STATISTICAL ANALYSIS PLAN

Randomized, Open label, Parallel-group Study Comparing the Pharmacokinetics and Immunogenicity of Alternating Use of SAR341402 and NovoLog® versus Continuous Use of NovoLog in Participants with Type 1 Diabetes Mellitus also Using Insulin Glargine

SAR341402-EFC15178
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AEs:	adverse events
AESI:	adverse event of special interest
AIA:	anti-insulin aspart antibodies
ALP:	alkaline phosphatase
ALT:	alanine aminotransferases
ARAC:	Allergic Reaction Assessment Committe
ATC:	anatomical therapeutic chemical
BMI:	body mass index
CMQ:	customized MedDRA queries
COVID-19:	coronavirus disease 2019
CV:	coefficient of variance
DBP:	diastolic blood pressure
EOS:	end of study
EOT:	end of treatment
GFR:	glomerular filtration rate
HbA1c:	Glycated hemoglobin
HLGT:	high level group term
HLT:	high level term
IMP:	investigational medicinal product
IRT:	Interactive response technology
ITT:	intent-to-treat
KM:	Kaplan-Meier
LLOQ:	lower limit of quantification
LPLV:	last patient last visit
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
NAb:	neutralizing antibody
NIMP:	non-investigational medicinal product
PCSA:	Potentially clinically significant abnormality
PEOT:	premature end of trial
PT:	preferred term
RBC:	red blood cell
SAEs:	serious adverse events
SBP:	systolic blood pressure
SMQ:	standardized MedDRA query
SOC:	system organ class
T1DM:	type 1 diabetes mellitus
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 /EFC15178.

1.1 STUDY DESIGN AND RANDOMIZATION

This is a randomized, open-label, active-controlled, 2-arm parallel-group multicenter Phase 3 trial comparing alternating use of SAR341402 solution for injection (100 U/mL) and NovoLog® (100 U/mL) versus continuous use of NovoLog in adults with type 1 diabetes mellitus (T1DM) also using insulin glargine (100 U/mL).

Participants with T1DM diagnosed for at least 12 months before screening, and who have been on a multiple daily injection regimen using NovoLog as mealtime insulin and insulin glargine 100 U/mL (Lantus®) as basal insulin for at least 12 weeks prior to screening, are eligible for the study. Patients who are not on NovoLog and insulin glargine (100 U/mL) for at least 12 weeks before screening are included in a run-in period of up to 12 weeks during which they are administered NovoLog and Lantus.

Patients are centrally randomized via Interactive Response Technology (IRT) (using permuted random block randomization schedule) in a 1:1 ratio to one of the following treatment groups:

- 4x4-week periods alternating use of SAR341402 and NovoLog (starting with NovoLog in the first treatment period and receiving SAR341402 during the last of the 4 treatment periods, “switching arm”) or
- 16 weeks continuous use of NovoLog (“non-switching arm”); see study design in Section 1.4.

Insulin glargine 100 U/mL (Lantus) is to be administered as mandatory background therapy throughout the treatment period of the study and during the run-in period if applicable, and is considered as non-investigational medicinal product (NIMP). NovoLog is also considered as NIMP during the run-in period, if applicable.

Approximately 184 patients were planned to be randomized at approximately 33 sites in the US.

Randomization is being stratified by glycated hemoglobin (HbA1c) (<8.0%, ≥8.0%) measurement obtained at the screening visit (Visit 1).

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate similarity in pharmacokinetics (PK) of SAR341402 and NovoLog after 4x4-week periods of alternating administration of SAR341402 and NovoLog compared to 16-week continuous use of NovoLog in participants with T1DM also using insulin glargine (100 U/mL).

1.2.2 Secondary objectives

The secondary objectives of this study are:

- To compare the effects of alternating administration of SAR341402 and NovoLog with continuous use of NovoLog on immunogenicity
- To evaluate the safety of alternating administration of SAR341402 and NovoLog versus continuous use of NovoLog
- To compare other PK parameters between the two treatment arms (alternating administration of SAR341402 and NovoLog and continuous use of NovoLog)

1.2.3 Tertiary/exploratory objectives

The tertiary/exploratory objectives of this study are:

- To compare the effects of alternating administration of SAR341402 and NovoLog with continuous use of NovoLog on insulin dose
- To compare the effects of alternating administration of SAR341402 and NovoLog with continuous use of NovoLog on glycemic control
- To compare clinical effects of treatment-emergent AIAs (anti-insulin aspart antibodies) on glycemic control, insulin dose and safety
- To compare the effects of alternating administration of SAR341402 and NovoLog with continuous use of NovoLog on additional immunogenicity parameters
- To compare clinical effects of treatment-emergent neutralizing antibodies on glycemic control and insulin dose

1.3 DETERMINATION OF SAMPLE SIZE

Approximately 184 participants are planned to be randomly assigned to either one of the following treatment groups: alternating use of SAR341402 and NovoLog or continuous use of NovoLog (in a 1:1 ratio), with a minimum of 146 evaluable participants (73 per treatment group) for the primary PK evaluation expected at the end of the study. If the number of study participants with evaluable PK data is determined to have been reached before all planned 184 participants are randomized, then the study randomization may be stopped sooner.

