AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**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**
Protocol number:	**EFC15178**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR341402 (insulin aspart)**
Short title:	**Comparison of SAR341402 to NovoLog in Adult Patients with Type 1 Diabetes Mellitus also Using Insulin Glargine (Gemelli X)**
Sponsor name:	
Legal registered address:	

Monitoring Team's Representative Name and Contact Information

Regulatory agency identifying number(s):

EudraCT number:	Not applicable
IND number:	136342
WHO number:	U1111-1197-7811
NCT number:	NCT03874715

Approval Date: 13-Aug-2019 Total number of pages: 81

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	13 August 2019, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	27 February 2019, version 1 (electronic 1.0)
Original Protocol		5 November 2018, version 1 (electronic 2.0)

Amendment 02 (13-Aug-2019)

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Based on current treatment practices in Type 1 diabetes mellitus patients in the US and to open up the pool of potentially eligible patients for the study, a run-in period has been added to allow for switching of patients who have not been using NovoLog and insulin glargine (100 U/mL) for at least 12 weeks prior to screening to ensure a sufficient amount of time on this background therapy prior to randomization.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.2 Schema; 1.3 Schedule of Activities (SoA); 2.1 Study Rationale; 3 Objectives and Enpoints; 4.1 Overall Design; 4.2 Scientific Rationale for Study Design; 5.1 Inclusion Criteria, 5.2 Exclusion Criteria; 5.3 Lifestyle Considerations; 5.4 Screen Failures; 6 Study Intervention; 6.1 Study Intervention(s) Administered; 6.3 Measures to Minimize Bias: Randomization and Blinding; 6.4 Study Intervention Compliance; 6.4.1 Return and/or Destruction of Treatment; 6.5 Concomitant Therapy; 8.1.2 Self-monitored plasma glucose	An up-to-12-week run-in period has been added for study participants who have not been on NovoLog and insulin glargine (100 U/mL) for at least 12 weeks prior to the screening visit. During this period, such patients will take NovoLog and insulin glargine (100 U/mL), ie, Lantus, so that they will have been on this background therapy for at least 12 weeks and would subsequently become eligible for study randomization (provided that all other eligibility criteria are met).	A run-in period has been added to accommodate change in patients' eligibility.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 2.1 Study Rationale; 3 Objectives and Endpoints; 9.4.2 Immunogenicity analyses	To compare the treatment effect on immunogenicity (secondary objective), the number of participants with treatment-emergent insulin aspart antibodies (AIA) will be used as endpoint rather than the AIA status (positive/negative) by visit (this endpoint has been moved to tertiary/exploratory).	According to the Sponsor internal technical recommendations, the AIA incidence seems to be a more relevant indicator than the AIA status by visit.
1.1 Synopsis; 4.1 Overall Design; 4.3 Justification for Dose; 6.5 Concomitant Therapy	In case of hypoglycemia, any countermeasure may be administered, instead of carbohydrates only.	To allow Investigator to select the most suitable countermeasure in case of hypoglycemia.
1.1 Synopsis; 4.1 Overall Design	The breakfast content on the day of PK visit will be determined per the Investigator's judgement, with focus on prevention of hypoglycemia or significant hyperglycemia during this period.	Clarification on breakfast content.
1.1 Synopsis; 1.3 Schedule of Activities (SoA)	For participants not requiring run-in, the screening period may be extended by up to a maximum of 3 days after the 2-week period. For participants requiring run-in, to ensure that the minimum of 12-week duration on NovoLog and insulin glargine (100 U/mL) is achieved and to facilitate participant's scheduling, the run-in period may be extended by up to a maximum of 3 days after the 12-week period.	To allow centers to adequately organize all screening and/or run-in activities prior to participant's randomization.
10.4 Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Injectable combined hormonal contraception and barrier contraception have been added as permitted contraception.	Injectable combined hormonal contraception and barrier contraception are deemed sufficiently effective to mitigate the risk of pregnancy in this trial.
1.1 Synopsis; 9.2 Sample Size Determination	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.	To prevent unnecessary enrolment.
6.4 Study Intervention Compliance	"Additionally, the use of any other insulin during the period after the last visit will be questioned" has been removed.	Sentence removed as this activity is not necessary.
7.1.1 Definitive Discontinuation	Only clinically-significant abnormal laboratory values will be rechecked for confirmation as soon as possible.	To ensure consistency with the current process, where participant's discontinuation is not triggered by non-clinically-significant abnormal laboratory findings and to facilitate a reasonable timeframe for follow-up activities.

Section # and Name	Description of Change	Brief Rationale
8.1.2 Self-monitored plasma glucose	Occasional use of the participant's personal glucometer or continuous glucose monitoring device allowed if deemed necessary for the safety of the participant	To guarantee safety of the participants.
8.1.2 Self-monitored plasma glucose	Nocturnal measurement plasma glucose has been added.	To be consistent with Section 1.3 Schedule of Activities.
8.3 Adverse Events and Serious Adverse Events	Immediate notification of adverse events of special interest has to be done within 24 hours.	To clarify the meaning of immediate notification.
9.4.3 Safety Analyses	MedDRA coding level has been removed.	This level of detail is not necessary in the protocol and it will be provided in the Statistical Analysis Plan.
10.1.5 Committees Structure	Events of potential loss of efficacy will be adjudicated by the Allergic Reaction Adjudication Committee (ARAC).	Updated information to ensure consistency with the ARAC charter.
1.1 Synopsis; 9.4.1 Pharmacokinetic analyses	The Hodges-Lehmann estimate for T_{max} for the shift in location between treatment groups has been removed.	This analysis will not be performed as descriptive statistics were deemed to be sufficient for this parameter.
1.3 Schedule of Activities (SoA)	The Visit 1 window has been changed (to minimum 7 days before Visit 3) for study participants who do not require run-in.	To have at least 7 days of insulin data before randomization.
6.1 Study Intervention(s) Administered	Specific conditions for Lantus dose increase have been removed.	To ensure consistency with the rest of the protocol, which requires that Lantus titration is done according to the Investigator's best judgment based on the local label requirements.
3 Objectives and Endpoints	A tertiary endpoint has been added to compare the clinical effects of anti-insulin aspart neutralizing antibodies on glycemic control and insulin dose.	Neutralizing antibodies can increase or decrease the investigational medicinal product (IMP) activity and it might have an impact on the efficacy and the insulin dose.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: 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

Short title: Comparison of SAR341402 to NovoLog in Adult Patients with Type 1 Diabetes Mellitus also Using Insulin Glargine (Gemelli X)

Rationale:

Study EFC15178 (Gemelli X) is designed to generate data to support the argument that SAR341402 solution is interchangeable with the intended reference product, NovoLog, for the treatment of diabetes mellitus and that switching between SAR341402 solution and NovoLog will not pose an additional risk beyond that of using NovoLog alone. The study takes into consideration the general principles delineated in Section 351(k)(4)(A) of the Public Health Service (PHS) Act (Safety standards for determining interchangeability) and the FDA's Considerations in Demonstrating Interchangeability with a Reference Product Guidance for Industry (1).

Objectives and endpoints

Objectives	Endpoints
Primary	
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 Type 1 diabetes mellitus (T1DM) also using insulin glargine	AUC_{last}, AUC, and C_{max} following injection of a predefined, fixed dose of SAR341402 or NovoLog (0.15 U/kg) at Week 16
Secondary	
To compare the effects of alternating administration of SAR341402 and NovoLog with continuous use of NovoLog on immunogenicity	Number of participants with treatment-emergent anti-Insulin aspart antibodies (AIAs) during the 16-week treatment period
To evaluate the safety of alternating administration of SAR341402 and NovoLog versus continuous use of NovoLog	Safety evaluations, which will include evaluation of the following (for the 16-week treatment period): - Number of participants with at least one hypoglycemic event - Number of hypoglycemic events per participant-year - Number of participants with adverse events (AEs) (see Section 8.3)

Objectives	Endpoints
To compare other PK parameters between the two treatment arms (alternating administration of SAR341402 and NovoLog and continuous use of NovoLog)	Time to C_{max} (T_{max}) following injection of a predefined, fixed dose of SAR341402 or NovoLog (0.15 U/kg) at Week 16

Overall design:

Randomized, open-label, active-controlled, 2-arm parallel-group multicenter Phase 3 trial in adults with T1DM also using insulin glargine.

Upon confirmation of eligibility based on the screening procedures, participants who have not been on NovoLog and insulin glargine (100 U/mL) for at least 12 weeks before screening will complete a run-in period of up to 12 weeks during which they will be administered NovoLog and Lantus. Run-in period duration will be such that, at the time of randomization, the participants have been on NovoLog and insulin glargine (100 U/mL) for at least 12 weeks.

Participants will be randomized 1:1 to 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 flow-chart in Section 1.2.

Randomization will be stratified by HbA1c (<8.0%, ≥8.0%) obtained at the screening visit (Visit 1).

Insulin glargine 100 U/mL (Lantus) will be administered as mandatory background therapy throughout the treatment period of the study.

At the end of the 16-week study treatment, participants will have blood sampling, including for PK determination, antibody measurements, HbA1c, and FPG. Participants need to come to the site fasting and without having injected any meal-time insulin (SAR341402 or NovoLog) for at least 8 hours. After blood sampling for the trough PK measurements, participants will receive a single subcutaneous (SC) injection of 0.15 U/kg SAR341402 (switching arm) or NovoLog (non-switching arm). Subsequent PK sampling will be conducted for 8 hours according to assessment schedule (Table 1). During the 8-hour PK period, the Investigator must closely oversee the patient and manage any hypoglycemia or hyperglycemia that the patient may experience according to his/her medical judgement and the protocol requirements. Specifically, countermeasures are to be administered if hypoglycemia is experienced and human insulin must be administered if additional meal-time insulin is needed during this period. Alternatively, administration of insulin lispro at low doses, according to the Investigator's judgement, is also permitted. Additionally, the breakfast content on the day of PK visit will be determined per the Investigator's judgement, with focus on prevention of hypoglycemia or significant hyperglycemia during this period.

An Allergic Reaction Adjudication Committee (ARAC), comprised of experts in the field of allergology and diabetes mellitus independent from the Sponsor and the Investigators and blinded for the treatment groups will adjudicate specific events, as described in Section 10.1.5.

Number of participants:

Approximately 184 participants will be randomly assigned to either one of the 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 146 study participants with evaluable PK data can be determined to have been reached before all planned 184 participants are randomized, then the study randomization may be stopped sooner.

Intervention groups and duration:

The study comprises up to 4 periods:

- An up to 14-day screening period
  - For participants on a multiple (≥3) daily injection insulin regimen using NovoLog as mealtime insulin and insulin glargine (100 U/mL) as basal insulin for at least 12 weeks prior to screening (ie, who do not require a run-in period), in situations where not all conditions required for the participant's randomization are met, the screening period may be extended by up to a maximum of 3 days after the 14-day period. This extension does not apply to participants who require a run-in period.
- An up to 12-week run-in period for all eligible participants (based on the screening evaluations) who have not been taking NovoLog and insulin glargine (100 U/mL) for at least 12 weeks before screening. Those participants will be administered NovoLog as meal-time insulin therapy and Lantus as basal insulin, which they will take throughout the run-in period
  - To ensure that a minimum of 12-week duration on this background therapy is achieved and to facilitate participant's scheduling, the run-in period may be extended by up to a maximum of 3 days after the 12-week period.
- 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).

Study intervention

Investigational medicinal products:

Test drug: SAR341402

- Formulation: 100 U/mL solution for SC injection supplied in 3-mL cartridges in a disposable SoloStar® pen.
- Route of administration: self-administered by SC injection.

- Dose regimen: per standard of care, according to the Investigator's judgement, based on the current NovoLog United States (US) package insert.

Control drug: NovoLog-US (US-approved NovoLog) (administered during the treatment period)

- Formulation: 100 U/mL solution for SC injection in the NovoLog FlexPen™ disposable pen.
- Route of administration: self-administered by SC injection.
- Dose regimen: per standard of care, according to the Investigator's judgement, based on the current NovoLog US package insert.

Noninvestigational medicinal product

Insulin glargine (Lantus)

- Formulation: 100 U/mL solution for SC injection in 3-mL cartridges as Lantus SoloStar disposable pen.
- Route(s) of administration: self-administered by SC injection.
- Dose regimen: once daily dose titrated by the Investigator according to the Lantus US package insert.

NovoLog-US (US-approved NovoLog) (administered during the run-in period)

- Formulation: 100 U/mL solution for SC injection in the NovoLog FlexPen™ disposable pen.
- Route of administration: self-administered by SC injection.
- Dose regimen: per standard of care, according to the Investigator's judgement, based on the current NovoLog US package insert.

Statistical considerations:

- **Primary analysis:**

  Primary PK analysis will be based on the PK population, defined as all participants without deviations that could significantly impact the PK analysis (eg, missing or incorrect SC injection on PK profile day), and for whom PK data are considered sufficient and interpretable. For participants with insufficient data for some but not all PK parameters, the evaluable PK parameters will be included in the analysis.

  PK parameters will be summarized by treatment group using descriptive statistics.

