprandial or next-meal preprandial (in the case of dinner, bedtime) SMPG will be used, depending on the preference of the investigator and patient and consistent with standard of care.

These SMPGs, supporting optimization of the basal and mealtime insulin dose are recommended to be recorded in the e-diary at least weekly; they will be uploaded in the Web Portal for review by the site or the Sponsor (titration oversight working group). See titration oversight manual. The results will be discussed between investigator and patient during on-site and scheduled or unscheduled telephone visits at the discretion of the investigator. 7-point SMPG can also be used for titration oversight.

For SMPG ≤3.0 mmol/L (≤70 mg/dL) the hypoglycemia form has to be completed.

l Eight-hour delay must be respected between the last mealtime insulin dose and antibody sampling.

m Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes, differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets.

n Clinical chemistry: sodium, potassium, creatinine, eGFR (MDRD), ALT, AST, ALP and total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin).

o Serum lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (in fasting conditions).

p For women of childbearing potential (WOCBP): Serum pregnancy test for screening; urine pregnancy test for subsequent monitoring.

Appendix C Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurements.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm	Categories are cumulative
	<50 bpm and decrease from baseline ≥20 bpm	
	<40 bpm	
	<40 bpm and decrease from baseline ≥20 bpm	
	<30 bpm	
	<30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm	
	>90 bpm and increase from baseline ≥20bpm	
	>100 bpm	
	>100 bpm and increase from baseline ≥20bpm	
	>120 bpm	
	>120 bpm and increase from baseline ≥20 bpm	
PR	>200 ms	Categories are cumulative
	>200 ms and increase from baseline ≥25%	
	> 220 ms	
	>220 ms and increase from baseline ≥25%	
	> 240 ms	
	> 240 ms and increase from baseline ≥25%	
QRS	>110 ms	Categories are cumulative
	>110 msec and increase from baseline ≥25%	
	>120 ms	
	>120 ms and increase from baseline ≥25%	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
QT	>500 ms	
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula.
	>450 ms	Absolute values categories are cumulative
	>480 ms	
	>500 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

EFC15081 16.1.9 Statistical Analysis Plan

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	01-Mar-2018 10:00 GMT+0100
[redacted]	Clinical Approval	01-Mar-2018 18:23 GMT+0100