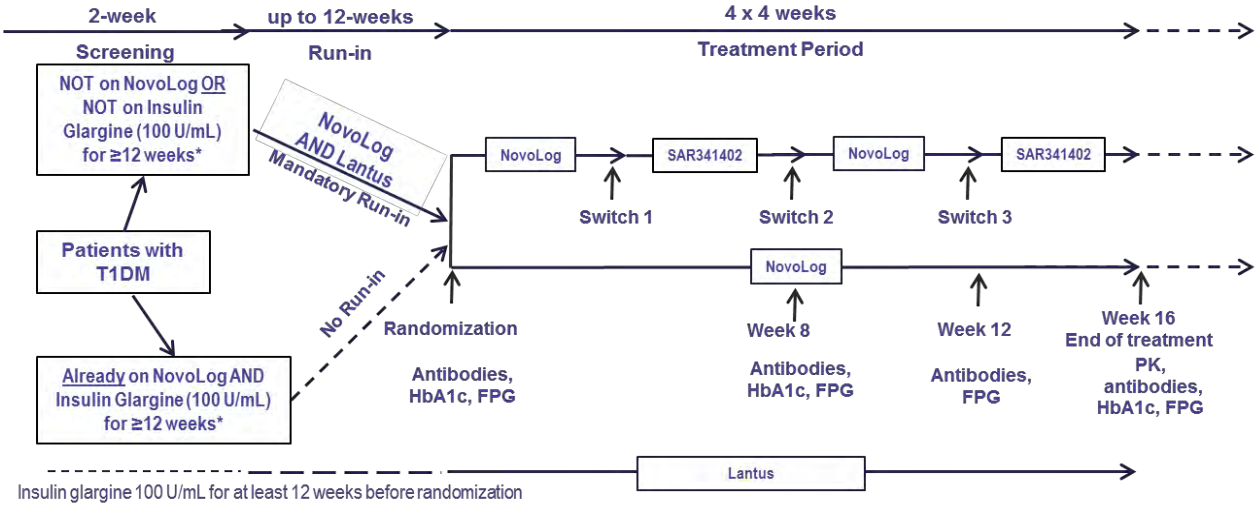
The sample size calculations were performed based on the expected variability of the primary PK endpoints AUC_{last}, AUC, and C_{max} following injection of a predefined, fixed dose of SAR341402 or NovoLog (ie, 0.15 U/kg) at Week 16.

A sample size of 146 evaluable participants (73 participants per arm) will ensure that the 90% CI for the estimated treatment ratio is within the acceptance range of [0.8 – 1.25] with at least 90% power; assuming a true ratio between 0.95 and 1.05 (switching arm / non-switching arm) and a total standard deviation on natural log scale of 0.35 or lower.

Sample size calculations were made using SAS® Software Version 9.4.

1.4 STUDY PLAN

The following figure describes the design of the study:



FPG: fasting plasma glucose; HbA1c: glycated hemoglobin A1c; PK: pharmacokinetics; T1DM: Type 1 diabetes mellitus; * prior to the screening visit

The study comprises up to 4 periods:

- An up to 14-day screening period
- An up to 12-week run-in period (only for patients not treated with NovoLog and insulin glargine (100 U/mL) for at least 12 weeks before screening)
- A 16-week open-label treatment period:
  - Participants in the non-switching arm will receive NovoLog for 16 weeks,
  - Participants in the switching arm will receive NovoLog for the first 4 weeks, then SAR341402 for 4 weeks, followed by NovoLog for 4 weeks and then SAR341402 for the last 4 weeks.
- A 1-day post-treatment follow-up period.

The study duration per participant will be less than 19 weeks (for participants who do not require the run-in period) and less than 31 weeks (for participants who require the run-in period).

At the end of the 16-week open-label treatment period, patients will have blood sampling, including for PK determination, antibody measurements, HbA1c, and FPG. After blood sampling for the trough PK measurements, patients will receive a single SC injection of 0.15 U/kg SAR341402 (switching arm) or NovoLog (non-switching arm). Subsequently, PK sampling will be conducted for 8 hours according to assessment schedule; see pharmacokinetic flow chart in Section 1.3 of the protocol.

The end of treatment (EOT) is at Visit 7 (Week 16) after randomization. The end of the study (EOS) is a follow-up contact (Visit 8, recorded as Visit 8010 in the clinical database) at the time of Week 16 plus 1 day.

In case of premature permanent investigational medicinal product (IMP) discontinuation, the patients will have a premature treatment discontinuation visit (recorded as Visit 8000 in the clinical database), which will consist of all procedures planned for Visit 7 and is intended to be conducted before the definitive discontinuation of the IMP, or as soon as possible after discontinuation.
Patients who discontinue study intervention should remain in the study, with the remaining visits occurring as scheduled where possible, including the assessments planned in the SoA (see Section 1.3 of the protocol) except serial PK samples that should only be collected at the time of early discontinuation visit and do not need to be repeated at Visit 7 (Week 16).

- During the period of the COVID-19 (Coronavirus disease 2019) pandemic, protocol deviations may occur due to lockdown restrictions. On-site visits may not be performed according to the protocol schedule for some patients. In such cases, changes in study visit schedule are allowed as needed, to accommodate patient's safe access to study sites and study medication while minimizing risks to trial integrity and data collection:Intermediary on-site visits (Visits 5 and 6) may be replaced by over-the-phone or at-home visits, if feasible.
- The end of treatment visit (Visit 7), which is the most critical one for primary endpoint assessment, may be delayed so that the visit can be conducted on-site while preserving the patient's safety.

Consequently, the open-label treatment period and study duration may be extended by up to approximately 8 weeks, and the assessments collected at "Week 16" visit may be performed up to approximately 24 weeks after randomization. All delayed assessments will be included in the analyses. No risk is foreseen by continuing treatment with IMP beyond the planned 16 weeks in both treatment arms. These changes are temporary and will not be sustained once the pandemic is over. Any delayed assessments will be recorded in the protocol deviations.