  The impact of switching between SAR341402 and NovoLog on AUC_{last}, AUC, and C_{max} will be assessed.

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 (SAR341402/NovoLog switching arm, NovoLog non-switching arm) and randomization strata. Estimate and 90% confidence interval (CI) for the ratio of geometric means between the two arms (SAR341402 from switching arm / NovoLog from non-switching arm) will be computed for AUC_{last}, AUC, and C_{max}, from the linear model framework using re-transformation. The 90% CI for the geometric mean ratio of AUC_{last}, AUC, and C_{max} should be within 80-125%.

- **Analysis of secondary endpoints:**

  Immunogenicity analyses will be based on the AIA population, defined as all randomized and exposed participants with at least one AIA sample available for analysis. 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.

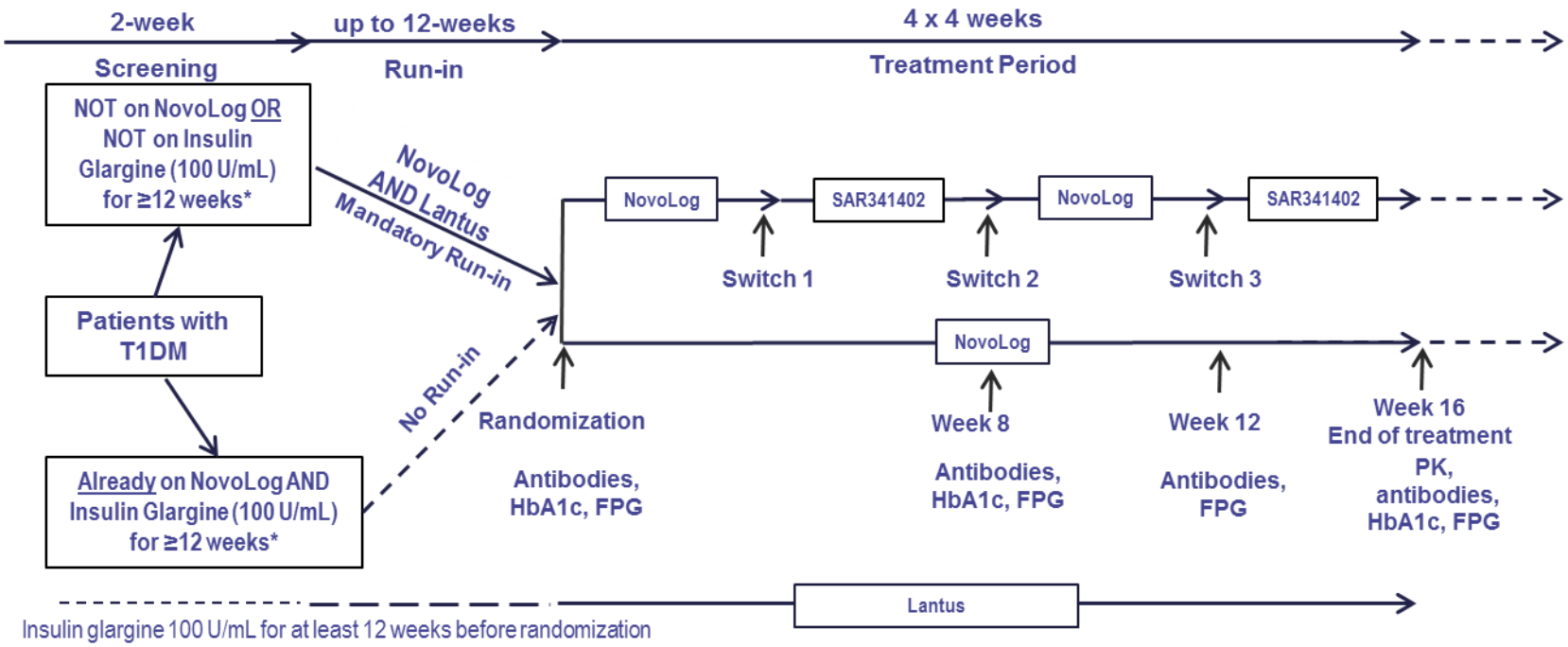
  Safety endpoints will be analyzed using descriptive statistics on the safety population, defined as all randomized participants who receive at least one dose of IMP, regardless of the amount of treatment administered.

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

- **Data Monitoring Committee: No**

1.2 SCHEMA

Figure 1 - Graphical study design



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

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 SoA for participants without run-in

This SoA is valid for participants who have been on NovoLog and insulin glargine (100 U/mL) for at least 12 weeks before screening and who therefore will not be included in the run-in period.

	Screening		Open-label Treatment Period					Follow-up	Notes
Week	**-2**[a]	**-1** ☎[b]	**0 (D1)**	**4**	**8**	**12**	**16** ***EOT***[c]	**16 + 1 day** ☎[b]	Visit Windows: Visit 1: 7 to 17 days before Visit 3; Visit 2: may be adjusted as appropriate to accommodate Visit 3 date; Visits 4 to 6: ±2 days; Visit 7: ±3 days; Visit 8: +2 days.
Day	-14[a]	-7	1	28	56	84	112	113	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Informed consent	X								Prior to any study-related procedures being performed.
Inclusion and exclusion criteria	X	X	X						Recheck eligibility before randomization.
Demography, medical/surgical/medication history, diabetes history	X								Including alcohol, drug abuse, and smoking history.
Physical examination	X						X		See Section 8.2.1
Blood pressure and heart rate	X		X				X		See Section 8.2.2
Body weight	X		X				X		
Height and BMI	X								
Dispensation of study glucometer/supplies and diary	X								Supplies may be re-dispensed any time during the study, as necessary.

	Screening		Open-label Treatment Period					Follow-up	Notes
Week	**-2**[a]	**-1** ☎[b]	**0 (D1)**	**4**	**8**	**12**	**16** *EOT*[c]	**16 + 1 day** ☎[b]	Visit Windows: Visit 1: 7 to 17 days before Visit 3; Visit 2: may be adjusted as appropriate to accommodate Visit 3 date; Visits 4 to 6: ±2 days; Visit 7: ±3 days; Visit 8: +2 days.
Day	-14[a]	-7	1	28	56	84	112	113	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Training and retraining on glucometer use, SMPG, hypoglycemia awareness and management, diary use and IMP/NIMP dosage self-adjustment	X	X	X	X	X	X			Site will provide training at Visits 1 and 3; regular refresher instructions will be provided at noted visit or as necessary throughout the study.
Diet and lifestyle counseling	X	X	X	X	X	X	X	X	As per current practice
IRT contact	X		X	X	X	X	X	X	Additional IRT contact (eg, to request additional IMP/NIMP) is permitted, as necessary
Randomization			X						Randomization must be performed only after all baseline evaluations have been done and eligibility of the participant has been confirmed
IMP and NIMP dispensation			X	X	X	X			Additional dispensing visits are permitted if necessary
Study intervention (IMP and NIMP administration)			←----------	----------	----------	----------	----------→		
Review of insulin dose		X	X	X	X	X	X		According to the Sponsor's instructions
Counting/collecting used and unused pens/Compliance check				X	X	X	X		
Diary data review and medical evaluation by Investigator		X	X	X	X	X	X		In addition to the scheduled visits, medical evaluation must also be performed in between visits, if data is available for review by the Investigator.
SMPG[d]	X	X	X	X	X	X	X		

	Screening		Open-label Treatment Period					Follow-up	Notes
Week	**-2**[a]	**-1** ☎[b]	**0 (D1)**	**4**	**8**	**12**	**16** *EOT*[c]	**16 + 1 day** ☎[b]	Visit Windows: Visit 1: 7 to 17 days before Visit 3; Visit 2: may be adjusted as appropriate to accommodate Visit 3 date; Visits 4 to 6: ±2 days; Visit 7: ±3 days; Visit 8: +2 days.
Day	-14[a]	-7	1	28	56	84	112	113	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
FPG			X		X	X	X		All fasting blood samples collections should take place prior to IMP administration.
Central laboratory									
PK sampling[e]							X		
HbA1c	X		X		X		X		
C-peptide (fasting)	X								
Anti-insulin aspart antibodies (AIA)			X		X	X	X		Antibody sampling at least 8 hours after the last SAR341402 or NovoLog dose, thus participants should come fasting, without injecting their meal-time insulin at all visits where AIAs are measured.
Anti-insulin aspart neutralizing antibodies			X		X	X	X		
Safety laboratory									
Hematology	X						X		See Appendix 2 (Section 10.2)
Clinical chemistry	X						X		See Appendix 2 (Section 10.2)
Pregnancy test (WOCBP only)	X		X		X		X		Serum pregnancy test for screening; urine pregnancy test for subsequent monitoring; additional testing per site's processes is permitted
Serum FSH and estradiol (Menopausal women only)	X								
AE/SAE/AESI reporting	Throughout the study								Report SAE and AESI to the Sponsor within 24 hours

	Screening		Open-label Treatment Period					Follow-up	Notes
Week	**-2**[a]	**-1** ☎[b]	**0 (D1)**	**4**	**8**	**12**	**16** ***EOT***[c]	**16 + 1 day** ☎[b]	Visit Windows: Visit 1: 7 to 17 days before Visit 3; Visit 2: may be adjusted as appropriate to accommodate Visit 3 date; Visits 4 to 6: ±2 days; Visit 7: ±3 days; Visit 8: +2 days.
Day	-14[a]	-7	1	28	56	84	112	113	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Concomitant medications	Throughout the study								
Hypoglycemia recording	Throughout the study								Details must be provided in case of SMPG ≤3.9 mmol/L (70 mg/dL) and/or in case of symptoms suggesting hypoglycemia

a In situations where not all conditions required for the participant's randomization are met, the screening period may be extended by up to a maximum of 3 days after the 2-week period as reflected in the "Notes" column for the Visit 1 window

b Mandatory telephone visit or optional on-site visit

c Or early IMP discontinuation (note that serial PK samples should only be collected at the time of early discontinuation visit and do not need to be repeated at Visit 7 even if participant remains in the study)

d Self-measured plasma glucose:

- Regular pre- postprandial and nocturnal SMPG is recommended throughout the study for optimal adjustment of the insulin regimen. These SMPGs support optimization of the basal and meal-time insulin dose. The results will be discussed between Investigator and participant during scheduled and unscheduled visits at the discretion of the Investigator;
- In case of hypoglycemic symptoms: whenever experienced (if possible prior to countermeasure, unless safety considerations necessitate immediate glucose/carbohydrate rescue prior to confirmation)

e Participants have to present at the site in fasting condition without having injected meal-time insulin in the morning (last meal-time insulin injection at least 8 hours prior to blood draw). Blood will be collected for the determination of insulin aspart concentrations as detailed in the PK flow chart below (Table 1). If additional meal-time insulin is needed during this period, human insulin must be administered. Alternatively, administration of insulin lispro at low doses, according to the Investigator's judgement, is also permitted. For study participants who definitively discontinue their IMP but continue in the study, PK blood sampling will be performed at the time of the Early Termination visit only (it will not be done at Visit 7 as well). Please refer to specific laboratory manual for details on blood sampling

AE: adverse event; AESI: adverse event of special interest; AIA: anti-insulin aspart antibody; BMI: body-mass index; EOT: end of treatment; FPG: fasting plasma glucose; FSH: follicle-stimulating hormone; HbA1c: glycated hemoglobin A1c; IMP: investigational medicinal product; IRT: interactive response technology; NIMP: non-investigational medicinal product; PK: pharmacokinetics; SAE: serious adverse event; SMPG: self-measured plasma glucose; WOCBP: woman of childbearing potential

1.3.2 SoA for participants with run-in

This SoA is valid for participants who have not been on NovoLog and insulin glargine (100 U/mL) for at least 12 weeks before the screening visit.

	Screening	Run-in		Open-label Treatment Period					Follow-up	Notes
Week	**-14**	**-12**[-]	**-1** ☎[-]	**0 (D1)**	**4**	**8**	**12**	**16** ***EOT***[-]	**16 + 1 day** ☎[-]	Visit Windows: Visit 1: 4 to 14 days before Visit RI; Visit RI: up to 87 days[-] before Visit 3 Visit 2: may be adjusted as appropriate to accommodate Visit 3 date; Visits 4 to 6: ±2 days; Visit 7: ±3 days; Visit 8: +2 days.
Day	-98	-84[-]	-7	1	28	56	84	112	113	
Visit	**1**	**RI**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Informed consent	X									Prior to any study-related procedures being performed.
Inclusion and exclusion criteria	X	X	X	X						Recheck eligibility before randomization.
Demography, medical/surgical/medication history, diabetes history	X									Including alcohol, drug abuse, and smoking history.
Physical examination	X							X		See Section 8.2.1
Blood pressure and heart rate	X			X				X		See Section 8.2.2
Body weight	X			X				X		
Height and BMI	X									
Dispensation of study glucometer/supplies and diary	X									Supplies may be re-dispensed any time during the study, as necessary.
Training and retraining on glucometer use, SMPG, hypoglycemia awareness and management, diary use and IMP/NIMP dosage self-adjustment	X	X	X	X	X	X	X			Site will provide training at Visits 1, RI, and 3; regular refresher instructions will be provided at noted visit or as necessary throughout the study.