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 19-March-2019. There are no planned interim analyses.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	27-Feb 2019	Removal of the standardized meal test	Remove the 2 endpoints : Change from baseline to Week 16 in the 30-minute, 1-hour and 2 hour postprandial plasma glucose (PPG) during the standardized meal test Change from baseline to Week 16 in plasma glucose excursion (30-minute, 1-hour and 2-hour PPG minus preprandial plasma glucose) during the standardized meal test Keep the endpoint “Change from baseline to Week 16 in FPG” as an independent tertiary endpoint.
2	13-Aug-2019	Change in sample size	If the planned number of study participants with evaluable PK data can be assumed to be reached before all planned 184 participants are randomized, then the study randomization may be stopped sooner.
		Simplification of the secondary PK endpoint analysis	Remove the Hodges-Lehmann estimate with 90% CI for the shift in location between treatment groups for Tmax.
		Change of the “secondary” and “tertiary/exploratory” status for immunogenicity endpoints	Secondary immunogenicity endpoint replaced by the evaluation of the number of participants with treatment-emergent anti-Insulin aspart antibody (AIA) during the 16-week treatment period. The number of participants by anti-Insulin aspart antibody (AIA) status (positive/negative) at baseline, Week 8, Week 12 and Week 16 becomes a tertiary/exploratory immunogenicity endpoint. For descriptive purpose, the difference between the switching arm and the non-switching arm in the percentage of participants with treatment-emergent AIAs (AIA incidence) will be provided with associated 2-sided 90% CI. Results will be obtained by fitting a binomial regression model with an identity-link function. The model will include fixed categorical effects for the treatment group and randomization strata. The risks within each treatment group and risk difference will be provided with their 90% CI using the adjusted least squares mean estimates of the treatment effect.

Amendment Number	Date Approved	Rationale	Description of statistical changes
		Addition of a tertiary/ exploratory immunogenicity objective and endpoint	Add the new objective “To compare clinical effects of treatment-emergent neutralizing antibodies on glycemic control and insulin dose” and the new endpoint “Clinical effects of anti-insulin aspart neutralizing antibodies on efficacy (HbA1c) and insulin dose”
		Simplification of the description of the secondary safety endpoint related to adverse events	Remove the sentence : “All AEs will be coded to a "LLT", “PT”, "HLT", “HLGT” and primary “SOC” using the version of MedDRA currently in use by the sponsor at the time of database lock”, as these details are provided in the SAP.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan and/or protocol. Changes listed under SAP Version 2 are additional analyses not defined in the protocol and/or protocol amendments at the time of that SAP version.

Table 2 - Statistical analysis plan Statistical changes

SAP Version Number	Date Approved	Rationale	Description of Statistical Changes
2.0	7-Jul-2020	Addition of COVID-19 related analyses	Update of the disposition section to include the treatment/study discontinuations related to COVID-19. Add a table of patient disposition by visit according to COVID-19 impact. Add the definition of patients impacted by COVID-19, a table of the number of patients impacted or not by the COVID-19, along with the type of impact, and a listing of patients impacted. Add a table of major or critical protocol deviations by COVID-19 impact. Update the categories in the extent of IMP exposure table. Add an extent of IMP exposure table and IMP exposure tables by COVID-19 impact (Non-impacted, Impacted) Add table of the number (%) of patients experiencing at least one treatment-emergent COVID-19 related adverse event by primary SOC and PT Add immunogenicity, safety and efficacy subgroup

SAP Version Number	Date Approved	Rationale	Description of Statistical Changes
			analyses by COVID-19 impact (Non-impacted, Impacted).
2.0	7-Jul-2020	Addition of PK sensitivity analyses	Add PK sensitivity analyses

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value for safety variables will be the last available value prior to the first injection of IMP. 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.

The baseline value for efficacy variables is defined as the last available value before or on the day of randomization, and before the time of first IMP injection if on the day 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 2.4.6).

Demographic characteristics

- Age (years) (as reported in the e-CRF),
- Age group (<65, ≥65 to <75, ≥75 years of age)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, More than One Race, Unknown, Not reported),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Not Reported),
- Country (US),
- Baseline weight (kg),
- Baseline body mass index (kg/m², calculated in the e-CRF),
- Baseline BMI by categories (<25, ≥25 to <30, ≥30 kg/m²),
- Baseline estimated glomerular filtration rate (GFR, modification of diet in renal disease [MDRD] formula, mL/min/1.73m²),
- Baseline estimated GFR categories (≥90, ≥ 60 to <90, ≥30 to <60, <30 mL/min/1.73m²),
- Randomization stratum of screening HbA1c categories (<8%, ≥8%)

Medical or surgical history

Medical or surgical history at baseline will be coded to a “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 of allergy and subject family history of allergy will also be recorded using summary tables.

Disease characteristics at baseline

- Fasting C-peptides (nmol/L) (values below the Lower Limit Of Quantitation (LLOQ) are imputed to the LLOQ/2),
- Fasting C-peptides (<0.023, ≥0.023 to <0.42, ≥0.42 nmol/L)
- Duration of type 1 diabetes (years),
- Duration of type 1 diabetes (<10, ≥10 years),
- Age (years) at onset of type 1 diabetes,
- Duration of basal insulin treatment (years),
- Duration of mealtime insulin treatment (years),
- Previous basal insulin treatment:
  - Type (insulin glargine (100U/mL)),
  - Duration (years),
- Previous mealtime insulin treatment:
  - Type (NovoLog),
  - 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).

A listing of patients with fasting C-peptide ≥0.42 nmol/L at baseline will also be provided.

Any technical details related to computation, dates, and imputations for missing data are described in Section 2.5.1.

2.1.2 Prior or concomitant medications

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

- Prior medications are those reported on the CRF (as per CRF completion instructions, it corresponds to the medications taken within 3 months before screening visit date) and

taken before the day of first IMP intake (excluded) for the non-antidiabetic medications or up to the day of first IMP (included) for the antidiabetic medications. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.

- Concomitant medications are any treatments received by the patient concomitantly to the IMP, defined as follows:
  - For non-antidiabetic medications: any treatments received from first injection of IMP (included) to the last injection of IMP +1 day (included).
  - For antidiabetic medications: any treatments received from the first injection of IMP + 1 day (included) to the day before the last injection of IMP (included).
  - A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in Section 2.1.5).
- Post-treatment medications are defined as follows:
  - For non-antidiabetic medications: medications taken in the period running from the last injection of IMP + 2 days (included) to the end of the study.
  - For antidiabetic medications: medications taken in the period running from the day of last injection of IMP (included) to the end of the study.

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

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

2.1.3 Pharmacokinetic endpoints

2.1.3.1 Primary pharmacokinetic endpoints

The primary pharmacokinetic variables are the AUClast, AUC, and Cmax parameters following injection of a predefined, fixed dose of SAR341402 or NovoLog (0.15 U/kg) at Week 16. Further details for the derivation of PK parameters are given in Section 2.5.7.1. Secondary pharmacokinetic endpoint.

2.1.3.2 Secondary pharmacokinetic endpoints

The secondary pharmacokinetic variable is tmax which is the time to reach Cmax following injection of a predefined, fixed dose of SAR341402 or NovoLog (0.15 U/kg) at Week 16.

2.1.4 Immunogenicity variables

As per protocol, only the number of patients with treatment-emergent anti-insulin aspart antibodies (AIA) during the 16-week treatment period is secondary. All other immunogenicity endpoints are tertiary/exploratory.

If a patient discontinues the treatment prematurely, the process described in Section 2.5.1 will be applied to retrieve immunogenicity assessments performed at the end of treatment visit (Visit 8000).

AIA measurements will be performed in a blinded fashion at a central laboratory (see study flowchart in Section 1.3 of the protocol) using a validated anti-insulin aspart antibody binding assay methodology. Only AIA results from samples collected during the on-treatment period and at least 8 hours after the last administration of mealtime insulin will be taken into account in the analysis.

Anti-insulin aspart antibodies evaluation will consist of:

- Anti-SAR341402/ NovoLog antibody positive/negative status
- Anti-SAR341402/ NovoLog 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) (1) :

- **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.

The peak titer will be defined as the maximal titer observed during the on-treatment period.

Anti-insulin aspart neutralizing antibody status (positive/negative) of confirmed AIA positive samples will also be part of the immunogenicity analyses, as tertiary/exploratory endpoint.

Anti-insulin aspart neutralizing antibody (NAb) status (positive/negative) and NAb titers of confirmed AIA positive samples will also be part of the immunogenicity analyses, as tertiary/exploratory endpoints. A patient with an AIA-negative sample at a given visit (thus not tested for NAbs) will be considered as NAb-negative for this visit.

The following definitions will be used to identify patients with a change in NAb response during the on-treatment period (see Section 2.1.4) (2):

- **Patients with treatment-induced NAbs** will be defined as patients with NAbs that developed de novo (seroconversion) following the IMP administration (ie, patients with at least one positive NAb sample at any time during the on-treatment period, in those patients without pre-existing NAb or with missing sample at baseline).
- **Patients with treatment-boosted NAbs** will be defined as patients NAb positive at baseline that were boosted to a significant higher NAb titer following the IMP administration (ie, patients with at least one NAb sample with at least a 4-fold increase in NAb titers compared to baseline value at any time during the on-treatment period, in those patients with preexisting NAb). The 4-fold increase in NAb 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 NAbs (Yes, No, Inconclusive) will be derived as follows:

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

The peak NAb titer will be defined as the maximal NAb titer observed during the on-treatment period.

2.1.5 Safety endpoints

The following safety endpoints are secondary and will be derived based on the following safety assessments collected during the 16-week treatment period:

- Hypoglycemia (according to ADA Workgroup on Hypoglycemia) (3)(4)(5),
- Adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs),
- Adverse events requiring specific monitoring (injection site reactions, hypersensitivity reactions),

The following safety parameters will also be summarized:

- Laboratory parameters,
- 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 2.5.1 will be applied to retrieve safety assessments performed at the premature end of treatment visit (Visit 8000).

Safety observation period

The observation period for 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 **on-treatment period** is defined as the time from the first injection of IMP up to the last injection of IMP + 1 day (included).
- The **post-treatment period** is defined as the time from the last injection of IMP + 2 days (included).

Analyses will focus on safety observations during 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).

2.1.5.1 Hypoglycemia

All hypoglycemia will be reported by the patient in the e-diary, transferred to the dedicated hypoglycemia event page in the e-CRF and reviewed by the investigator, or directly completed in other dedicated hypoglycemia event pages 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)(4)(5) 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 (response “Required assistance because subject was not capable of helping self” to the question “Assistance Required?” in the e-CRF).
- **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 (also 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).

Hypoglycemia not classified in one of the above categories will be presented separately as non-classified hypoglycemia. Any technical details to categorize hypoglycemia in case of missing hypoglycemia information are described in Section 2.5.1.

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 described.

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 2.1.5).
- Post-treatment hypoglycemia are events that occurred during the post-treatment period.

2.1.5.2 Adverse events variables

All AEs (including serious adverse events [SAEs], adverse events of special interest [AESI] and adverse events requiring specific monitoring) will be coded to a 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 AE observations will be classified per the observation periods of safety data as defined in Section 2.1.5 :

- **Pre-treatment AEs** are AEs that developed or worsened or became serious during the pre-treatment period.
- **Treatment-emergent AEs (TEAEs)** are AEs that developed or worsened or became serious during the on-treatment period.
- **Post-treatment AEs** are AEs that developed or worsened or became serious during the post-treatment period.

Adverse events requiring specific monitoring

The AEs requiring specific monitoring for this study are as follows:

- **Injection site reactions:** any sign related to local non-allergic reactions at the IMP/NIMP injection site.
- **Hypersensitivity reactions:** allergic reactions or possible allergic reactions. Hypersensitivity reactions will be adjudicated by the Allergic Reaction Assessment Committee (ARAC).

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 (AESI) include:

- 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/NIMP,
- Symptomatic overdose (serious or non-serious) with IMP/NIMP,
- Increase in alanine aminotransferases (ALT) > 3 x ULN.

These events will be identified through the AESI category in the adverse event page of the CRF.

2.1.5.3 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

2.1.5.4 Laboratory safety variables

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

Only laboratory data collected according to the protocol (see study flowchart in Section 1.3 of the protocol) will be analyzed. The laboratory parameters will be classified as follows:

- **Hematology:**
  - Red blood cells and platelets including hemoglobin, hematocrit, red blood cell count and platelet count,
  - White blood cells including white blood cell count, neutrophils, lymphocytes, monocytes, basophils and eosinophils.
- **Clinical chemistry:**
  - Metabolism : albumin,
  - Electrolytes including sodium, potassium,
  - Renal function including creatinine and estimated GFR (MDRD),
  - Liver function including alanine aminotransferase (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.