	Screening	Run-in		Open-label Treatment Period					Follow-up	Notes
Week	**-14**	**-12**[-]	**-1** ☎[-]	**0 (D1)**	**4**	**8**	**12**	**16** ***EOT***[-]	**16 + 1 day** ☎[-]	Visit Windows: Visit 1: 4 to 14 days before Visit RI; Visit RI: up to 87 days[-] before Visit 3 Visit 2: may be adjusted as appropriate to accommodate Visit 3 date; Visits 4 to 6: ±2 days; Visit 7: ±3 days; Visit 8: +2 days.
Day	-98	-84[-]	-7	1	28	56	84	112	113	
Visit	**1**	**RI**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Diet and lifestyle counseling	X	X	X	X	X	X	X	X	X	As per current practice
IRT contact	X			X	X	X	X	X	X	Additional IRT contact (eg, to request additional IMP/NIMP) is permitted, as necessary
Background therapy dispensation (NovoLog and Lantus)		X								If necessary for NovoLog or Lantus resupply, or as deemed appropriate by the Investigator to ensure participant's oversight, the participants may undergo unscheduled visit(s), as appropriate.
Background therapy administration (NovoLog and Lantus)		←----------→								All study participants must take NovoLog and insulin glargine (100 U/mL) for at least 12 weeks before randomization
Randomization				X						Randomization must be performed only after all baseline evaluations have been done and eligibility of the participant has been confirmed
IMP and NIMP dispensation				X	X	X	X			Additional dispensing visits are permitted if necessary
Study intervention (IMP and NIMP administration)				←----------→						
Review of insulin dose		X	X	X	X	X	X	X		According to the Sponsor's instructions
Counting/collecting used and unused pens/Compliance check				X	X	X	X	X		At Visit 3, study participants will be asked to return their used and unused NIMP pens; no compliance check will be performed

	Screening	Run-in		Open-label Treatment Period					Follow-up	Notes
Week	**-14**	**-12**	**-1 ☎**	**0 (D1)**	**4**	**8**	**12**	**16 *EOT***	**16 + 1 day ☎**	Visit Windows: Visit 1: 4 to 14 days before Visit RI; Visit RI: up to 87 days before Visit 3 Visit 2: may be adjusted as appropriate to accommodate Visit 3 date; Visits 4 to 6: ±2 days; Visit 7: ±3 days; Visit 8: +2 days.
Day	-98	-84	-7	1	28	56	84	112	113	
Visit	**1**	**RI**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Diary data review and medical evaluation by Investigator		X	X	X	X	X	X	X		In addition to the scheduled visits, medical evaluation must also be performed in between visits, if data is available for review by the Investigator.
SMPG	X	X	X	X	X	X	X	X		
FPG				X		X	X	X		All fasting blood samples collections should take place prior to IMP administration.
Central laboratory										
PK sampling								X		
HbA1c	X			X		X		X		
C-peptide (fasting)	X									
Anti-insulin aspart antibodies (AIA)				X		X	X	X		Antibody sampling at least 8 hours after the last SAR341402 or NovoLog dose, thus participants should come fasting, without injecting their meal-time insulin at all visits where AIAs are measured.
Anti-insulin aspart neutralizing antibodies				X		X	X	X		
Safety laboratory										
Hematology	X			X				X		See Appendix 2 (Section 10.2)
Clinical chemistry	X			X				X		See Appendix 2 (Section 10.2)

	Screening	Run-in		Open-label Treatment Period					Follow-up	Notes
Week	**-14**	**-12**-	**-1** ☎-	**0 (D1)**	**4**	**8**	**12**	**16** ***EOT***-	**16 + 1 day** ☎-	Visit Windows: Visit 1: 4 to 14 days before Visit RI; Visit RI: up to 87 days- before Visit 3 Visit 2: may be adjusted as appropriate to accommodate Visit 3 date; Visits 4 to 6: ±2 days; Visit 7: ±3 days; Visit 8: +2 days.
Day	-98	-84-	-7	1	28	56	84	112	113	
Visit	**1**	**RI**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Pregnancy test (WOCBP only)	X	X		X		X		X		Serum pregnancy test for screening; urine pregnancy test for subsequent monitoring; additional testing per site's processes is permitted
Serum FSH and estradiol (Menopausal women only)	X									
AE/SAE/AESI reporting	Throughout the study									Report SAE and AESI to the Sponsor within 24 hours
Concomitant medications	Throughout the study									
Hypoglycemia recording	Throughout the study									Details must be provided in case of SMPG ≤3.9 mmol/L (70 mg/dL) and/or in case of symptoms suggesting hypoglycemia

- To ensure that the minimum of 12-week duration on NovoLog and insulin glargine (100 U/mL) is achieved and to facilitate participant's scheduling, the run-in period may be extended by up to a maximum of 3 days after the 12-week period
- Mandatory telephone visit or optional on-site visit
- Or early IMP discontinuation (note that serial PK samples should only be collected at the time of early discontinuation visit and do not need to be repeated at Visit 7 even if participant remains in the study)
- Self-measured plasma glucose:
- Regular pre- postprandial and nocturnal SMPG is recommended throughout the study for optimal adjustment of the insulin regimen. These SMPGs support optimization of the basal and meal-time insulin dose. The results will be discussed between Investigator and participant during scheduled and unscheduled visits at the discretion of the Investigator;
- In case of hypoglycemic symptoms: whenever experienced (if possible prior to countermeasure, unless safety considerations necessitate immediate glucose/carbohydrate rescue prior to confirmation)
- Participants have to present at the site in fasting condition without having injected meal-time insulin in the morning (last meal-time insulin injection at least 8 hours prior to blood draw). Blood will be collected for the determination of insulin aspart concentrations as detailed in the PK flow chart below (Table 1). If additional meal-time insulin is needed during this period, human insulin must be administered. Alternatively, administration of insulin lispro at low doses, according to the Investigator's judgement, is also permitted. For study participants who definitively discontinue their IMP but continue in the study, PK blood sampling will be performed at the time of the Early Termination visit only (it will not be done at Visit 7 as well). Please refer to specific laboratory manual for details on blood sampling

AE: adverse event; AESI: adverse event of special interest; AIA: anti-insulin aspart antibody; BMI: body-mass index; EOT: end of treatment; FPG: fasting plasma glucose; FSH: follicle-stimulating hormone; HbA1c: glycated hemoglobin A1c; IMP: investigational medicinal product; IRT: interactive response technology; NIMP: non-investigational medicinal product; PK: pharmacokinetics; SAE: serious adverse event; SMPG: self-measured plasma glucose; WOCBP: woman of childbearing potential

1.3.3 Pharmacokinetic flow-chart

Table 1 - Pharmacokinetic flow chart

	End of Treatment (Week 16 or Early Discontinuation Visit)																														
Time	**0h 00**	**0h 10**	**0h 20**	**0h 30**	**0h 40**	**0h 50**	**1h 00**	**1h 10**	**1h 20**	**1h 30**	**1h 40**	**1h 50**	**2h 00**	**2h 15**	**2h 30**	**2h 45**	**3h 00**	**3h 15**	**3h 30**	**3h 45**	**4h 00**	**4h 20**	**4h 40**	**5h 00**	**5h 20**	**5h 40**	**6h 00**	**6h 30**	**7h 00**	**7h 30**	**8h 00**
Win-dow (min)		±2	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
PK sample	P00	P01	P02	P03	P04	P05	P06	P07	P08	P09	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22	P23	P24	P25	P26	P27	P28	P29	P30

- Predose

PK: pharmacokinetics

2 INTRODUCTION

SAR341402 is insulin aspart, a human insulin analog of recombinant deoxyribonucleic acid (DNA) origin. Insulin aspart is the active ingredient of a rapid-acting insulin product currently marketed as NovoLog in the US and NovoRapid® in Europe. SAR341402 solution for injection is being developed as interchangeable biosimilar to NovoLog in accordance with the relevant guidelines (2, 3, 4).

2.1 STUDY RATIONALE

Per FDA Guidance (1), a biological product is considered interchangeable with the reference product if the information submitted is sufficient to show that the biological product "is biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient" and that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch." Biosimilarity is generally supported by similarity in overall level of antibody produced to the proposed biosimilar and the reference product. Differences in immune responses may be detected in a switching study. Indeed, with switching between the proposed biosimilar and the reference product, repeated exposure to each product can prime the immune system to recognize subtle structural differences between products, which may theoretically increase the overall immune response. This immunologic response is highly dependent on the structural differences between the proposed interchangeable product and the comparator product and other potential differences between the products (eg, impurities).

Study EFC15178 (Gemelli X) is designed to generate data to support the argument that SAR341402 solution is interchangeable with the intended reference product, NovoLog, for the treatment of diabetes mellitus and that switching between SAR341402 solution and NovoLog will not pose an additional risk beyond that of using NovoLog alone. The study takes into consideration the general principles as delineated in Section 351(k)(4)(A) of the PHS Act (Safety standards for determining interchangeability) and FDA's Considerations in Demonstrating Interchangeability with a Reference Product Guidance for Industry (1).

The primary objective of study EFC15178 will be to demonstrate similarity in PK exposure of SAR341402 and NovoLog US 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. The secondary objectives will be the comparison of the immunogenicity of alternating administration of SAR341402 and NovoLog versus continuous use of NovoLog in terms of number of participants with treatment-emergent AIAs, the comparison of T_{max}, and the evaluation of safety (hypoglycemia and AEs, including SAEs, hypersensitivity reactions, and injection site reactions). Additional AIA-related parameters, including the clinical effects of treatment-emergent AIAs on efficacy (HbA1c), insulin dose, and safety (hypoglycemia, hypersensitivity reaction, injection site reaction) will be assessed as part of the tertiary objectives of the study.

2.2 BACKGROUND

In vitro nonclinical pharmacology and physicochemical characterization studies were conducted to thoroughly demonstrate the biological and structural/compositional similarity of insulin aspart SAR341402 and insulin aspart supplied as NovoLog and NovoRapid. Similar PK exposure and PD activity were demonstrated for SAR341402 solution to both NovoLog and NovoRapid, as well as between NovoLog and NovoRapid in a PK/PD study using the euglycemic clamp technique in patients with T1DM study (PDY12695). All treatments were well tolerated with no relevant difference in safety related parameters between the treatments.

A Phase 3 study is currently being conducted to compare efficacy and safety including immunogenicity of SAR341402 and NovoLog/NovoRapid when used in combination with Lantus in participants with T1DM and T2DM (study EFC15081). Objectives of the study are to compare the efficacy, safety and immunogenicity of SAR341402 solution with NovoLog in the US and NovoRapid in the European Union (EU) to further support similarity of SAR341402 solution and NovoLog and NovoRapid.

2.3 BENEFIT/RISK ASSESSMENT

Adults with T1DM who are currently on a multiple daily injection regimen will be eligible to participate. Due to the objectives of the study and duration of treatment, eligible participants will not immediately benefit from the outcome of this study.

NovoLog, the comparator IMP used in the current study, is indicated for the treatment of patients with diabetes mellitus and has been marketed in the US since 2000. Its safety and efficacy profile is well documented. The adverse reactions observed with NovoLog (US) are known in the pharmacological class of blood glucose lowering drugs and common to insulin products. A comparable safety and efficacy profile to that of NovoLog is expected for SAR341402 solution.

As therapeutic proteins, insulin and insulin analogues may trigger immunological responses, although clinically meaningful immunological reactions were reported mostly for animal insulin products and are rarely reported for highly purified recombinant insulin analogues (5, 6). Based on these considerations, the relatively low structural complexity of insulin aspart and the analytical similarity of SAR341402 to NovoLog shown in physicochemical characterizations, and based on Phase 1 results, no meaningful differences in the immunogenicity of SAR341402 and NovoLog are expected to be found in study EFC15178.

More detailed information about the known and expected benefits and risks and reasonably expected AEs associated with SAR341402 may be found in the Investigator's Brochure (7).

Further details on NovoLog can be found in the US product information (8).