2.1.5.5 Vital signs variables

Vital signs include heart rate (bpm), and systolic and diastolic blood pressure (mmHg) (see study flowchart in Section 1.3 of the protocol).

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

2.1.5.6 Electrocardiogram variables

Not applicable

2.1.6 Efficacy endpoints

Efficacy endpoints are tertiary/exploratory.

HbA1c and FPG are measured in a blinded fashion at a central laboratory, for scheduled (see study flowchart in Section 1.3 of the protocol) and unscheduled assessments.

In case of premature permanent IMP discontinuation, the process described in Section 2.5.1 will be applied to retrieve efficacy assessments performed at the end of treatment visit (Visit 8000).

Efficacy observation period

- The randomized period for efficacy variables is defined as the time from randomization date up to Week 16 (Visit 7), regardless of study treatment discontinuation.

Efficacy endpoints

All efficacy endpoints will be derived on the randomized period using the intent-to-treat (ITT) population. All HbA1c/FPG values will be used, regardless of adherence to treatment.

The following efficacy endpoints will be calculated:

- Change from baseline to Week 16 in HbA1c (%), defined as the HbA1c value at Week 16 - HbA1c value at baseline.
- Change from baseline to Week 16 in FPG (in mg/dL and mmol/L), defined as the FPG value at Week 16 - FPG value at baseline.

2.1.7 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.8 Quality-of-life endpoints

Not applicable.

2.1.9 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.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary tables

- Screened patients, defined as all patients who signed the informed consent.
- Screen failure patients and reasons for screen failure.
- Randomized patients, as defined in Section 2.3.
- Treated but not randomized patients.
- Randomized and not treated patients.

- Randomized and treated patients,
  - Completed patients: Patients who completed the **treatment period** (as reported on the EOT CRF page).
  - Patients who did not complete the **study treatment** as per protocol.
  - Patients who discontinued the **study treatment** by main reason (related to COVID-19 or not for reasons "Adverse event" and "Other") for definitive treatment discontinuation.
  - Patient's reason (related to COVID-19 or not for reasons "Adverse event" and "Other") for permanent **treatment** discontinuation.
- Patients who completed the **study period** (as reported on the EOS CRF page).
  - Patients who discontinued the **study** by main reason (related to COVID-19 or not for reason "Other") 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.

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

- Treated but not randomized patients.
- Randomized and not treated patients.
- 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. 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.

Lists of participants who prematurely discontinued treatment and/or study will be provided with reasons for discontinuation, including reasons related to COVID-19.

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). Critical or major protocol deviations will also be summarized according to COVID-19 impact.

Patients impacted by COVID-19 are defined as patients with major impact of COVID-19 on study conduct, including premature EOT/EOS due to COVID-19 and/or critical or major protocol deviations related to COVID-19. The number and percentage of patients impacted or not by COVID-19 will presented, along with the type of impact, and a listing of participants impacted by COVID-19 will be provided.

A table of patient disposition by visit according to COVID-19 impact will also be provided, based on the eCRF comment page. Each impacted visit will be described according to the following categories:

- Visit not done,
- Visit partially done on site,
- Visit partially done by phone,
- Complete visit but delayed.

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

- PK population as defined in Section 2.3.1,
- Anti-insulin aspart antibody population as defined in Section 2.3.3,
- Safety population as defined in Section 2.3.2,
- Efficacy population: ITT population as defined in Section 2.3.4.

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 at Visit V3 (treated but not randomized) 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 will be documented separately in the clinical study report.

The randomized population consists of all screened patients who have a treatment kit number allocated and recorded in the IRT database, 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 Pharmacokinetic population

The pharmacokinetic population is defined as all randomized participants without deviation that could significantly impact the PK analysis (eg, missing or incorrect IMP injection on PK profile day) and for whom PK data are considered sufficient and interpretable.

All exclusions from the PK population (before and after database lock) will be documented in the CSR together with their reasons.

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.

- Randomized patients having taken at least one kit of SAR341402 will be considered in the switching arm. Patients randomized in the switching arm but having taken only Novolog as treatment will be considered in the non-switching arm.

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 (ie, collected during the on-treatment period and at least 8 hours after the last administration of mealtime insulin). Patients will be analyzed according to the treatment actually received.

2.3.4 Efficacy population

2.3.4.1 Intent–to-treat population

The 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.

2.4 STATISTICAL METHODS

Continuous data will be summarized by treatment group (switching arm or non-switching arm) using, if not stated otherwise, the number of observations available (N), mean, SD, minimum, median, and maximum. These apply to all data, except PK data which will be described as detailed in Section 2.5.7.

Categorical and ordinal data (except PK data, see Section 2.5.7) will be summarized by treatment group (switching arm or non-switching arm) using the number and percentage of patients.

In general, descriptive statistics of parameters (result and change from baseline, if applicable) 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 reallocation algorithm of premature end of treatment provided in Section 2.5.3.

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.

Analyses for the PK population will be performed if the size of the PK population is less than 90% the size of the randomized population for any treatment group.

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

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

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

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.

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 switching arm. 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.

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).

Observation period

The observation period for exposure is defined as the time from the first injection of IMP up to the day of last injection of IMP.

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 2.5.1 for calculation in case of missing or incomplete data).

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

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

The process described in Section 2.5.1 will be applied to define the date of the last IMP administration. 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 are grouped as follows:

- Up to 4 weeks,
- >4 to 8 weeks,
- >8 to 12 weeks,
- >12 to 15 weeks,
- >15 to 16 weeks,
- >16 to 24 week,
- >24 weeks.

The cumulative duration of exposure will be described using the following time periods:

- ≥ 1 day,
- >4 weeks,
- >8 weeks,
- >12 weeks,
- >15 weeks,
- >16 weeks,
- >24 weeks.

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient-years.

If the number of patients impacted by COVID-19 is sufficient, the duration of IMP exposure will also be presented by subgroup of COVID-19 impact (Non-impacted, Impacted) (see definition Section 2.2).

Daily insulin doses

All insulin doses will be reported by patient in e-diary, transferred to the IMP/NIMP e-diary page of the eCRF and reviewed by the investigator in dedicated items. In case the insulin doses reported by the patient are incorrect, the investigator will invalidate them and enter correct doses in the IMP/NIMP back-up e-diary page of the eCRF. For the analyses, the investigator entries will prevail when compared from the transferred e-diary data.

The process described in Section 2.5.3 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 follows:

- Daily basal insulin dose at baseline (U and U/kg) = median of daily basal insulin doses available up to 7 days before the day of first IMP,
- Daily mealtime insulin dose at baseline (U and U/kg) = median of daily mealtime insulin doses available up to 7 days before the day of first IMP,
- Daily total insulin dose at baseline (U and U/kg) = median of daily total insulin doses available up to 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 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. Figures will be provided.

The ratio of the daily basal insulin/total insulin dose observed and change from baseline will be described at baseline and at each visit.

The daily insulin doses (basal, mealtime, total) will be summarized according to categories of HbA1c change from baseline to Week 16 (<-1%, ≥-1% to ≤1%, >1%).

If the number of patients impacted by COVID-19 is sufficient, daily insulin doses will also be presented by subgroup of COVID-19 impact (Non-impacted, Impacted) (see definition Section 2.2).

Any technical details related to the calculation of doses and the imputations for missing data are described in Section 2.5.1.

2.4.3.2 Compliance

Not applicable.

2.4.4 Analyses of pharmacokinetic endpoints

2.4.4.1 Analyses of primary pharmacokinetic endpoints

Primary analysis

The primary analysis will be performed on the PK population, based on natural log-transformed AUC_{last}, AUC, and C_{max}. The 90% CI for the ratio of geometric means for AUC_{last}, AUC, and C_{max} between the two treatment arms (switching arm versus non-switching arm) should be within 80-125%, corresponding to the following composite null and alternative hypotheses tested at an alpha level of 0.05:

- H0: The ratio of geometric means for AUC_{last}, AUC, or C_{max} between the switching arm and the non-switching arm is outside the predefined acceptance range 80-125%
- H1: The ratio of geometric means for AUC_{last}, AUC, and C_{max} between the switching arm and the non-switching arm is within the predefined acceptance range 80-125%

For primary analysis, the natural log-transformed AUC_{last}, AUC, and C_{max} will be statistically analyzed using an analysis of variance, including the fixed categorical effects of treatment arm (switching arm, non-switching arm) and randomization stratum (screening HbA1c <8.0%, ≥8.0%).
Estimate and 90% CI for the ratio of geometric means between the two arms (switching arm / non-switching arm) will be computed separately for AUC_{last}, AUC, and C_{max}, from the linear model framework using re-transformation. The 90% CIs for the ratio of geometric means of AUC_{last}, AUC, and C_{max} should be within 80–125%.
Additionally, PK parameters will be summarized by treatment using descriptive statistics (for details, see Section 2.5.7).

Subgroup analyses

If it will be deemed necessary for interpretation of results, PK parameters may also be summarized for selected subgroups.

Sensitivity analyses

Exploratory statistical sensitivity analyses may be performed for primary PK parameters. They will be performed in a corresponding manner as the primary analysis, with

- Inclusion of those primary PK parameters affected by major deviations (ie., excluded from primary PK analysis)
- Exclusion of implausible PK parameters and PK parameters suspected to result from apparent but not documented PK irregularities.

2.4.4.2 Analysis of secondary pharmacokinetic endpoints

T_{max} will be summarized by treatment group in the PK population using descriptive statistics.

2.4.4.3 Multiplicity issues

The type of analysis for multiple primary PK endpoints cannot inflate the type 1 error risk above 0.05. No adjustment of alpha/confidence level will be performed.

Further PK endpoints will be analyzed purely descriptively.

2.4.4.4 PK parameters at premature end of trial

For patients with a PK profile at premature end of trial (PEOT), PK parameters will be derived.

Descriptive statistics of PK parameters from profiles at PEOT will be generated per treatment arm.

2.4.5 Analyses of safety data

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

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 A).
- 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 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 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, using events occurring during the on-treatment period (as defined in Section 2.1.5).

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 2.1.5.1). 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 compared for the switching arm versus the non-switching arm using a logistic regression method. The model will include fixed-effect terms for treatment group and the randomization stratum of screening HbA1c (<8%, ≥8). If the logistic model does not converge (e.g., due to sparse data), the randomization stratum may be removed from the model. Odds-ratios and 95% CIs will be displayed using forest plots.
- The number (%) of patients with at least one hypoglycemia leading to permanent IMP discontinuation will be provided by treatment group.
- Incidence of patients with at least one severe hypoglycemia with neuroglycopenic symptoms and/or SMPG <2.8 mmol/L (50 mg/dL) will be summarized.
- If the number of patients impacted by COVID-19 is sufficient, the incidence of patients with at least one hypoglycemia (any, severe, documented symptomatic) will also be

presented by subgroup of COVID-19 impact (Non-impacted, Impacted) (see definition Section 2.2) and compared between treatment groups using a similar logistic regression model as described above, with added fixed-effect terms for the subgroup and the subgroup-by-treatment interaction. Odds-ratios and 95% CIs will be presented across subgroups using forest plots. The significance level of the subgroup-by-treatment interaction will also be provided for descriptive purpose.

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 2.1.5.1). Non classified hypoglycemia will be displayed.
- For any hypoglycemia the cumulative mean number of hypoglycemia per patient 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 compared for the switching arm versus the non-switching arm 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 the randomization stratum of screening HbA1c (<8%, ≥8%). If a model does not converge (eg, due to sparse data), the randomization stratum may be removed from the model. Rate ratios and 95% CIs will be displayed using forest plots.
- The number of severe hypoglycemia with neuroglycopenic symptoms and/or SMPG <2.8 mmol/L (50 mg/dL) per patient-year of exposure will be summarized by treatment group.