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
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 Type 1 diabetes mellitus (T1DM) also using insulin glargine	AUC_{last}, AUC, and C_{max} following injection of a predefined, fixed dose of SAR341402 or NovoLog (0.15 U/kg) at Week 16
Secondary	
To compare the effects of alternating administration of SAR341402 and NovoLog with continuous use of NovoLog on immunogenicity	Number of participants with treatment-emergent anti-Insulin aspart antibodies (AIAs) during the 16-week treatment period
To evaluate the safety of alternating administration of SAR341402 and NovoLog versus continuous use of NovoLog	Safety evaluations, which will include evaluation of the following (for the 16-week treatment period): • Number of participants with at least one hypoglycemic event - Number of hypoglycemic events per participant-year - Number of participants with adverse events (AEs) (see Section 8.3)
To compare other PK parameters between the two treatment arms (alternating administration of SAR341402 and NovoLog and continuous use of NovoLog)	Time to C_{max} (T_{max}) following injection of a predefined, fixed dose of SAR341402 or NovoLog (0.15 U/kg) at Week 16
Tertiary/exploratory	
To compare the effects of alternating administration of SAR341402 and NovoLog with continuous use of NovoLog on insulin dose	Change in Insulin dose (basal, meal-time [SAR341402 or NovoLog], total) from baseline to Week 16
To compare the effects of alternating administration of SAR341402 and NovoLog with continuous use of NovoLog on glycemic control	Change from baseline to Week 16 in HbA1c Change from baseline to Week 16 in FPG
To compare clinical effects of treatment-emergent AIAs on glycemic control, insulin dose and safety	Clinical effects of AIAs on efficacy (HbA1c), insulin dose and safety (hypoglycemia, hypersensitivity reactions, injection site reactions)

Objectives	Endpoints
To compare the effects of alternating administration of SAR341402 and NovoLog with continuous use of NovoLog on additional immunogenicity parameters	Number of participants with treatment-induced AIA (among the participants AIA-negative or missing at baseline) (during the 16-week treatment period) Number of participants with treatment-boosted AIA (among the participants AIA-positive at baseline) (during the 16-week treatment period) Number of participants by AIA status (positive/negative) at baseline, Week 8, Week 12 and Week 16 Anti-Insulin aspart antibody titer at baseline, Week 8, Week 12 and Week 16 Number of participants by AIA cross-reactivity to human insulin at baseline, Week 8, Week 12 and Week 16 Number of participants by anti-insulin aspart neutralizing antibody status (positive/negative) at baseline, Week 8, Week 12 and Week 16
To compare clinical effects of treatment-emergent neutralizing antibodies on glycemic control and insulin dose	Clinical effects of anti-insulin aspart neutralizing antibodies on efficacy (HbA1c) and insulin dose

3.1 APPROPRIATENESS OF MEASUREMENTS

The primary endpoints will be AUC_{last}, AUC, and C_{max} following injection of a single dose of 0.15 U/kg SAR341402 (in the switching arm) or NovoLog (in the non-switching arm) at Week 16. As the rapid-acting insulins SAR341402 and NovoLog are used flexibly as prandial insulin at meal-times, no dosing intervals can be defined. Consequently, the primary endpoints will be C_{max}, AUC_{last}, and AUC and not AUC_{tau} as proposed in the FDA Guidance for Interchangeability (1). Blood samples for these PK measurements will be taken for an 8-hour period, taking into account the PK profile of SAR341402 observed in the previous Phase 1 study PDY12695. In this study, a median T_{max} of approximately 1.2 hour and a mean half-life of approximately 1.2 hours were observed for SAR341402. Thus, an 8-hour sampling period is deemed appropriate to sufficiently cover (90% of AUC according to FDA guidance) individual PK profiles.

HbA1c is an index of average glucose over the preceding weeks-to-months. It is a "weighted" average of blood glucose levels during the preceding 120 days, as glucose levels in the 30 days prior to the measurement contribute substantially more to the level of HbA1c than do glucose levels 90-120 days earlier (9). HbA1c is also the most widely accepted measure of overall, long-term blood glucose control in patients with diabetes (4, 10).

HbA1c will be determined in a central laboratory blinded to study treatment. The assessment of HbA1c and insulin dose changes will support the assessment of the clinical relevance of treatment emergent AIAs and any outliers identified in the PK analysis. As the study is not powered for efficacy evaluations, the data obtained will be considered of supportive value only to the (primary) PK and (secondary) immunogenicity data obtained.

Immunogenicity analyses will include the determination of the AIA status, AIA titers, anti-insulin aspart neutralizing antibodies, and cross-reactivity with human insulin. The potential impact of AIAs on safety, particularly as related to hypersensitivity reactions and local injection site reactions will be evaluated. Anti-insulin aspart antibodies may change the PK and PD of the insulin by binding the insulin, resulting in an overall unstable glycemic control. Therefore, the potential effect of AIAs on glycemic control (HbA1c), insulin dose and hypoglycemia will also be assessed.

The general safety evaluation will include hypoglycemia (classification according to American Diabetes Association definition) (11, 12, 13), AEs, including SAEs, hypersensitivity reactions and injection site reactions.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a randomized, open-label, active-controlled, 2-arm parallel-group multicenter Phase 3 trial in adults with T1DM also using insulin glargine.

Upon confirmation of eligibility based on the screening procedures, participants who have not been on NovoLog and insulin glargine (100 U/mL) for at least 12 weeks before screening will complete a run-in period of up to 12 weeks during which they will be administered NovoLog and Lantus. Run-in period duration will be such that, at the time of randomization, the participants have been on NovoLog and insulin glargine (100 U/mL) for at least 12 weeks.

Participants will be randomized 1:1 to 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 flow-chart in Section 1.2.

Randomization will be stratified by HbA1c (<8.0%, ≥8.0%) obtained at the screening visit (Visit 1).

Insulin glargine 100 U/mL (Lantus) will be administered as mandatory background therapy throughout the treatment period of the study.

At the end of the 16-week study treatment, participants will have blood sampling, including for PK determination, antibody measurements, HbA1c, and FPG. Participants need to come to the site fasting without having injected any meal-time insulin (SAR341402 or NovoLog) for at least 8 hours. After blood sampling for the trough PK measurements, participants 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 (Table 1). During the 8-hour PK period, the Investigator must closely oversee the patient and manage any hypoglycemia or hyperglycemia that the patient may experience according to his/her medical judgement and the protocol requirements. Specifically, countermeasures are to be administered if hypoglycemia is experienced and human insulin must be administered if additional meal-time insulin is needed during this period. Alternatively, administration of insulin lispro at low doses, according to the Investigator’s judgement, is also permitted. Additionally, the breakfast content on the day of PK visit will be determined per the Investigator’s judgement, with focus on prevention of hypoglycemia or significant hyperglycemia during this period.

The study will include an up to 2-week 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, and 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).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

In accordance with the FDA guidance on interchangeability (1), the study is designed to demonstrate PK similarity of SAR341402 and NovoLog after 4x4-week periods of alternating administration of SAR341402 and NovoLog compared to 16-week continuous use of NovoLog.

The study is an open-label design as the test and control IMPs are easily identifiable. However, measures to minimize bias will be implemented (for details see Section 6.3).

Participants with T1DM on insulin treatment for at least one year who have been on basal bolus therapy using insulin glargine (100 U/mL) for at least 12 weeks and NovoLog for at least 12 weeks (either prior to Visit 1 or following the run-in period) are eligible for randomization in the study.

Participants with T1DM are deemed adequately sensitive to detect differences in the PK (primary endpoint) due to their lack of endogenous insulin. Additionally, due to the underlying autoimmune disorder, this population is considered more sensitive to evaluate potential differences in the immune response and the effects of AIAs on efficacy and safety, when compared with the type 2 diabetes mellitus population (5).

Due to the relatively short duration of action of SAR341402 and NovoLog and their clinical use as rapid-acting insulin products, no accumulation occurs and thus steady state conditions do not need to be established. Therefore no lead-in period is required for participants pre-treated with insulin glargine (100 U/mL) as basal insulin and NovoLog as meal-time insulin for at least 12 weeks. This pre-treatment is considered to be of sufficient duration to ensure that all participants are on a stable insulin regimen before randomization. Participants not pre-treated with NovoLog and insulin glargine (100 U/mL) for at least 12 weeks need to be enrolled into a run-in period to establish stable conditions.

When SAR341402 solution is approved and marketed, patients may potentially switch between SAR341402 solution and NovoLog. With switching, multiple exposures to each product can prime the immune system to recognize subtle structural differences between products, which may theoretically increase the overall immune response. This immunologic response is highly dependent on the structural differences between the proposed interchangeable product and the comparator product and other potential differences between the products (eg, impurities).

The 16-week treatment duration has been chosen to ensure a sufficiently long treatment duration to assess HbA1c as efficacy parameter. The 4-week duration of each treatment period in the "switching arm" has been chosen to ensure a sufficiently long treatment duration to assess development of AIA in each treatment cycle. Potential allergic reactions may occur within hours post injection at any time during the treatment; however, as mentioned in Section 2.3, these reactions are very rare for highly purified insulin analogues including NovoLog (14).

AIAs of the immunoglobulin G isotype usually appear about 2 weeks after first exposure to the antigen, or, in case of a re-exposure to the antigen ("secondary response"), even earlier within 1 week (15, 16, 17), thus, these AIA responses would occur well within the planned study period of 16 weeks and 4 week exposure intervals in the "switching group".

4.3 JUSTIFICATION FOR DOSE

After randomization, participants in both treatment arms will continue to individually dose and titrate NovoLog per the standard of care as judged by the Investigator.

It is recommended that the study drug doses are titrated to achieve a 2 hour postprandial plasma glucose of <180 mg/dL (10 mmol/L) while avoiding hypoglycemia and taking into consideration the content of the meal. Good clinical judgment is to be exercised while titrating the meal-time insulin dose.

In both treatment arms insulin doses of 0.15 U/kg will be administered for PK assessment. This dose is considered sufficient to cover for carbohydrate intake during breakfast without significantly increasing the risk of hypoglycemia (appropriate meal-adjustments and/or potential administration of countermeasures are to be performed by the Investigators to ensure minimization and mitigation of any such risks) and also to provide interpretable insulin profiles over the PK assessment period of 8 hours.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last visit of the last participant in the study (as scheduled per protocol [PP]).

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be at least 18 years of age, inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with T1DM.

I 03. Type 1 diabetes diagnosed at least 12 months before screening.

I 04. Participants on continuous insulin treatment for at least 12 months prior to screening.

I 05. Participants exclusively on a multiple (≥3) daily injection insulin analogue regimen using:

a NovoLog as mealtime insulin for at least 12 weeks prior to screening.

AND

b Insulin glargine (100 U/mL) as basal insulin for at least 12 weeks prior to screening.

Note: Participants not meeting this criterion may also qualify, provided that they complete the run-in period during which NovoLog and Lantus will be administered so that, at the time of randomization, the participants have been on NovoLog and insulin glargine (100 U/mL) for at least 12 weeks (including any potential pre-screening administration).

Note: Off-label twice-daily (BID) dosing of insulin glargine is not permitted during the study and any participant administering Lantus BID prior to the study must be switched to once-daily (QD) dosing after signing the Informed Consent for the study (daily time of administration to be agreed between the participant and the study doctor).

I 06. HbA1c less or equal to 10% (85.79 mmol/mol) at screening.

Note: The Sponsor will monitor baseline HbA1c levels and may limit enrollment of participants with HbA1c values <7.0% at a certain point during the conduct of the study to ensure an acceptably high average HbA1c for the study. Sites will be appropriately and timely informed if and when such a decision has been reached.

Weight

I 07. Body mass index ≤35 kg/m² at screening.

Sex

I 08. Male or Female.

- Female participants: A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least one of the following conditions applies:
  - Not a WOCBP as defined in Appendix 4 (Section 10.4),

    OR
  - A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the intervention period and for at least 5 weeks after the last dose of study intervention.

Informed Consent

I 09. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Any clinically significant abnormality identified either in medical history, during physical examination, laboratory tests, or vital signs at the time of screening or any AE during screening period which, in the judgment of the Investigator, would preclude safe completion of the study or constrains PK, immunogenicity, safety, or efficacy assessments.

E 02. Pancreatectomy and/or islet cell transplantation.

E 03. Severe renal disease defined as estimated glomerular filtration rate (GFR) (modification of diet in renal disease [MDRD] formula) <30 mL/min/1.73/m² or on renal replacement treatment.

E 04. Known presence of factors that interfere with the HbA1c measurement (eg, specific hemoglobin variants, hemolytic anemia) compromising the reliability of HbA1c assessment or medical conditions that affect interpretation of HbA1c results (eg, blood transfusion or severe blood loss in the last 3 months prior to randomization, any condition that shortens erythrocyte survival).

E 05. Laboratory findings at screening:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times upper limit of the normal (ULN). Or
- Total bilirubin >1.5 times ULN (except in case of documented Gilbert's syndrome).

E 06. History of severe hypoglycemia requiring emergency room admission or hospitalization within 3 months prior to screening.

E 07. Hospitalization for recurrent diabetic ketoacidosis within 3 months prior to screening.

E 08. Retinopathy or maculopathy with one of the following treatments, either recent (within 3 months of screening) or planned: intravitreal injections or laser or vitrectomy surgery.

Prior/concomitant therapy

E 09. Likelihood to require treatment prohibited by the protocol during the study.

E 10. Use of glucose lowering treatments other than the multiple dose injection (MDI) and basal insulin regimen, as described in I 05 (including use of insulin pump therapy), within 12 weeks prior to screening.

E 11. Participants having received systemic glucocorticoids for one week or more within 3 months prior to screening (topical, nasal spray, inhaled or intra-articular applications are allowed).

E 12. Participants having received systemic immunosuppressive agents within 6 month prior to screening (please refer to E 11 for restrictions related to glucocorticoids).

Prior/concurrent clinical study experience

E 13. Exposure to any investigational drugs in the last 4 weeks or 5 half-lives, whichever is longer, prior to screening or concomitant enrollment in any other clinical study involving an investigational study treatment. Patients having received SAR341402 at any time prior to screening are not permitted to participate in the study.

Diagnostic assessments

Not applicable.

Other exclusions

E 14. Any contraindication to use of insulin glargine and/or NovoLog as defined in the national product labels.