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.

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 2.5.1.

Adverse event incidence tables will present by SOC and/or PT, 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 switching arm.

Analyses of all TEAE(s) will be generated for the safety population.

Analysis of all TEAE(s)

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAEs,
  - Serious TEAEs,
  - TEAEs leading to death,
  - TEAEs leading to permanent treatment discontinuation.
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT in the switching group.
- 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 PT in the switching group within SOC. This sorting order will be applied to all other tables, unless otherwise specified. If the number of patients impacted by COVID-19 is sufficient, TEAEs will also be presented by subgroup of COVID-19 impact (Non-impacted, Impacted) (see definition Section 2.2).
- All TEAEs regardless of relationship and related to IMP by primary SOC and PT, showing number (%) of patients with at least one TEAE, sorted by the sorting order defined above.
- 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.

Analysis of all treatment-emergent SAE(s)

- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC and PT, showing number (%) of patients with at least 1 serious TEAE, sorted by SOC internationally agreed order and decreasing incidence of PTs according to all TEAE summary within SOC.

Analysis of all TEAE(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to permanent IMP discontinuation, by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order and decreasing incidence of PTs according to all TEAE summary within SOC.

Analysis of all TEAE(s) requiring specific monitoring

- All TEAE(s) 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 based on results for the switching group.
- The number of events sent for adjudication to the ARAC and the number (%) of events positively adjudicated as allergic reaction or not by the ARAC will be summarized for each treatment group.
- A listing of all events adjudicated by ARAC will be provided with the result of ARAC adjudication.

Analysis of adverse events of special interest

- Number (%) of patients experiencing AESI presented by categories described in Section 2.1.5.2.

Analysis of pretreatment and posttreatment adverse events

- Depending on the number, a listing or a table of all pre-treatment and post-treatment AEs will be provided.

Analysis of TEAEs related to COVID-19

All TEAEs related to COVID-19 by primary SOC and PT, showing the number (%) of patients with at least one TEAE related to COVID-19, sorted by the internationally agreed SOC order and decreasing incidence of PTs according to all TEAE summary within SOC. TEAEs related to COVID-19 will be identified using a CMQ (customized MedDRA queries) list.

2.4.5.3 Deaths

The following deaths summaries will be generated on the safety population.

- Number (%) of patients who died by study period (on-study, on-treatment 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 and PT, showing number (%) of patients sorted by SOC internationally agreed order and decreasing incidence of PTs according to all TEAE summary within SOC.
- 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, Week 16, and last on-treatment value)

by treatment group. This section will be organized by biological function as specified in Section 2.1.5.4.

The incidence of PCSAs (list provided in Appendix A) at any time during the 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, alkaline phosphatase, 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 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 ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

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

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 2.1.5.5 including body weight, will be calculated for each visit or study assessment (baseline, Week 16, last on-treatment value) by treatment group.

The incidence of PCSAs at any time during the on-treatment period will be summarized by treatment irrespective of the baseline level.

2.4.5.6 Analyses of electrocardiogram variables

Not applicable.

2.4.6 Analyses of anti-insulin aspart antibody data

2.4.6.1 Analyses of anti-insulin aspart antibody data

The analyses of immunogenicity data will be descriptive (no formal statistical testing) and based on the AIA population.

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 the switching arm and the non-switching arm 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 and the randomization stratum of screening HbA1c (<8%, ≥8%). If the model does not converge (e.g., due to sparse data), randomization strata may be removed from the model. 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 peak titer will be described using median, Q1 and Q3.

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).

A listing with inconclusive patients will be provided.

Anti-insulin aspart antibody data by visit

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

On the group of patients with anti-SAR341402/NovoLog antibody positive sample at a given visit, anti-SAR341402/NovoLog 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 for patients with treatment-emergent AIAs.

Subgroup analyses

Exploratory analyses will be performed by the subgroups defined by the Anti-SAR341402/NovoLog antibody status at baseline (Positive, Negative), and by COVID-19 impact (Non-impacted, Impacted; see subgroup definition in Section 2.2). The second subgroup analysis will be performed only if the number of patients is sufficient. 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 safety/efficacy assessments will be summarized by treatment-emergent AIA (Yes, No) and for each treatment group:

- 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.
- TEAEs: descriptive statistics presented by primary SOC and PTs, showing number (%) of patients with at least one TEAE, sorted by SOC internationally agreed order and decreasing incidence of PTs according to all TEAE summary within SOC.
- Serious TEAEs: descriptive statistics by primary SOC and PTs, showing number (%) of patients sorted by SOC internationally agreed order and decreasing incidence of PTs according to all TEAE summary within SOC.
- Injection site and hypersensitivity reactions: descriptive statistics by PT, showing number (%) of patients sorted by decreasing incidence of PT in the switching group.

- Efficacy endpoint (change from baseline to Week 16 in HbA1c): descriptive statistics by visit.
- Change in daily insulin doses (basal, mealtime, total) as defined in Section 2.4.3: descriptive statistics by visit.

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:

- 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
- Efficacy endpoint (change from baseline to Week 16 in HbA1c)
- Change in daily insulin doses (U/kg) from baseline to Week 16

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).

Listings of anti-insulin aspart antibody, insulin doses, and HbA1c data will be provided for patients with treatment-emergent AIAs and HbA1c change from baseline > 1% at Week 16.

A listing of patients with treatment-emergent AIA at end of treatment and potential effects on glycemic control will be provided with the result of adjudication by the ARAC diabetologist (including AIA-mediation and potential need for AIA post-study follow-up).

2.4.6.2 Analyses of anti-insulin aspart neutralizing antibody data

Neutralizing antibody response

The number and percentage of patients will be provided by treatment group for each of the following categories:

- Patients with treatment-induced NAb,
- Patients with treatment-boosted NAb,
- Patients with treatment-emergent NAb (NAb incidence),
- Patients without treatment-emergent NAb,
- Patients with pre-existing NAb or treatment-induced NAb (NAb prevalence).

For patients with treatment-induced and treatment-boosted NAbs, the peak NAb titer will be described using median, Q1 and Q3.

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

A listing with inconclusive patients will be provided.

Anti-insulin aspart neutralizing antibody data by visit

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

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

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

Boxplots of NAb 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-emergent NAbs.

Subgroup analyses

Exploratory analyses will be performed for the subgroup defined by the Anti-SAR341402/NovoLog neutralizing 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 assessments

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

The following efficacy assessments will be summarized by treatment-emergent NAb (Yes, No) and for each treatment group:

- Efficacy endpoint (change from baseline to Week 16 in HbA1c): descriptive statistics by visit.
- Change in daily insulin doses (basal, mealtime, total) as defined in Section 2.4.3: descriptive statistics by visit.

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

- Efficacy endpoint (change from baseline to Week 16 in HbA1c).
- Change in daily insulin doses (U/kg) from baseline to Week 16.

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

A listing of AIA/NAb status, insulin doses, and HbA1c data will be provided for patients with treatment-emergent NAbs and HbA1c change from baseline > 1% at Week 16.

2.4.7 Analyses of efficacy endpoints

Analyses of efficacy endpoints (change in HbA1c and FPG from baseline to Week 16 as defined in the Section 2.1.6) will be descriptive with no formal statistical testing, and based on the ITT population (ie, regardless of adherence to treatment, as per definition) . All post-baseline data available during the randomized period will be described.

HbA1c, FPG and change from baseline values (% for HbA1c and mmol/L and mg/dL for FPG) will be presented by visit for each treatment group, using descriptive statistics and/or graphs.

Additionally, if the number of patients impacted by COVID-19 is sufficient, efficacy endpoints will also be presented by subgroup of COVID-19 impact (Non-impacted, Impacted) (see definition Section 2.2).

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) = (Date of informed consent – Date of first intake of mealtime Anti-hyperglycemic therapy +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

Renal function formula

GFR will be derived using MDRD formula:

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

2.5.2 Missing data

2.5.2.1 Handling of missing PK parameters

For participants with insufficient data for some but not all PK parameters, the evaluable PK parameters will be included in the analysis. No imputations of missing PK parameters are planned.

2.5.2.2 Handling of other missing parameters

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, the date of the last dose of IMP will be defined as the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

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

Rules 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 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 for the main meal (breakfast, lunch and dinner) and no more than 1 snack will be required to calculate the daily mealtime insulin dose. For the days with more than one snack or more than one main meal with an insulin dose of 0 unit, the daily dose won't be calculated.

The daily total insulin dose will be calculated as the sum of the daily basal (only the doses not null will be kept) 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 (unscheduled or not) will be used.

2.5.3 Visit allocation

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 8), and for unscheduled assessments. No reallocation of visit will be performed for PK.

Insulin doses

In the clinical database, 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 7, 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, except for the PK assessments, as the PK profiles of patients who prematurely discontinued the treatment will not be included in the primary PK analysis.

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 (except PK assessment) performed at the end of treatment visit (Visit 8000) and will apply to insulin doses assigned to Visit 8000 following the process described above.

2.5.4 Unscheduled visits

The determination of baselines for safety and efficacy parameter variables is based on all measurements from both scheduled and unscheduled visits (measurements from the central laboratory only), as mentioned in Section 2.5.3. The determination of the last on-treatment value for safety 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.

2.5.5 Pooling of centers for statistical analyses

All centers will be pooled for statistical analysis. Centers will not be taken into account in the statistical analysis.

2.5.6 Study-specific conventions

In the statistical appendices and in-text tables, the following treatment labels will be used:

- Switching arm
- Non-Switching arm

2.5.7 Handling for pharmacokinetic data

2.5.7.1 Individual PK parameters

Individual PK parameters will be provided by a vendor.

AUC values extrapolated by more than 20% will be excluded from any pharmacokinetic statistical analysis.

2.5.7.2 Descriptive analyses

Descriptive analyses and graphical descriptive display of PK parameters will be provided by a vendor, under responsibility of PK function.

For ease of presentation, mean values will be arithmetic mean unless specified.

Individual concentration values below the lower limit of quantification (LLOQ) will be treated as zero in calculating mean values but reported as <LLOQ. Mean values below LLOQ will be reported as <LLOQ in the tables.

Mean calculations and their associated statistics will be generated from unrounded numbers and may differ slightly from those values that would be determined using the rounded numbers displayed in the tables.

Values expressed in tables will be for ease of presentation and will not be meant to imply accuracy to more than 3 significant figures.

Plasma concentrations and pharmacokinetic parameters will be summarized by arithmetic mean, geometric mean, SD, SE, CV(%), minimum, median, maximum, and number of observations by treatment.

2.5.8 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

It is planned to lock the database approximately 7 weeks after the last patient last visit (LPLV).

5 SOFTWARE DOCUMENTATION

Descriptive analyses for PK parameters will be generated using version 6.4 of Phoenix WinNonlin.

All other summaries and statistical analyses will be generated using SAS 9.4 or higher.

6 REFERENCES

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2. Kock GG. Comments on 'Current issues in non-inferiority trials' by Thomas R. Fleming, Statistics in Medicine, DOI: 10.1002/sim.2855. Stat Med. 2008 Feb 10;27(3):333-42.

3. American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005 May;28(5):1245-9.

4. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.

5. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L(54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-7.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities criteria

Appendix A 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.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
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.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Uric Acid		Harrison- Principles of internal Medicine 17th Ed., 2008.
Hyperuricemia	>408 µmol/L	
Hypouricemia	<120 µmol/L	
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
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.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
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)	
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.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
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	
	>90 bpm	Categories are cumulative
	>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%	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	
QTc	Absolute values (ms) >450 ms >480 ms >500 ms Increase from baseline Increase from baseline]30-60] ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. Absolute values categories are cumulative QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.

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Approve & eSign	[redacted]

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