E 15. Hypersensitivity to any of the study treatments, or components thereof.

E 16. History of drug or alcohol abuse within 6 months prior to screening.

E 17. Night shift workers.

E 18. Participant is an employee of the Sponsor, or is the Investigator or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

Additional criteria at the end of the screening period (for participants who do not undergo run-in) or at the end of the run-in period (for participants who undergo run-in)

E 19. Participants unwilling or unable to comply with study procedures as outlined in the protocol.

E 20. Participants who withdraw consent during the screening period (starting from signed ICF) or the run-in period.

E 21. Participants who used glucose lowering treatments other than Novolog and insulin glargine (100 U/mL) (including use of insulin pump therapy) during the screening period (for participants who do not undergo run-in) or run-in period (if applicable).

5.3 LIFESTYLE CONSIDERATIONS

Lifestyle and diet recommendations will be given by trained and qualified study staff at Screening and during the study and should be consistent with international or local guidelines for participants with T1DM. Compliance with the diet and lifestyle counseling will be assessed and discussed with the participant throughout the study.

Fasting conditions

- For all on-site study visits (except for Visit RI [run-in; if applicable] and Visit 4 [Week 4]), participants need to come to the study center after an overnight fast of at least 8 hours, consisting of no food or liquid intake, other than water, and no meal-time insulin injection.
- Fasting (pre-breakfast) SMPGs to be performed based on SoA.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention (including patients who failed study eligibility during the screening or run-in period). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. In cases where original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment, the participant can be rescreened one time for this study. A participant must not be randomized more than once (ie, entered the randomized period twice).

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

The IMPs are SAR341402 (tested drug) and NovoLog (comparator drug) for SC injection administered during the treatment period.

Insulin glargine 100 U/mL (Lantus), which will be used as mandatory background insulin therapy during the run-in (if applicable) and treatment periods, along with NovoLog, which will be administered during the run-in period to the applicable participants, are considered the NIMPs.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 3 - Overview of study interventions administered

Study intervention name	SAR341402	NovoLog-US	Lantus
Dosage formulation	100 U/mL solution for SC injection supplied in 3-mL cartridges in a SoloStar disposable pen	100 U/mL solution for SC injection in the NovoLog FlexPen disposable pen	100 U/mL solution for SC injection in 3-mL cartridges as Lantus SoloStar disposable pen
Unit dose strength(s)/Dosage level(s)	Each pen contains in total 300 units of SAR341402 (3 mL of 100 units/mL SAR341402 solution). This pen allows dose setting in the range of 1 to 80 units with minimum of 1 unit increment	Each pen contains in total 300 units of insulin aspart (3 mL of 100 units/mL insulin aspart solution). This pen allows dose setting in the range of 1 to 60 units with minimum of 1 unit increment	Each pen contains in total 300 units of insulin glargine (3 mL of 100 units/mL insulin glargine solution). This pen allows dose setting in the range of 1 to 80 units with minimum of 1 unit increment.
Route of administration	SC injection	SC injection	SC injection
Dosing instructions	Every effort will be made to inject the SAR341402 or NovoLog immediately (within 5-10 minutes) before a meal. Occasional postprandial injection soon after meal intake may be done if deemed necessary and if allowed by the national product label for NovoLog.		Inject SC once daily consistent with the local label. Off-label twice-daily (BID) dosing of insulin glargine is not permitted during the study and any participant administering Lantus BID prior to the study must be switched to once-daily (QD) dosing after signing the Informed Consent for the study (daily time of administration to be agreed between the participant and the study doctor).

Study intervention name	SAR341402	NovoLog-US	Lantus
Dosing instructions (continued)	SAR341402 and Novolog will be self-administered by SC injection, in the abdominal wall, buttock, thighs, or upper arms. The area of the injections will be consistent with the habits of the individual participant. Within that area, injection sites will be changed (rotated) at each time. Changes in the area of injection during the study should be avoided as far as possible. It is recommended that, for participants randomized in the IMP switching arm, SAR341402 and Novolog will be injected on different sides (left or right) of the body. The starting dose of NovoLog will be the same (Unit for Unit) as the insulin aspart dose used at the end of the screening or run-in period. If the participant is not on insulin aspart at the end of the screening period, the starting dose will be determined by the Investigator in agreement with the national product label. Changes in the SAR341402 or NovoLog dose will be based on SMPG values and the meal content (when available). It is recommended that doses will be titrated by the participants to achieve a 2-hour PPG of <10 mmol/L (180 mg/dL) while avoiding hypoglycemia, according to the Investigator's instructions. If pre-prandial glucose tests are used, the target range of 4.4 to 7.2 mmol/L (80 to 130 mg/dL) is recommended. For the purpose of this protocol, 2 hours postprandial is defined as 2 hours after the start of the meal. Glycemic targets may be adapted for individual participants, if deemed necessary, eg, due to age, comorbid conditions, and individual considerations. The individual targets will be recorded in source documents. The doses of the meal-time insulin will be reviewed when the basal insulin dose is increased, as they may have to be reduced to avoid daytime hypoglycemia. In the non-switching arm, NovoLog will be administered for 16 weeks. In the switching arm, NovoLog will be administered alternately with SAR341402, starting with NovoLog for 4 weeks, followed by SAR341402 for 4 weeks, then NovoLog for 4 weeks and ending with SAR341402 for the last 4 weeks (ie, a total of 4 x 4-week treatment periods with 3 switches). At the end of Week 16, a 0.15 U/kg of SAR341402 in the switching arm or NovoLog in the non-switching arm will be given in fasting conditions. Mixing of either SAR341402 or NovoLog with other insulin is not allowed nor is dilution.		The area for the injection sites for Lantus injection must be different from that of the IMP. The time of injection will be fixed at randomization (Visit 3, Baseline) according to participant and Investigator's preference and maintain (±2 hours) throughout the study. The starting dose of Lantus will be the same as the last dose of insulin glargine used at the end of the screening or run-in period. If the participant is not on Lantus at the end of the screening period, the starting dose will be determined by the Investigator in agreement with the national product label. Changes in the Lantus dose are based on fasting/ prebreakfast SMPG values. Lantus doses can be titrated by the participant, according to the Investigator's instructions, to achieve fasting, pre-breakfast SMPG of 4.4 to 7.2 mmol/L (80 to 130 mg/dL), while avoiding hypoglycemia. The increase of the Lantus dose should not exceed 10% of the daily dose of Lantus, unless deemed necessary, according to the clinical judgement of the Investigator. The Investigator may choose to change the rapid-acting insulin doses instead of increasing the basal insulin dose. Whenever the basal insulin dose is changed, the rapid-acting insulin doses need to be reviewed to avoid hypoglycemia. Mixing of Lantus with other insulin is not allowed nor is dilution.

Study intervention name	SAR341402	NovoLog-US	Lantus
Packaging and labeling	Both NovoLog and Lantus will be provided during the run-in period (if applicable). Efforts will be made to dispense the appropriate number of kits to cover up to the randomization visit. However, if necessary according to the Investigator, the study participants may undergo unscheduled visits for resupply and to ensure Investigators' oversight. Commercially available NovoLog (NIMP) and Lantus (NIMP) will be additionally labeled. The content of the labeling will be in accordance with the local regulatory specifications and requirements. Study treatment will be provided during the treatment period in accordance with the administration schedule. The appropriate number of kits will be dispensed to cover up to the next dispensing visit. Commercially available comparator NovoLog and NIMP (Lantus) will be repackaged in study specific kits and relabeled. The content of the labeling is in accordance with the local regulatory specifications and requirements for the IMP and the NIMP.		

Between the protocol-scheduled on-site visits, interim visits may be required for both IMP and NIMP dispensing. As an alternative to these visits, IMP and/or NIMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP and NIMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of storage conditions for IMP and NIMP provided by the Sponsor, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the IMP and NIMP will be managed according the rules provided by the Sponsor.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The site will instruct the participant to store the in-use prefilled pens (IMP and NIMP) in accordance with the storage conditions indicated on the label of each product.

Any quality issue noticed with the receipt or use of an IMP/NIMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.6).

A potential defect in the quality of IMP/NIMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP/NIMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP/NIMP to a third party (except for direct-to-patient shipment, for which a courier company has been approved by the Sponsor), allow the IMP/NIMP to be used other than as directed by this clinical trial protocol, or dispose of IMP/NIMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All participants will be centrally assigned to randomized study treatment using an IRT system.

Randomization will be stratified by HbA1c obtained at the Visit 1 (<8.0% versus ≥8.0%). Randomization ratio is 1:1.

A randomized participant is a screened participant who has a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used. A participant cannot be randomized more than once in the study.

The treatment kit number list is generated centrally by Sanofi. The IMPs and NIMPs for the treatment period are packaged in accordance with this list. Designated Sanofi personnel provide the treatment kit number list and the randomization scheme to the centralized treatment allocation system (IRT). Then, the IRT generates the participant randomization list according to which it allocates treatment arms to the participants.

The treatment kits for the treatment period, open-label boxes identified with treatment numbers, are allocated to the participants by the IRT using the treatment number of the boxes.

At Visit 1, the Investigator or designee contacts the IRT for allocation of the participant number. The participant identification (participant number) is composed of 12-digit number containing the 3-digit country code, the 4-digit center code and the 5-digit participant chronological number (which is 00001 for the first participant screened in a center, 00002 for the second participant screened in the same center etc.).

At Visit 3 (Day 1, Randomization), the Investigator or designee has to contact the IRT for the first treatment kit(s) allocation (randomization) by providing some information (such as participant number provided by IRT at Visit 1, etc.). Afterwards the IRT is contacted again each time a new treatment kit(s) allocation is necessary, ie, the visits as indicated in the SoA (see Section 1.3) or when additional IMP/NIMP supplies are needed.

Returned IMPs and NIMPs must not be re-dispensed to the participants.

SAR341402 in the SAR341402 SoloStar pen and the control drug, NovoLog in the NovoLog FlexPen are distinguishable. Therefore administration of SAR341402/NovoLog throughout the trial is to be open-label. Potential bias will be reduced by the following steps:

- The specific IMP to be taken by a participant will be assigned centrally using an IRT.
- Pharmacokinetic values, antibodies, blood glucose values from samples collected at the sites, as well as HbA1c values are determined in central laboratories blinded to the treatment received.
- Selected AEs (see Section 10.1.5) will be adjudicated in a blinded fashion.
- The Sponsor study team involved in the data review and analysis will remain blinded to treatment group until database lock:
  - Investigators will be requested not to report unblinded information related to IMP in the electronic case report form (eCRF) and SAE reports,
  - Members of the study team may review compliance with dosing and titration blinded to treatment (monitoring team is not blinded when reviewing),
  - The study team will review data in descriptive statistics without treatment assignment during data review meetings,
  - The unblinded treatment group allocation variable will be included in the clinical study database only at the time of the database lock, to perform the corresponding analyses; summary results by treatment arm will therefore not be available to anyone before database lock.

6.4 STUDY INTERVENTION COMPLIANCE

Measures taken to ensure and document treatment compliance and IMP/NIMP accountability include the following:

- At each visit, the Investigator or his/her delegate asks the participant about administered doses of IMP (SAR341402 or NovoLog) and NIMP (Lantus).
- All medication treatment kits (whether empty, partially used or unused) will be returned by the participant at each visit when treatment dispensing is planned.
- The Investigator or his/her delegate will track treatment accountability/compliance by completing the appropriate Product Accountability forms.
- The mandatory background NIMP (including Novolog and Lantus administered during the run-in period) will be recorded in the eCRF.

6.4.1 Return and/or destruction of treatment

The Investigator will not destroy any IMP/unused NIMP unless the Sponsor provides written authorization. A detailed treatment log of the destroyed IMP/unused NIMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

The destruction is recommended to be performed at site depending on IMP/NIMP specificities and local requirements but IMP/NIMP can be returned to the Sponsor for destruction.

A potential defect in the quality of IMP/NIMP may initiate a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP/NIMP and eliminate potential hazards.

6.5 CONCOMITANT THERAPY

A concomitant medication is any treatment received by the participant from the time of Screening through EOT visit. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of signing the ICF or receives during the study must be recorded in the eCRF.

The following drugs are **not** permitted during the screening period (if no run-in period is required), the run-in period (if applicable), and the randomized open-label treatment periods:

- Any glucose-lowering agents other than the IMP, ie, authorized insulin analog SAR341402 or NovoLog, and the background NovoLog and basal anti-diabetic therapy (insulin glargine 100 U/mL).

  Note:

  - Short term therapy (up to 10 days maximum) with either basal insulin or short acting insulin that may occur due to acute illness or surgery is allowed after the first administration of IMP but not during the screening and run-in periods,
  - Any antidiabetic medication, according to local standard of care, per the Investigator's judgment can be used after definitive premature IMP discontinuation,
  - Administration of additional meal-time insulin during the 8-hour PK period, according to the Investigator's judgement is also permitted. Due to considerations related to the sensitivity of the insulin aspart PK assay, human insulin must be used during this timeframe. Alternatively, administration of insulin lispro at low doses, according to the Investigator's judgement, is also permitted.
- Systemic glucocorticoids for more than 10 days (topical, nasal spray, inhaled or intra-articular applications are allowed).
- Immunosuppressive agents.
- Any other investigational product (ie, participation in another clinical trial).

Concomitant medications should be kept to an absolute minimum and doses should be kept stable unless safety concerns indicate changes of dose.

There is no rescue therapy defined in this study. Hypoglycemia will be managed as appropriate, by administering countermeasures, according to the clinical judgement of the Investigator.

6.5.1 Evaluation of participants not meeting glycemic goals

- In case of SMPG not meeting the target in spite of successive insulin dose titration, the Investigator should ensure and document that no reasonable explanation exists for insufficient glucose control and in particular that:
  - Fasting plasma glucose was actually measured in fasting condition (ie, after at least 8 hours fasting),
  - Rebound hyperglycemia is excluded,
  - IMP/NIMP doses are properly adjusted,
  - Correction doses for pre-prandial glucose values above goal are used by participant,
  - There is no inter-current disease which may jeopardize glycemic control (eg, infectious disease),
  - Compliance to diet and lifestyle is appropriate, in particular, dosage adjustment for changes in meal content and SMPG.
- If any of the above can reasonably explain the insufficient glycemic control, the Investigator should undertake appropriate action, eg:
  - Further titrate the IMP/NIMP, if deemed safe by the Investigator,
  - Set up adequate investigation and treatment of inter-current disease (to be reported in AE/SAE/concomitant medication parts of the eCRF),
  - Stress the absolute need to be compliant to treatment,
  - Stress the importance of consistency in meals and insulin dosing, particularly during this time of poor glycemic control,
  - Monitor night time glucose,
  - If deemed appropriate, organize a specific interview with a Registered Dietician or other medically qualified person to stress on the absolute need to be compliant to diet and lifestyle recommendations, in particular with attention to awareness of the meal content and covering all snacks with a dose of rapid-acting insulin.

6.6 DOSE MODIFICATION

Study participants adjust dose of IMP and NIMP as described in Table 3 and with site oversight according to standard of care.

6.7 INTERVENTION AFTER THE END OF THE STUDY

The IMPs/NIMP will not be provided after the end of the treatment period.

When an individual's participation in the study ends, he/she will consult with his/her Investigator to decide on best available treatment.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Withdrawal of consent for treatment should be distinguished from (additional) withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up (eg, medical record checks). The site must specifically document the type for each case of withdrawal of consent.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

The IMP should be continued whenever possible.

In case the IMP is stopped, it should be determined whether the stop can be made temporary; definitive IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF. In any case, the participant should remain in the study as long as possible.

Definitive intervention discontinuation is any intervention discontinuation associated with the definitive decision from the Investigator not to re-expose the participant to the IMP at any time during the study, or from the participant not to be re-exposed to the IMP whatever the reason.

The participants may withdraw from treatment with IMP if they decide to do so, at any time, and irrespective of the reason. Participants are encouraged to discuss their intent of stopping the IMP with the site before doing so in order for questions to be addressed, concomitant therapy to be adjusted if needed, and a follow-up assessment arranged. All efforts must be made to document the reasons for treatment discontinuation in the source documents and in the eCRF.

A participant should withdraw from treatment with IMP and NIMP in case of the following:

- Temporary discontinuation of the IMP of more than 10 days in total.
- Intercurrent conditions that require discontinuation of IMP/NIMP (eg, for laboratory abnormalities according to the decision tree in Appendix 5 [Section 10.5] as long as the abnormality persists and if the casual relationship of the concerned event and the IMP/NIMP is possible according to the Investigator's best medical judgment).
- If, in the Investigator's opinion, continuation with the administration of IMP/NIMP would be detrimental to the participant's well-being.
- Pregnancy (in female participants).
- Confirmed intolerance to the allocated dose of IMP/NIMP.
- At the participant's own request, ie, withdrawal of consent for treatment.

It is important to collect data for all participants, under treatment or not, during the whole duration of the study. A high rate of missing data could jeopardize interpretation of the study results. Refer to the SoA (Section 1.3) for data to be collected at the time of IMP discontinuation and follow-up and for any further evaluations that need to be completed.

Note: as an exception to the requirement mentioned above, participants who prematurely and definitively discontinue IMP will have their serial PK samples (0 to 8 hours) collected at the time of the early discontinuation visit, not at the time of Week 16 visit (Visit 7) as planned per SoA (Section 1.3).

Any clinically-significant abnormal laboratory value will be rechecked for confirmation as soon as possible before making a decision of definitive discontinuation of the IMP for the concerned participant.

Handling of participants after definitive intervention discontinuation

Every effort should be made to maintain participants in the study. Participants will be followed according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed as specified in this protocol, whichever comes last.

If possible, the participants will be assessed using the procedure planned for the EOT Visit (Visit 7) before the definitive discontinuation of the IMP, or as soon as possible after discontinuation. For participants who discontinue intervention but remain in the study, the remaining visits should occur as scheduled where possible, including the assessments planned in SoA (Section 1.3) 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. The Investigator should discuss with them key visits to attend.

The value of all their study data collected during their continued involvement will be emphasized to study participants as important to the study. Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary IMP discontinuation corresponds to more than 1 dose not administered to the participant.

All IMP discontinuation should initially be considered as temporary unless definitive discontinuation is mandated by the protocol (see Section 7.1), and the Investigator should make best effort to resume IMP treatment as early as practically possible. There is a limit to up to 10 days in total (during the study) for IMP discontinuations to be deemed as temporary. If the sum of temporary discontinuations durations exceeds 10 days, discontinuation should be considered and managed as definitive.

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or due to any other reason.

7.1.2.1 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2). In case of IMP intolerance, a one-time rechallenge is recommended following temporary discontinuation before deciding to definitively discontinue the IMP.

Note: To allow for rechallenge, IMP discontinuation should not be reported in the IRT until definitive discontinuation is confirmed.

Participants who temporarily discontinue IMP should be reassessed at every visit to determine whether it is possible to safely resume IMP. If a decision has been made that the discontinuation is definitive (see Section 7.1.1), then the participant should be considered as definitively discontinued and the corresponding eCRF page should be completed. Please note that definitive discontinuation should be a last resort.

It is in the interest of the participant to monitor plasma glucose during the temporary discontinuation period, therefore SMPG or other regular determination of plasma glucose is recommended to be performed and documented.

During any temporary treatment discontinuation, doses of alternative treatment used for plasma glucose control will be recorded in the eCRF.

Use of a different insulin during the time of temporary treatment discontinuation is recorded as concomitant medication (such as during a hospitalization) with the name and doses recorded in the eCRF.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

Participants who have withdrawn from the study cannot be rerandomized in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (eg, contact patient's family or private physician, review available registries). Attempts to contact such patients (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods) must be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- In addition to the scheduled laboratory samples collection, as presented in the SoA (Section 1.3), repeat or unscheduled samples may be collected for safety reasons or due to technical issues with the samples.

8.1 EFFICACY ASSESSMENTS

8.1.1 Glycated hemoglobin A1c

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified level I "National Glycohemoglobin Standardization Program" (NGSP) central laboratory.

Conversion of HbA1c values between % and mmol/mol units will be done according to the International Federation of Clinical Chemistry – National Glycohemoglobin Standardization Program (IFCC NGSP).

8.1.2 Self-monitored plasma glucose

At the screening visit, the Investigator or a member of the investigational staff will provide participants with a glucometer and corresponding supplies (lancets, test strips, etc.). Intensive training on the correct handling of the glucometer will be provided as appropriate at the screening visit, run-in visit (if applicable) and at the randomization visit. Regular refresher instructions will be provided at each appropriate visit throughout the study. Participants will be instructed to bring the glucometers provided by the Sponsor with them to each office visit. If applicable, the glucometers must be calibrated according to manufacturer's instructions and the investigational site must also check regularly the glucometers using the provided control solutions for data validity. All self-monitored plasma glucose values collected in the study have to be measured by the participant using the sponsor-provided glucometer (and not by using the participant's personal glucometer or continuous glucose monitoring [CGM] device), unless occasionally deemed necessary for the safety of the participant.

Study participants will be provided with a diary and will receive detailed instructions for its use. The diary needs to be brought to each on-site visit.

Self-monitored plasma glucose measurements are scheduled as follows:

- **SMPG to support basal and meal-time insulin titration/dosing** is recommended daily during the first weeks of study treatment until reaching target ranges for SMPG, and thereafter on at least 3 days during the week before each visit or more frequently as requested by the Investigator; pre-meal, 2-hour postprandial, and nocturnal SMPG will be used consistent with standard of care. The results will be discussed between Investigator and participant during scheduled and unscheduled visits at the discretion of the Investigator.
  For SMPG ≤3.9 mmol/L (≤70 mg/dL), the participant will be required to complete the hypoglycemia specific information.
- **SMPG during episodes of symptoms of hypoglycemia**: whenever the participants feel hypoglycemic symptoms, plasma glucose should be measured by the participant (or others, if applicable), if possible.

8.1.3 Fasting plasma glucose

Blood samples for FPG measurement are taken and measured at central laboratory according to the SoA (Section 1.3).

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A complete physical examination (including, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems) will be performed as per clinical practice in order to assess the health status of the participant at Screening and evaluate the inclusion/exclusion criteria.
- At EOT a limited physical examination focused on any affected body area or organ or organ system will be performed.
- Height will be measured and BMI will be calculated at Visit 1 only.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any clinically-significant new finding or worsening of previous finding must be reported as an AE.

8.2.2 Vital signs

Vital signs parameters are heart rate (HR), systolic blood pressure (BP) and diastolic BP.

- Blood pressure and HR measurements will be performed for each participant according to the schedule displayed in the SoA (Section 1.3) prior to procedures involving venipuncture or injections.
- Devices for BP measurement should be regularly recalibrated according to manufacturers' instructions.

8.2.3 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF as an AE/SAE, as appropriate.
- Decision trees for the management of certain laboratory abnormalities are provided in Appendix 5 (Section 10.5).

8.2.4 Hypoglycemia

8.2.4.1 Documentation and Classification of Hypoglycemia

During the study, participants must be instructed to document all hypoglycemia episodes in their diary as soon after the event as possible. Hypoglycemia will be recorded or integrated in the specific eCRF page. Hypoglycemia fulfilling the seriousness criteria will be documented in addition on the AE/SAE form in the eCRF.

Hypoglycemic events will be categorized (11, 12, 13) as follows:

- **Severe hypoglycemia:** Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. The definition of severe symptomatic hypoglycemia includes all

episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place participants at risk for injury to themselves or others. Note that "requiring assistance of another person" means that the participant could not help himself or herself. Assisting a participant out of kindness, when assistance is not required, must not be considered a "requiring assistance" incident.
Severe hypoglycemia will be qualified as an SAE only if it fulfills SAE criteria (see Section 10.3). For example, events of seizure, unconsciousness or coma must be reported as SAEs.

- **Documented symptomatic hypoglycemia:** Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than or equal to 3.9 mmol/L (70 mg/dL). Clinical symptoms that are considered to result from a hypoglycemic episode are, eg, increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, or coma.
- **Asymptomatic hypoglycemia:** Asymptomatic hypoglycemia is an event not accompanied by typical 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 is an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 3.9 mmol/L (70 mg/dL); symptoms treated with oral carbohydrate.
- **Relative hypoglycemia:** (termed in 12 "pseudo-hypoglycemia") is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration greater than 3.9 mmol/L (70 mg/dL).

In addition to the threshold of plasma glucose of less than or equal to 3.9 mmol/L (70 mg/dL), documented symptomatic hypoglycemia and asymptomatic hypoglycemia with a measured plasma glucose concentration less than 3.0 mmol/L (54 mg/dL) will also be analyzed (13).

Hypoglycemic events will be evaluated regardless the time of onset during the day.

8.2.4.2 Self-measured plasma glucose during symptomatic hypoglycemia

Whenever the participants feel hypoglycemic symptoms, plasma glucose should be measured by the participant (or others, if applicable), if possible. The study glucometer must be used for these measurements. Participants should be instructed to measure plasma glucose levels prior to carbohydrate intake or administration of glucose whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate carbohydrate/glucose rescue prior to confirmation.

Exceptionally, and only during hypoglycemic events during which there is no possibility to use the study glucometer, plasma glucose may be recorded with other devices. These events are to be recorded in the diary by the study participants, ensuring that most complete information (including but not limited to the event date and the plasma glucose value, if available) is provided.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification (within 24 hours) by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- **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.
  - It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]),
  - In the event of pregnancy in a female participant, IMP should be discontinued,
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4]).
- **Symptomatic overdose (serious or nonserious) with IMP/NIMP.**
  - A symptomatic overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the participant and resulting in clinical symptoms and/or signs and considered a "significant overdose" by the Investigator. It will be recorded in the eCRF in all cases and will be qualified as an SAE only if it fulfills the SAE criteria.
- **Increase in ALT>3 × ULN** (see Section 10.5).

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention and/or study (see Section 7).

Adverse events requiring specific monitoring

An AE requiring specific monitoring is a serious or nonserious AE of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring may be appropriate. Such events may require further investigation to characterize and understand them. These events should be reported on the AE page and additional information required on the specific eCRF page (where applicable) and will only qualify for expedited reporting when serious (fulfilling SAE criteria).

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

- **Injection site reactions.**
  In case the Investigator or the participant recognizes any sign related to local non-allergic reactions at the IMP/NIMP injection site, this should be recorded on the AE page in the eCRF.
  If a participant reports an injection site reaction between the on-site visits or during a phone call visit, it is recommended that the Investigator ask him/her to come to the study site on the same or the next day or as clinically appropriate, so that the event can be properly assessed and reported.
- **Hypersensitivity reactions.**
  Allergic reactions or possible allergic reactions will be adjudicated by the ARAC (see Appendix 1, Section 10.1.5).
  If a participant reports a hypersensitivity reaction between the on-site visits or during a phone call visit, it is recommended that the Investigator ask him/her to come to the study site on the same or the next day or as clinically appropriate, so that the event can be properly assessed and reported.
  Virtually all symptoms listed on the allergic reaction complementary form are possible adverse reactions that may be allergic in nature and may need to be addressed after medical judgment, excluding another etiology than allergy.
  Sometimes transient injection site reactions, irritant in nature may occur requiring no intervention and are of dubious significance. These reactions would not be considered to be allergic reactions. Adverse events that are obviously not of allergic origin (eg, local injection site reactions) should not be recorded on the designated Allergic Reaction eCRF Form.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit.

All SAEs and AESI will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs and non-serious AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt (within 24 hour) notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adverse events that are considered expected will be specified in the reference safety information.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Pregnancies in female participants and female partners of male participants will be reported after the start of study intervention until the follow-up visit.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Guidelines for reporting product complaints

Any defect in the IMP/NIMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, it is recommended that the Investigator take the following actions:

1. Contact the Medical Monitor, if deemed necessary.
2. Closely monitor the participant for any hypoglycemia, AEs/SAEs and laboratory abnormalities, as appropriate.
3. Document appropriately in the eCRF (see Section 8.3).

Decisions regarding dose interruptions or modifications will be made by the Investigator based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

- Whole blood samples will be collected for measurement of plasma concentrations of insulin aspart as specified in the PK flow chart (see Section 1.3). Instructions for the collection and handling of biological samples will be provided by the Sponsor or designee. The actual date and time (24-hour clock time) of each sample must be recorded.
- Samples will be used to evaluate the PK of SAR341402/insulin aspart. Each plasma sample will be divided into 2 aliquots (1 each for PK and a back-up). Samples collected for analyses of SAR341402/insulin aspart plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

8.7 GENETICS

Genetics are not evaluated in this study.

8.8 BIOMARKERS

8.8.1 Immunogenicity assessments

Antibodies to insulin aspart, including neutralizing antibodies, will be evaluated in plasma samples collected from all participants according to the SoA (Section 1.3). Additionally, plasma samples should also be collected at the final visit from participants who discontinued study intervention. Participants need to come to the site fasting without having injected any meal-time insulin (SAR341402 or NovoLog) for at least 8 hours. Blood samples for antibody measurements will be collected before any insulin is administered and in a fasting state. All samples will be tested by a central laboratory blinded to intervention allocation.

Plasma samples will be screened for antibodies binding to insulin aspart and the titer and cross-reactivity to human insulin of confirmed positive samples will be reported. Other analyses including assessment of neutralizing capacity of confirmed positive samples may be performed to further characterize the immunogenicity of insulin aspart.

The detection and characterization of antibodies to insulin aspart will be performed using a validated assay method by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Further analyses of immune responses to insulin aspart may be conducted up to two years after the last sample collection.

8.9 HEALTH ECONOMICS

Health Economics and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary analysis will be performed 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 (SAR341402/NovoLog switching arm and NovoLog 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 SAR341402/NovoLog switching arm and NovoLog non-switching arm is outside the pre-defined acceptance range 80-125%.
- H1: The ratio of geometric means for AUC_{last}, AUC, and C_{max} between SAR341402/NovoLog switching arm and NovoLog non-switching arm is within the pre-defined acceptance range 80-125%.

9.2 SAMPLE SIZE DETERMINATION

Approximately 184 participants will be randomly assigned to either one of the 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 are 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 (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.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 4):

Table 4 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF
Randomized	All screened participants who have a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used
Evaluable for PK (PK)	All participants without deviation that could significantly impact the PK analysis (eg, missing or incorrect SC injection on PK profile day) and for whom PK data are considered sufficient and interpretable
Intent to Treat (ITT)	All randomized participants, irrespective of compliance with the study protocol and procedures, analyzed in the treatment group to which they are randomized
Per Protocol (PP)	Subset of the ITT population, which includes all randomized and exposed participants, who do not definitively discontinue IMP allocated by randomization during the 16-week period, who perform Week 16 visit and who do not present major or critical protocol deviations that could significantly impact the analysis
Safety	All randomized participants who receive at least one dose of IMP (regardless of the amount of IMP administered). Participants will be analyzed according to the intervention they actually received.
Immunogenicity (AIA)	All participants 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 meal-time insulin). Participants will be analyzed according to the intervention they actually received.

AIA: anti insulin aspart antibody; ICF: informed consent form; IMP: investigational medicinal product; IRT: interactive response technology; ITT: intent to treat; PK: pharmacokinetic; PP: per protocol; SC: subcutaneous

9.4 STATISTICAL ANALYSES

A statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints and any changes to the planned analyses will be addressed in the SAP.

9.4.1 Pharmacokinetic analyses

Table 5 - Pharmacokinetic analyses

Endpoint	Statistical Analysis Methods
Primary: AUC_{last}, AUC, C_{max} following injection of a predefined, fixed dose of SAR341402 or NovoLog (0.15 U/kg) at Week 16	Primary PK analysis will be based on the PK population. For participants with insufficient data for some but not all PK parameters, the evaluable PK parameters will be included in the analysis. PK parameters will be summarized by treatment using descriptive statistics. The impact of switching between SAR341402 and NovoLog on AUC_{last}, AUC, and C_{max} will be assessed. 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 (SAR341402/NovoLog switching arm, NovoLog non-switching arm) and randomization strata. Estimate and 90% CI for the ratio of geometric means between the two arms (SAR341402 from switching arm / NovoLog from non-switching arm) will be computed for AUC_{last}, AUC, and C_{max}, from the linear model framework using re-transformation. The 90% CI for the ratio of geometric means of AUC_{last}, AUC, and C_{max} should be within 80-125%.
Secondary: Time to C_{max} (T_{max}) following injection of a predefined, fixed dose of SAR341402 or NovoLog (0.15 U/kg) at Week 16	T_{max} will be summarized by treatment in the PK population using descriptive statistics.

AUC: area under the concentration curve; C_{max}: maximum concentration; PK: pharmacokinetic; T_{max}: time to maximum concentration

9.4.2 Immunogenicity analyses

Table 6 - Immunogenicity analyses

Endpoint	Statistical Analysis Methods
Secondary: Number of participants with treatment-emergent AIA during the 16-week treatment	Immunogenicity analyses will be based on the AIA population. Only AIA results from samples collected during the on-treatment period and at least 8 hours after the last administration of meal-time insulin will be taken into account in the analysis. 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.

AIA: anti insulin aspart antibody; IMP: investigational medicinal product

9.4.3 Safety analyses

All safety analyses will be descriptive and performed on the Safety Population.

The **observation period for safety data** is 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 1 day after the last injection of IMP.

- The post-treatment period is defined as the time starting 1 day after last injection of IMP (after the on-treatment period).

The AE observations will be classified per the observation periods of safety data as defined above:

- **Pre-treatment AEs** are AEs that developed or worsened or became serious during the pre-treatment period.
- **Treatment-emergent AEs** 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.

Analyses will focus on safety observations during the on-treatment period.

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

Table 7 - Safety analyses

Endpoint	Statistical Analysis Methods
Secondary: Number of participants with at least one hypoglycemic event for the 16-week treatment period	Proportions of participants with at least one hypoglycemic event will be presented overall and by type of event for each treatment group.
Secondary: Number of hypoglycemic events per participant-year for the 16-week treatment period	Incidences of hypoglycemia per participant-year will be computed as: 365.25 x (number of episodes of hypoglycemia)/(number of days exposed) and summarized overall and by type of event for each treatment group. For exploratory purpose, odds-ratios and rate ratios of hypoglycemic event may be provided for SAR341402/NovoLog switching group versus NovoLog non-switching group, overall and for some categories of hypoglycemia. Details will be provided in the SAP. Further analyses (eg, by subgroup, over time) may be done as appropriate and will be detailed in the SAP.
Secondary: Number of participants with AE for the 16-week treatment period	All AEs will be coded using the version of MedDRA currently in use by the sponsor at the time of database lock. Adverse event incidence tables will present using the MedDRA hierarchy, the number and percentage of participants experiencing an AE for each treatment group. Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent SAEs, all TEAEs leading to definitive treatment discontinuation and all TEAEs leading to death. The number and proportion of participants with injection site and hypersensitivity reactions (identified by MedDRA search) will also be summarized by treatment group, and events adjudicated as possible hypersensitivity reactions by the ARAC will be described.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; SAE: serious adverse event; TEAE: treatment-emergent adverse event

9.4.4 Other analyses

Other AIA endpoints will be derived from AIA assessments (status, titer) as follows:

a Participants with treatment-induced AIAs will be defined as participants with AIAs that developed de novo (seroconversion) following the IMP administration.

b Participants with treatment-boosted AIAs will be defined as participants with pre-existing AIAs that were boosted to a significant higher titer following the IMP administration (at least 4 fold increase in titer values).

c Participants with treatment-emergent AIAs (AIA incidence) will be defined as participants with treatment-induced or treatment-boosted AIAs.

Analysis of tertiary/exploratory endpoints (other AIA endpoints, clinical effects of AIA, change in insulin dose, and efficacy analyses) will be described in the statistical analysis plan finalized before database lock.

9.5 INTERIM ANALYSES

No interim analysis is planned.

9.5.1 Data Monitoring Committee (DMC)

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,
  - Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines,
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC,
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures,
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation).

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Subject race and ethnicity will be collected in this study as part of the data comprising the baseline characteristics of the population.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.1.5 Committees Structure

An ARAC, a committee of experts in the field of allergology and diabetes mellitus independent from the Sponsor and the Investigators, blinded for the treatment groups, will adjudicate hypersensitivity reactions, hypersensitivity-like reactions, and events of potential loss of efficacy, according to criteria as defined in the ARAC charter. The ARAC members may recommend additional follow-up (ie, AIA titers measurement) after the end of study per SoA (Section 1.3) in specific participants with treatment-emergent AIAs at the end of study with potential impact on glycemic control or safety. Details of these activities and assessments are being outlined in the ARAC charter.

10.1.6 Dissemination of Clinical Study Data

Sanofi shares information about clinical trials and results on publically accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after the end of the clinical study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and site closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

The tests detailed in Table 8 will be performed by the central laboratory.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 8 - Protocol-required laboratory assessments

Laboratory assessments	Parameters			
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit		White blood cell (WBC) count with differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
Clinical chemistry[a]	Creatinine	Potassium	AST	Total bilirubin (if values above the normal range, differentiation in conjugated and non-conjugated bilirubin)
	Albumin	Sodium	ALT	Estimated GFR (MDRD formula)
			Alkaline phosphatase	
Efficacy laboratory	HbA1c	Glucose fasting		
Anti-insulin aspart	Anti-insulin aspart antibodies; if positive, titer, cross-reactivity to human insulin, and neutralizing capacity			

Laboratory assessments	Parameters
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) at Screening • Urine pregnancy testing will be performed subsequent to Screening. If the urine test is positive, serum β-hCG should be tested for confirmation of the pregnancy[b] • C-peptide

NOTES :

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 10.5. All events of ALT >3 × upper limit of normal (ULN) and bilirubin >2 × ULN (>35% direct bilirubin) or ALT >3 × ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE

b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GFR: glomerular filtration rate; HbA1c: glycated hemoglobin A1c; hCG: human chorionic gonadotropin; IEC: Independent Ethics Committee; INR: international normalized ratio; IRB: Institutional Review Board; MDRD: modification of diet in renal disease; ULN: upper limit of the normal; RBC: red blood cells; WBC: white blood cells.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), ie:
  - Symptomatic, and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP/NIMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a) **Results in death.**

b) **Is life-threatening.**

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization.

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity.

- The term disability means a substantial disruption of a person's ability to conduct normal life functions,
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect.

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include:

- Invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse,
- Laboratory results that may indicate severe liver injury (possible Hy's Law, see Table 8).

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.

- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor representative in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor representative. However, **it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor representative.**

- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will make every effort to provide the Sponsor representative a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

REPORTING OF SAEs

SAE reporting to the Sponsor representative via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor representative will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor representative by telephone.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal.
2. Female with 1 of the following:
   - Documented hysterectomy,
   - Documented bilateral salpingectomy,
   - Documented bilateral oophorectomy.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female.
   - A postmenopausal state is defined as no menses for at least 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient,
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9.

In addition, WOCBP must refrain from donating ova for the duration of the study and for 5 weeks after the last dose of study intervention.

Table 9 - Contraceptives allowed during the study

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal • Injectable
Progestogen only hormonal contraception associated with inhibition of ovulation[c] • Oral • Injectable
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)[b] • Bilateral tubal occlusion • Vasectomized partner *(Vasectomized partner is a highly effective contraception method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Acceptable methods[d]
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide[e] • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

NOTES:

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates may differ from those when used consistently and correctly.

c Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

d Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

e Male condom and female condom should not be used together (due to risk of failure with friction).

PREGNANCY TESTING:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing during the intervention period as presented in the SoA (see Section 1.3) and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

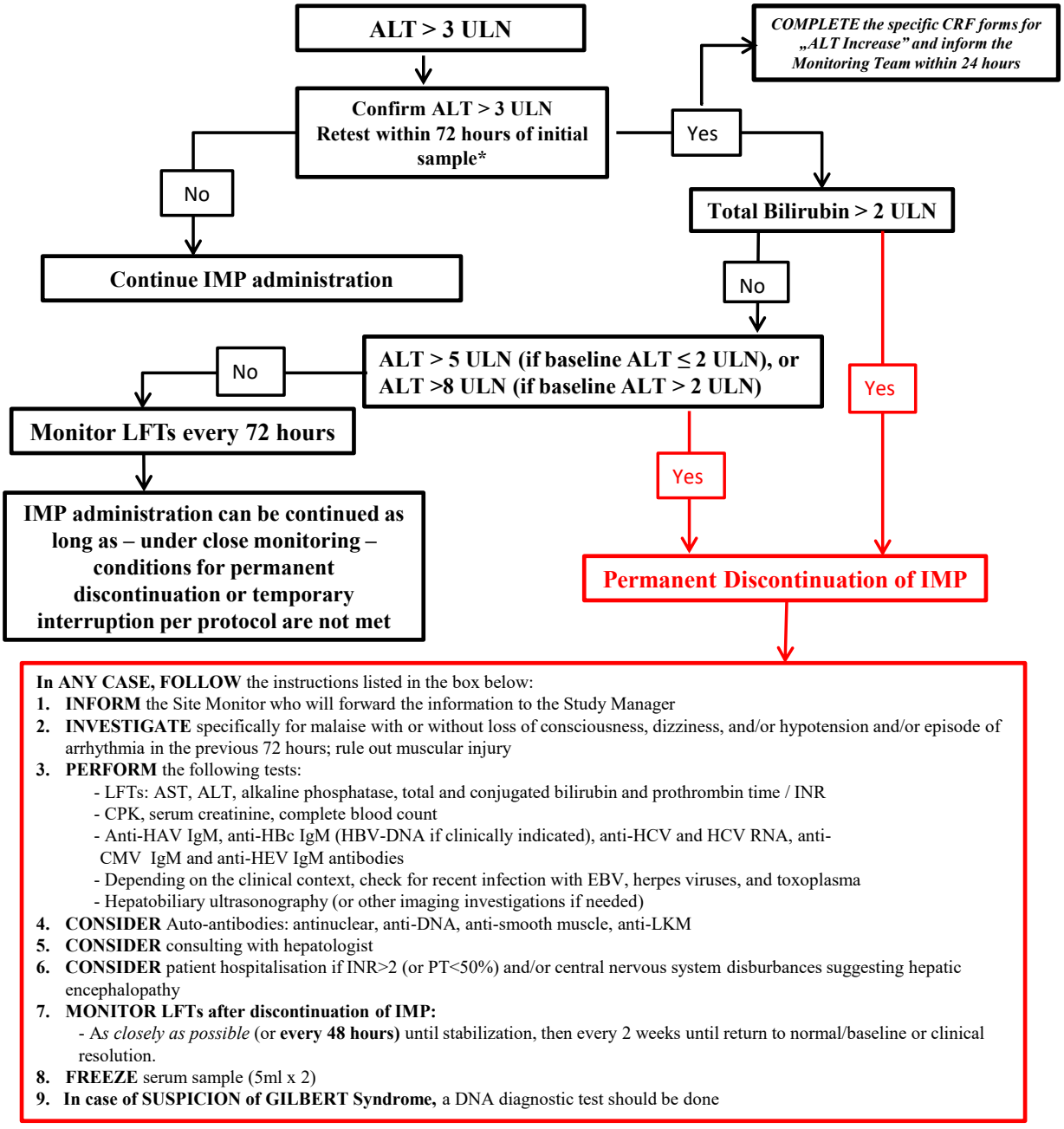
- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 APPENDIX 5: LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

INCREASE IN ALT



In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 10.3 for guidance on safety reporting.
- Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

10.6 APPENDIX 6: MEDICAL DEVICE INCIDENTS: DEFINITION AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.8 APPENDIX 8: ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest, adverse event of special interest
AIA:	anti-insulin aspart antibody
ALT:	alanine aminotransferase
ARAC:	Allergic Reaction Adjudication Committee
AST:	aspartate aminotransferase
AUC:	area under the concentration curve
BID:	twice daily
BMI:	body-mass index, body-mass index
BP:	blood pressure
CFR:	Code of Federal Regulations
CGM:	continuous glucose monitoring
CI:	confidence interval
CIOMS:	Council for International Organizations of Medical Sciences
Cmax:	maximum concentration
CONSORT:	Consolidated Standards of Reporting Trials
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
eCRF:	electronic case report form
EOT:	end of treatment, end of treatment
EU:	European Union
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose, fasting plasma glucose
FSH:	follicle-stimulating hormone, follicle-stimulating hormone
GCP:	Good Clinical Practice
GDPR:	Global Data Protection Regulation
GFR:	glomerular filtration rate
H0:	null hypothesis
H1:	alternative hypothesis 1
HbA1c:	glycated hemoglobin A1c
hCG:	human chorionic gonadotropin
HIPAA:	Health Insurance Portability and Accountability Act
HR:	heart rate

HRT:	hormonal replacement therapy
IB:	investigator's brochure
ICF:	informed consent form
ICH:	International Conference on Harmonization
IEC:	Independent Ethics Committee
IFCC:	International Federation of Clinical Chemistry
INR:	international normalized ratio
IRB:	Institutional Review Board
IRT:	interactive response technology, interactive response technology
ITT:	intent to treat
IUD:	intrauterine device
IUS:	intrauterine hormone-releasing device
MDI:	multiple dose injection
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
NGSP:	National Glycohemoglobin Standardization Program
NIMP:	noninvestigational medicinal product
PD:	pharmacodynamic(s)
PHS:	Public Health Service
PK:	Pharmacokinetic(s)
PP:	per protocol
PPG:	postprandial plasma glucose
QD:	once daily
RBC:	red blood cells
SAE:	serious adverse event, serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SMPG:	self-measured plasma glucose, self-measured plasma glucose
SoA:	schedule of activities
SUSAR:	suspected unexpected serious adverse reaction
T1DM:	type 1 diabetes mellitus
TEAE:	treatment-emergent adverse event
Tmax:	time of maximum concentration
ULN:	upper limit of the normal
US:	United States
WBC:	white blood cells
WOCBP:	woman of childbearing potential, woman of childbearing potential

10.9 APPENDIX 9: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 01 (27 February 2019)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The standardized meal test has been removed from this study because the Food and Drug Administration (FDA) noted several safety and methodological concerns associated with its performance, and because the standardized meal test would not add clinical value to the study. The study can adequately evaluate the effect of switching on pharmacodynamics (PD) parameters without the standardized meal test through collection of data on insulin dose over time and on the most clinically relevant measures of glycemia (glycated hemoglobin A1c [HbA1c] and fasting plasma glucose [FPG]).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis; Section 1.2 Schema; Section1.3 Schedule of Activities (SoA); Section 3 Objectives and Endpoints; Section 3.1 Appropriateness of Measurements; Section 4.1 Overall Design; Section 8.1.3 Standardized Meal Test; Section 8.1.4 Fasting Plasma Glucose; Appendix 2 Clinical Laboratory Tests	Standardized meal test has been removed	Several safety and methodological concerns were associated with standardized meal test performance and the standardized meal test would not have added any clinical value to the study
Section 1.1 Synopsis; Section1.3 Schedule of Activities; Section 4.1 Overall Design; Section 6.5 Concomitant Therapy	Add recommendations regarding the management of participants' glycemia during the end of treatment (EOT) visit	Additional meal-time insulin will likely be needed in all patients for the duration of the 8-hour PK assessment. The listed insulins do not interfere with the reliability of PK measurements
Section 6.5 Concomitant Therapy	Mention that hypoglycemia will be managed as appropriate by administering carbohydrates according to the clinical judgement of the Investigator	Clarification
Section 4.3 Justification for Dose; Section 6.1 Study intervention(s) administered	Remove mention that the dosing regimen will be continued after each switch as it was used prior to the switch	To ensure consistency with the instruction that the Investigators should titrate SAR341402 and NovoLog according to the NovoLog label and their clinical judgement

Section # and Name	Description of Change	Brief Rationale
Appendix 4: Contraceptive guidance and collection of pregnancy information	All female participants with documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy are not considered of childbearing potential	Clarification
Section 5.2 Exclusion Criteria E21; Section 6.5 Concomitant Therapy	Exclusion of participants who used glucose lowering treatments other than the MDI and basal insulin regimen, as described in inclusion criterion I05 (including use of insulin pump therapy) during the screening period	To ensure a similar baseline in all participants in terms of insulin treatment before the start of the study treatment period
Section 5.1 Inclusion Criteria I01	Mention that participants must be <u>at least</u> 18 years old to participate to the study	Clarification
Section 5.1 Inclusion Criteria I06	Mention that participants must have "HbA1c less or equal to 10%" instead of "below 10% (inclusive)"	Clarification
Section 1.3 Schedule of Activities (SoA)	"Documentation of insulin dose" replaced with "Review of insulin dose"	Clarification that dose is documented on an ongoing basis but reviewed at the study visits
Section 1.3 Schedule of Activities (SoA)	Mention that blood samples for measuring fasting plasma glucose should be taken before IMP administration	Clarification
Section 6.1 Study intervention(s) administered	Mention that the Lantus dose may be increased by more than 10% if deemed necessary by the Investigator	Clarification
Section 8.3 Adverse Events and Serious Adverse Events	The following sentences were removed: "Note: Asymptomatic overdose has to be reported as a standard AE"	Asymptomatic overdose does not meet the definition of an AE
	"In case a participant experiences an event identified as a potential hypersensitivity reaction (an allergic reaction or an allergic-like reaction), this has to be reported as an AE and recorded in the eCRF on the AE page, selecting the "suspected allergic event" category; additional information is collected on specific eCRF forms. "	These operational details are subject to change
Appendix 3: Adverse events: definitions and procedures for recording, evaluating, follow-up, and reporting	Addition of guidance on which laboratory abnormalities to be considered clinically significant	To limit the number of queries related to laboratory abnormalities

11 REFERENCES

1. U.S. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); Guidance for Industry. Considerations in Demonstrating Interchangeability with a Reference Product. 2019:1-23.

2. U.S. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER). Guidance for Industry. Applications covered by Section 505(b)(2). Draft. 1999:1-15.

3. US Department of Health and Human Services, FDA, CEDR. Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. 2015:1-24.

4. US Department of Health and Human Services, FDA, CEDR. Guidance for Industry. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Contains Nonbinding Recommendations; Draft-Not for Implementation. FDA. 2008:1-34.

5. Fineberg SE, Kawabata TT, Finco-Kent D, Fountaine RJ, Finch GL, Krasner AS. Immunological Responses to Exogenous Insulin. Endocrine Reviews. 2007;28(6):625–52.

6. Schernthaner G. Immunogenicity and Allergenic Potential of Animal and Human Insulins. Diabetes Care. 1993;16 Suppl 3:155-65.

7. Investigator's Brochure SAR341402, latest Edition.

8. NovoLog(R) (insulin aspart injection 100 Units/mL) US Prescribing information 12/2018.

9. NGSP. HbA1c and Estimated Average Glucose (eAG) [Online]. [cited 2017 May 30]. Available from: URL:http://www.ngsp.org/A1ceAG.asp.

10. American Diabetes Association. Standards of Medical Care in Diabetes-2017. Diabetes Care. 2017;40(Suppl 1):11-56.

11. American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes, Diabetes Care.2005;28(5):1245-9.

12. 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.

13. 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.

14. Lindholm A, Jensen LB, Home PD, Raskin P, Boehm BO, Rastam J. Immune Responses to Insulin Aspart and Biphasic Insulin Aspart in People With Type 1 and Type 2 Diabetes. Diabetes Care. 2002;25(5):876-82.

15. Uhr JF, Finkelstein MS. The kinetics of antibody formation. Prog Allergy. 1967;10:37-83.

16. Ogra PL, Kerr-Grant D, Umana G, Dzierba J, Weintraub D. Antibody response in serum and nasopharynx after naturally acquired and vaccine-induced infection with rubella virus. NEJM. 1971;285(24):1333-9.

17. Ogra PL, Karzon DT, Righthand F, MacGillivray M. Immunoglobulin response in serum and secretions after immunisation with live and inactivated poliovaccicne and natural infection. NEJM. 1968;279(17):893-900.

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